

# Syncope in Young Women: Broadening the Differential Diagnosis

Nachiket Patel, MD,<sup>1</sup> Naila Choudhary, MD,<sup>2</sup> Christine Tompkins, MD, MS,<sup>3</sup> Khawaja Afzal Ammar, MD,<sup>4</sup> A. Jamil Tajik, MD,<sup>4</sup> Krishnaswamy Chandrasekaran, MD,<sup>5</sup> Timothy E. Paterick, MD, JD, MBA<sup>4</sup>

<sup>1</sup>Banner/University of Arizona College of Medicine, Phoenix, AZ; <sup>2</sup>Rochester General Hospital, Rochester, NY;

<sup>3</sup>University of Colorado School of Medicine, Aurora, CO; <sup>4</sup>Aurora Medical Center, Milwaukee, WI; <sup>5</sup>Mayo Clinic, Rochester, MN

Syncope is defined as a sudden transient loss of consciousness (TLOC) with concomitant loss of postural tone followed by spontaneous recovery. It is a subset of a broader class of medical conditions, including postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, and neurally mediated syncope (NMS), that may result in TLOC. The overlap of these clinical conditions leads to confusion regarding syncope classification that can hinder evaluation strategies, and pose challenges for diagnosis and treatment, particularly in young women. In this article, we review POTS, orthostatic hypotension, and NMS with an emphasis on NMS. These diverse orthostatic clinical entities may be associated with syncope and are frequently observed in young, healthy women. The importance of considering NMS as a diagnosis of exclusion cannot be overstated. We report a series of three young, otherwise healthy women, initially diagnosed with NMS, whose clinical course evolved over time into more sinister diagnoses that were overlooked and associated with devastating clinical outcomes. These cases highlight the importance of maintaining a broad differential diagnosis when considering the diagnosis of NMS. Each case synopsis provides key clinical features that must be considered to avoid overlooking more serious clinical conditions.

[*Rev Cardiovasc Med.* 2017;18(3):100–114 doi: 10.3909/ricm0865]

© 2017 MedReviews®, LLC

## KEY WORDS

Syncope • Healthy young women • Neurally mediated syncope • Orthostatic syncope  
• Postural orthostatic tachycardia syndrome • Transient loss of consciousness • Disorders without impairment of consciousness • Clinical outcome

**T**he term *syncope* describes a specific pathophysiology involving transient loss of consciousness (TLOC) and postural tone from global cerebral hypoperfusion with spontaneous and complete recovery without neurologic sequelae. Syncope is a subset of a broader range of TLOC conditions including seizures, concussions, and intoxications. Syncope is distinguished from the other conditions by loss of consciousness accompanied by loss of postural tone. Only those conditions in which loss of consciousness can reasonably be attributed to transient cerebral hypoperfusion with loss of arousability and postural tone are considered syncope.

Determining its etiology allows assessment of prognosis, risk of recurrence, and avoidance of injury or death. It is important to have a systematic approach to the causes of syncope, as patients may have several root causes.

## Postural Mediated Tachycardia Syndrome

Postural tachycardia syndrome (POTS) is a common manifestation of orthostatic intolerance. A spectrum of POTS exists in adolescent girls, ranging from dizziness to disabling autonomic dysfunction, that may result in presyncope and infrequently syncope.<sup>1</sup> POTS is defined by an increase in heart rate of  $\geq 30$

the required heart rate increase is 40 beats/min.<sup>2</sup> The orthostatic tachycardia may be accompanied by symptoms of cerebral hypoperfusion manifesting as lightheadedness, blurred vision, cognitive impairment, presyncope, and generalized weakness.<sup>3</sup> POTS is more frequent in girls and women (female to male ratio, 4.5:1); the most frequent presentation is between the ages of 15 and 25 years.<sup>4</sup> POTS orthostatic intolerance overlaps with orthostatic hypotension and neurally mediated syncope (NMS). The orthostatic intolerance of POTS may result in cerebral hypoperfusion and reflex sympathetic activation. Approximately one-third of POTS patients develop secondary orthostatic-triggered NMS.<sup>5</sup>

POTS is not a unique nosologic entity, and its treatment can be recalcitrant and must be individualized. The management of POTS includes patient education, volume restitution, physical training countermaneuvers, graded exercise training, and pharmacotherapy. Potential medications include fludrocortisone, midodrine,  $\beta$ -blockers, droxidopa, and pyridostigmine. Droxidopa is approved for treatment of neurogenic orthostatic hypotension associated with Parkinson disease, multisystem atrophy, and pure autonomic failure.<sup>6</sup> Ivabradine is an off-label treatment for POTS when

The potential for fetal toxicity mandates counseling all patients on ivabradine who are using contraception. A physician who possesses the necessary clinical acumen and expertise in the management of orthostatic syndromes should prescribe all the potential medications used to treat POTS.<sup>7</sup>

## Neurally Mediated Syncope

Neurally mediated TLOCs are of several types and are best known as vasovagal fainting. Vasovagal fainting occurs both in healthy people and in people with disease. Vasovagal syncope is typically associated with nausea and perspiration before fainting, and the individual may appear pale and feel clammy. After fainting, the individual may feel tired for hours to days. Other types of vasovagal syncope include carotid sinus hypersensitivity and situational faints elicited by blood draws, emotional trauma, pain, micturition and defecation, coughing, or swallowing.<sup>8</sup>

## Orthostatic Syncope

Orthostatic syncope, which results from hypotension associated with altered consciousness, is common and most frequently precipitated by a change in posture from lying to sitting/standing or sitting to standing. This occurs when the blood pressure is slow to respond to a change in posture and cerebral perfusion is compromised, resulting in feelings of lightheadedness to TLOC. Transient orthostatic hypotension does not necessarily represent a warning sign for underlying sinister disease. This autonomic imbalance in blood pressure response occurs in the elderly, with dehydration,

*POTS is defined by an increase in heart rate of  $\geq 30$  beats/min within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension...*

beats/min within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension; the standing heart rate is frequently  $>120$  beats/min. For individuals aged 12 to 19 years,

tachycardia contributes to symptoms. It works by reducing the diastolic depolarization slope in the sinoatrial node, thereby decreasing heart rate by direct inhibition of the sinoatrial node.

and from commonly prescribed medications such as diuretics,  $\beta$ -blockers, vasodilators, and inadequate fluid intake. More threatening etiologies

risk. Altered consciousness can occur at the initiation or cessation of the abnormal rhythm. Channelopathies are rare, but may result in syncope or sudden

accounting for orthostatic TLOC result from diseases that structurally alter the autonomic nervous system, such as amyloids, diabetes, and Parkinson disease.<sup>9</sup>

## **Structural Heart Diseases Resulting in Syncope**

Structural heart diseases can result in TLOC. The mechanism can result from hemodynamic alterations due to arrhythmias, outflow obstructions, or neurally mediated mechanisms. Conditions include acute myocardial infarction, hypertrophic cardiomyopathy, acute aortic dissection, cardiac tamponade, severe pulmonary hypertension, and severe aortic stenosis. TLOC in these conditions is relatively rare, but important to recognize, as it is potentially life threatening. The abnormal morphology and physiology makes patients with these conditions prone to potentially life-threatening rhythm disturbances.<sup>10,11</sup>

## **Rhythm Alteration Resulting in Syncope**

Rhythm alteration can result in TLOC, more commonly in older individuals. Various forms of bradycardia and tachycardia are common causes of TLOC. This can occur in healthy people with supraventricular tachycardia, but people with underlying cardiovascular disease are at higher

death, typically in younger individuals. The two most prevalent channelopathies are long QT syndrome (LQTS) and Brugada syndrome. The diagnosis of both conditions relies on a careful family history and analysis of the electrocardiogram (ECG). Family screening is important when an index patient is identified, although sporadic cases can occur.<sup>12,13</sup>

## **Central Nervous System Rarely Accounts for Syncope**

The central nervous system rarely accounts for TLOC. Causes include vertebral basilar transient ischemic attacks, but there are universally accompanying neurologic deficits such as cranial nerve deficits, paresis, and gait abnormalities. Additional

causes include subclavian steal syndrome and carotid sinus hypersensitivity. Other causes that should not be confused with TLOC include seizures, sleep disturbances, psychiatric conditions,

New insights into NMS are usually classified based on the efferent autonomic pathway most involved. The term *vasodepressor type* is used if hypotension due to a loss of upright vasoconstrictor tone prevails, *cardioinhibitory type* is used when bradycardia or asystole predominate, and *mixed* is used when both mechanisms are present.

NMS has a diverse nomenclature, including vasovagal syncope, cough, swallowing, and micturition syncope, or carotid sinus syncope. This condition is defined by a relatively sudden change in autonomic nervous system activity resulting in a drop in blood pressure, heart rate, and cerebral perfusion. NMS is a reflex with afferent, central, and efferent pathways.<sup>20,21</sup>

several seconds of asystole. The stimulus for NMS can be central, including emotions, pain, or blood phobia, or peripheral, including prolonged standing and increased carotid sinus or trigeminal efferent activity. The precise afferent nerve pathways and central nervous system pathways are elusive in NMS. Other environmental or physical factors may contribute to the drop in blood pressure and cerebral hypoperfusion. These include heat exposure resulting in peripheral vasodilation, straining with a closed glottis, reducing venous return, and increasing intracranial pressure and hyperventilation-induced vasodilation in skeletal muscles.<sup>20,21</sup>

NMS may also be classified based on its trigger, for example, micturi-

autonomic nervous system failure. Carotid sinus hypersensitivity syncope deserves special mention. It is a rare spontaneous form of TLOC that is triggered by mechanical manipulation of the carotid sinuses. In the more common form no mechanical trigger is found and it is diagnosed by carotid sinus massage.<sup>23</sup>

Herein, we describe a series of interesting, thought-provoking cases of initially diagnosed NMS. These clinical courses evolved over time into more grave diagnoses with adverse clinical sequelae. The key features that raised a suspicion of serious disease are highlighted. The synopsis of each case should be considered the critical teaching points and allow for insights into distinguishing benign NMS from more sinister etiologies (Table 1).

*Clinically, NMS is typically preceded by prodromal symptoms that may occur up to 1 minute prior to loss of consciousness. Classic prodromal features include pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing, and hyperventilation.*

Clinically, NMS is typically preceded by prodromal symptoms that may occur up to 1 minute prior to loss of consciousness. Classic prodromal features include pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing, and hyperventilation. The prodromal symptoms are followed by the features of cerebral and retinal hypoperfusion resulting in visual and auditory disturbances, diminished concentration, and slowing of cognition.<sup>20,21</sup>

During the clinical syndrome of NMS, efferent sympathetic vasoconstrictor nerve activity decreases, leading to a loss of blood vessel tone and vagal outflow increases, resulting in slowing of the heart rate. The range of bradycardia observed clinically varies greatly in NMS. The range in heart rate change varies from modest reduction in peak heart rate to

tion or defecation syncope. The triggering situations vary considerably between individual patients. In most cases, the efferent pathway does not depend strongly on the nature of the trigger as both micturition and vasovagal syncope may present as cardioinhibitory or vasodepressor syncope. Knowing the various triggers is clinically important, as recognition may be contributory in diagnosing the type of syncope.

Vasovagal syncope is mediated by emotion or by orthostatic stress. It is usually preceded by prodromal symptoms of autonomic activation such as sweating, pallor, and nausea. Situational syncope traditionally refers to reflex syncope associated with some specific circumstance. Postexercise syncope can occur in young athletes as a form of reflex syncope, as well as in middle-aged and elderly subjects as an early manifestation of

## Patient 1

A 15-year-old girl presents for evaluation of recurrent fainting episodes over the past 3 years. These episodes occur at a frequency of two to three times monthly during mild physical exertion or after exercise, but rarely during a competitive sporting activity. In general, episodes are without prodromal symptoms such as palpitations, presyncope, chest discomfort, or dyspnea. She correlated two of these episodes prior to the start of her menses. Her most recent episode occurred while jumping rope in front of her house. She fainted without warning, hitting the back of her head on the ground. Another episode occurred while running to catch a bus. She fell forward, causing minor facial lacerations.

She was evaluated by a cardiologist who thought her symptoms were most consistent with neurally mediated hypotension (NMH).



**TABLE 1**

Synopsis of Clinical Cases			
	Patient 1	Patient 2	Patient 3
Clinical Presentation	Syncope during physical activity but rarely with competitive sports	Palpitations and recurrent syncope preceded with nausea, vomiting, and lightheadedness	Recurrent episodes of syncope during venipuncture, radiograph of leg, and sight of blood; palpitations
ECG	Normal sinus rhythm, unremarkable	Normal sinus rhythm with VPC, T-wave inversion in V <sub>1</sub> -V <sub>4</sub> , III, and aVF	Normal sinus rhythm, QTc ranging 435-520 msec
Exercise Treadmill Test	Frequent unifocal VPCs during exercise that resolved in recovery	Occasional VPCs during exercise and multifocal VPCs in early recovery	Maximum heart rate 187 beats/min (95% of maximum predicted); no evidence of ischemia or arrhythmias
Holter Monitor	Mean heart rate of 50-60 beats/min, few episodes of heart rate up to 132 beats/min, and 130 ventricular ectopic beats	Heart rates ranging from 46-160 beats/min, 5107 ventricular ectopic beats, with 1 8-beat run of nonsustained VT	Heart rates ranging from 47-133 beats/min; 3 isolated VPCs, and 18 supraventricular ectopic beats without any symptoms
Echocardiography	Normal size and function of heart with no valvular abnormalities	Prior to cardiac arrest, normal size and function of heart with no valvular abnormalities; after cardiac arrest, severely decreased LV systolic function (EF 25%), moderately dilated RV with thinning and hypokinesis of RV free wall and RVOT	Normal biventricular structure and function with no valvular abnormalities
Genetic Testing	Not performed	Positive for 2 separate mutations for ARVC	Positive for congenital long QT syndrome

ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; EF, ejection fraction; LV, left ventricular; RV, right ventricle; RVOT, right ventricular outflow tract; VPC, ventricular premature complex; VT, ventricular tachycardia.

She was instructed to increase dietary intake of sodium and to maintain hydration. She had a subsequent episode of syncope despite these conservative measures and presented for a second opinion. She is a high school sophomore and plays varsity basketball. She does not take any medications. Her family history includes death of maternal uncle while sleeping at age 50. Her physical examination is unremarkable. Her baseline ECG is shown in Figure 1. The conservative

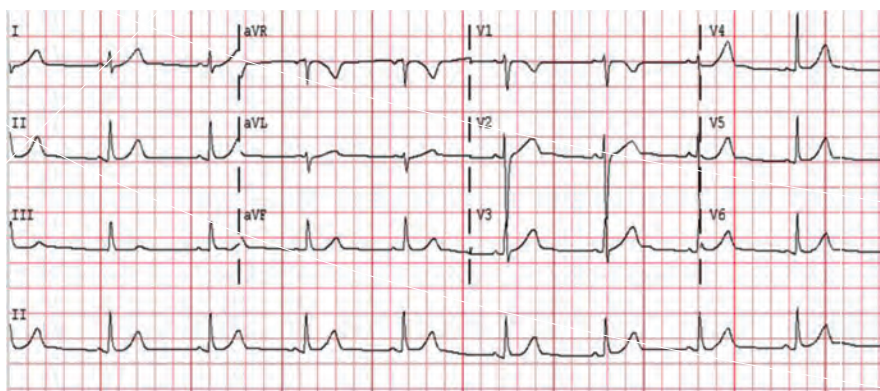


Figure 1. Baseline electrocardiogram of Patient 1.

measures for treatment of NMH were not efficacious. Further cardiac evaluation included an echocardiogram, 24-hour Holter monitor, and an exercise treadmill test (ETT). The echocardiogram was interpreted as showing normal size and function of the cardiac chambers and no valvular abnormalities. The Holter monitor revealed mean heart rate of 50 to 60 beats/min, few episodes of heart rate up to 132 beats/min, and 130 ventricular ectopic beats. ETT revealed maximum heart rate of 191 beats/min and maximum blood pressure of 144/64 mm Hg. The test was stopped at 13 minutes for fatigue. She developed frequent unifocal ventricular premature complexes (VPCs), occasionally in bigeminy on exertion, that resolved spontaneously during recovery. No ECG tracings of her ETT were available.

Based on the finding of increased ventricular ectopy during exercise and activity-related syncope, she was referred for an electrophysiology (EP) study with the intention of placing an implantable loop recorder (ILR) if a negative study result was obtained. The EP study, however, showed polymorphic ventricular tachycardia (VT) with rapid degeneration into ventricular fibrillation (VF) with double extrastimuli once (400-240-190 msec) and triple stimuli (400-200-190-190 msec) during epinephrine infusion. There were increased VPCs and a ventricular bigeminal rhythm on epinephrine, but no other inducible arrhythmias. No evidence of antegrade or retrograde conducting accessory pathways was found. An ILR was placed and she was subsequently started on  $\beta$ -blocker therapy.

She had another episode of syncope while playing basketball despite  $\beta$ -blocker therapy. Interrogation of the ILR revealed

wide complex tachycardia at 214 beats/min with evidence of A-V dissociation and capture beats consistent with VT (Figure 2).

Patient 1 is believed to have catecholaminergic polymorphic VT (CPVT) and continued to have VT despite  $\beta$ -blocker therapy. Placement of an implantable cardioverter defibrillator (ICD) was discussed with the patient and her family, and the patient was advised to refrain from competitive sports. However, she and her family were interested in continued participation in competitive

sports. She therefore sought further evaluation at another institution where she underwent VT ablation and activities were liberalized. She continued to follow-up after the ablation. Avoidance of rigorous physical activity was again emphasized when ETT following the ablation procedure showed ventricular bigeminy as well as multifocal VPCs with exercise. Despite these recommendations, she continued to participate in sports and remained noncompliant with  $\beta$ -blocker therapy. She had cardiac arrest during dance

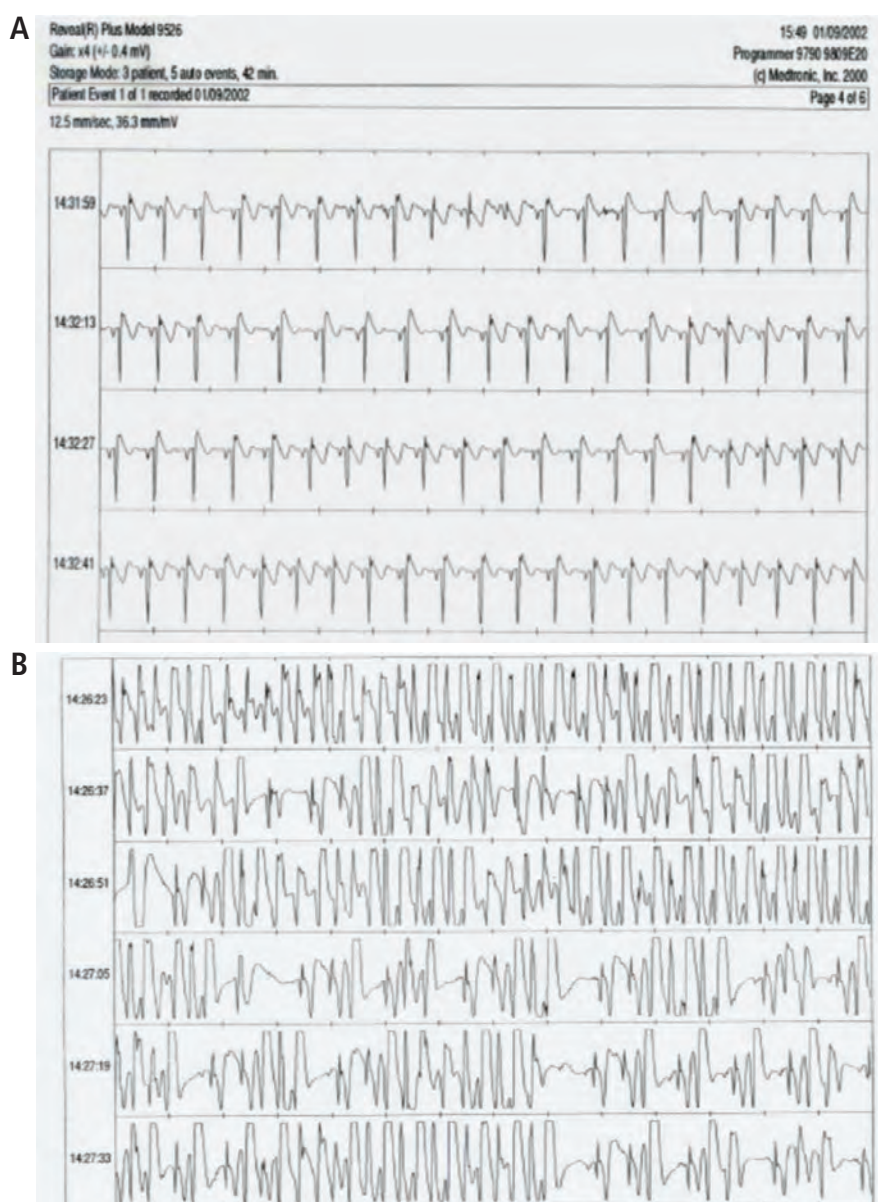


Figure 2. (A) Implantable loop recorder tracings of Patient 1 during early phase of exercise. (B) Implantable loop recorder tracings of Patient 1 while playing basketball.

class, and resuscitative measures were unsuccessful.

The patient's clinical history was suggestive of syncope secondary to a serious malady. The recurrent syncope with physical injury is always an ominous signal. Additionally, the family history of a maternal uncle with sudden cardiac death (SCD) during sleep at age 50 years is significant. The unremarkable physical examination, ECG, and echocardiogram results suggest absence of a structural heart disease. Given the clinical and family history, it would have been prudent to perform genetic testing to allow for an accurate diagnosis and a comprehensive discussion of lifestyle changes and therapy. Genetic testing can identify mutations in up to 65% of patients with a clinical diagnosis of CPVT.<sup>24</sup>

Review of the ETT results revealed complex ventricular arrhythmias. The VT recorded on the ILR is helpful and is an ominous finding while a patient is on  $\beta$ -blocker therapy. The finding of inducible VT/VF on the EP study is concerning and worrisome but not diagnostic. Her presentation was considered consistent with idiopathic VT at the outside institution and the diagnosis of CPVT was not entertained at that time.

CPVT is a rare form of inherited malignant ventricular tachyar-

thought to involve abnormal regulation of cellular calcium homeostasis, which triggers delayed afterdepolarization. Few studies have reported association of clinical presentation with sex. Priori and colleagues<sup>27</sup> reported that in RYR2-positive CPVT patients, younger age and male sex were risk factors for cardiac events, whereas RYR2-negative symptomatic CPVT patients were predominantly women who presented later in life.

Once the diagnosis of CPVT is considered, patients should be started on  $\beta$ -blockers as the mainstay of therapy.  $\beta$ -blockers should be titrated to the maximum tolerated dose, and an ETT while on  $\beta$ -blockers is recommended to assess the efficacy of therapy. Patients should also be instructed to refrain from competitive sports. In patients who continue to have ventricular arrhythmia despite optimal  $\beta$ -blocker therapy, other therapies must be considered. Left cardiac sympathetic denervation in these patients has been efficacious in reducing the incidence of life-threatening ventricular arrhythmia by preventing nor-epinephrine release in the heart.<sup>21</sup> ICD therapies should be considered as last option due to their potential proarrhythmic effect in this patient population, as both appropriate and inappropriate

complex tachycardia on  $\beta$ -blocker therapy represents a case that needs careful clinical evaluation and a search for a serious underlying pathophysiologic disorder. The appropriate clinical approach should have been genetic testing, disqualification from sports, aggressive  $\beta$ -blocker therapy, and strong consideration of ICD therapy after a careful risk-to-benefit discussion.

### Patient 2

A 16-year-old healthy girl presents for evaluation following multiple episodes of syncope, which began at age 14 years. She described her episodes as preceded by symptoms of nausea, vomiting, lightheadedness, and dizziness, followed by loss of consciousness. She is usually noted to be pale and diaphoretic during these episodes, and generally does not have any confusion afterward. One such episode occurred immediately after smelling sour milk; syncope was abrupt, resulting in facial lacerations and broken eyeglasses. She has also had syncope during the cool-down phase after running in a track meet.

In addition to these episodes of syncope, she has palpitations described as the abrupt onset of rapid heartbeats that last for a few seconds. Palpitations typically occur at rest and are not associated with lightheadedness, dizziness, or chest pain. She is very active and unaware of palpitations with activities such as tennis and running track. Her maternal grandfather died suddenly at age 44 due to a myocardial infarction. Her father has coronary artery disease. She has one sister and two brothers who are healthy. She is a nonsmoker and has no history of alcohol or illicit substance abuse. Results of her physical

*CPVT is a rare form of inherited malignant ventricular tachyarrhythmia induced by adrenergic stimuli.*

rhythmia induced by adrenergic stimuli. Mutations in the ryanodine receptor gene RYR2 (autosomal dominant), the cardiac calsequestrin gene CASQ2 (autosomal recessive), and the transmembrane sarcoplasmic reticulum protein TRDN (autosomal recessive) have been linked to CPVT. The underlying pathogenesis is

shocks can trigger release of catecholamines leading to VT storm and death.<sup>27</sup>

### Take Home Points

This athletic adolescent girl with recurrent syncope resulting in physical injury, a positive family history, a normal echocardiogram result, and an ILR wide



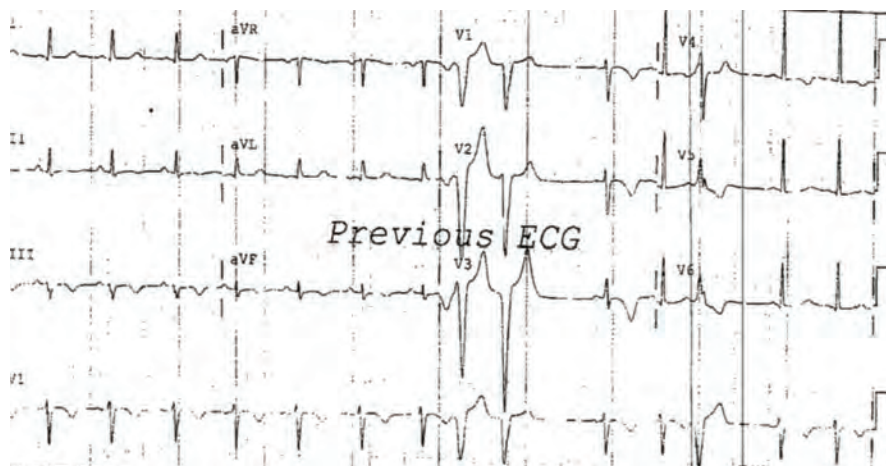


Figure 3. Baseline electrocardiogram of Patient 2.

examination at the time of initial presentation were reported to be unremarkable. Her baseline ECG is shown in Figure 3.

She underwent additional cardiac testing that included an echocardiogram, 24-hour Holter monitoring, an ETT, and tilt-table testing. The echocardiogram reportedly showed normal biventricular size and function, with no valvular abnormalities.

The Holter monitor showed sinus rhythm with heart rates ranging from 46 to 160 beats/min. Ventricular ectopic activity

consisted of 5107 beats with one 8-beat run of nonsustained VT at a heart rate of 106 beats/min, 60 triplets, and 512 couplets (Figure 4). She did not have symptoms while wearing the Holter monitor.

ETT showed occasional VPCs during exercise and multifocal VPCs in early recovery (Figure 5). She was started on  $\beta$ -blocker therapy. Tilt-table testing was performed, which revealed NMH with hypotension followed by sinus bradycardia and reproduction of the prodromal symptoms and impending syncope.

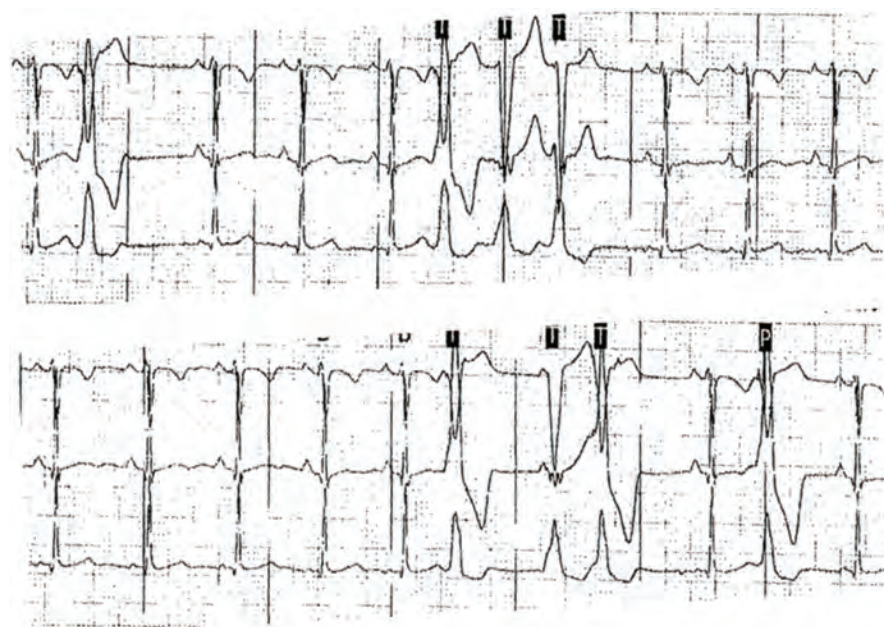


Figure 4. Holter monitor recordings of Patient 2.

She was observed to be pale and diaphoretic during the test, and was started on fludrocortisone.  $\beta$ -blockers were discontinued.

She continued to have syncope despite conservative measures to treat NMH. Subsequent Holter monitoring showed a heart rate variability of 45 to 152 beats/min and 10,803 VPCs, of which the longest ventricular run was 26 beats (Figure 6). The fastest ventricular run consisted of 7 beats with a maximum heart rate of 235 beats/min with no symptoms.

Two months later, she had another episode of syncope, losing consciousness five times during this episode, with recurrent vomiting. Emergency medical services was notified and reported a systolic blood pressure of 40 mm Hg, and a heart rate of 200 beats/min. She spontaneously reverted to sinus rhythm with improvement in blood pressure. No tracing was obtained.

She underwent repeat cardiac evaluation with a repeat echocardiogram; results were again reported as normal with no evidence of structural abnormalities. Repeat Holter monitoring showed multiple episodes of coupled VPCs and 23-beat run of VT. She did not have any symptoms with VPCs or VT.

An EP study was performed and revealed a single focus of ventricular ectopy on the free wall of the right ventricular outflow tract (RVOT), which was successfully ablated. She was subsequently diagnosed with idiopathic RVOT VT in addition to her diagnosis of NMH, and midodrine was added to fludrocortisone for continued syncope. She remained off  $\beta$ -blockers.

Six months later, she had an episode of near-syncope associated with frequent extra beats and was given an event monitor.



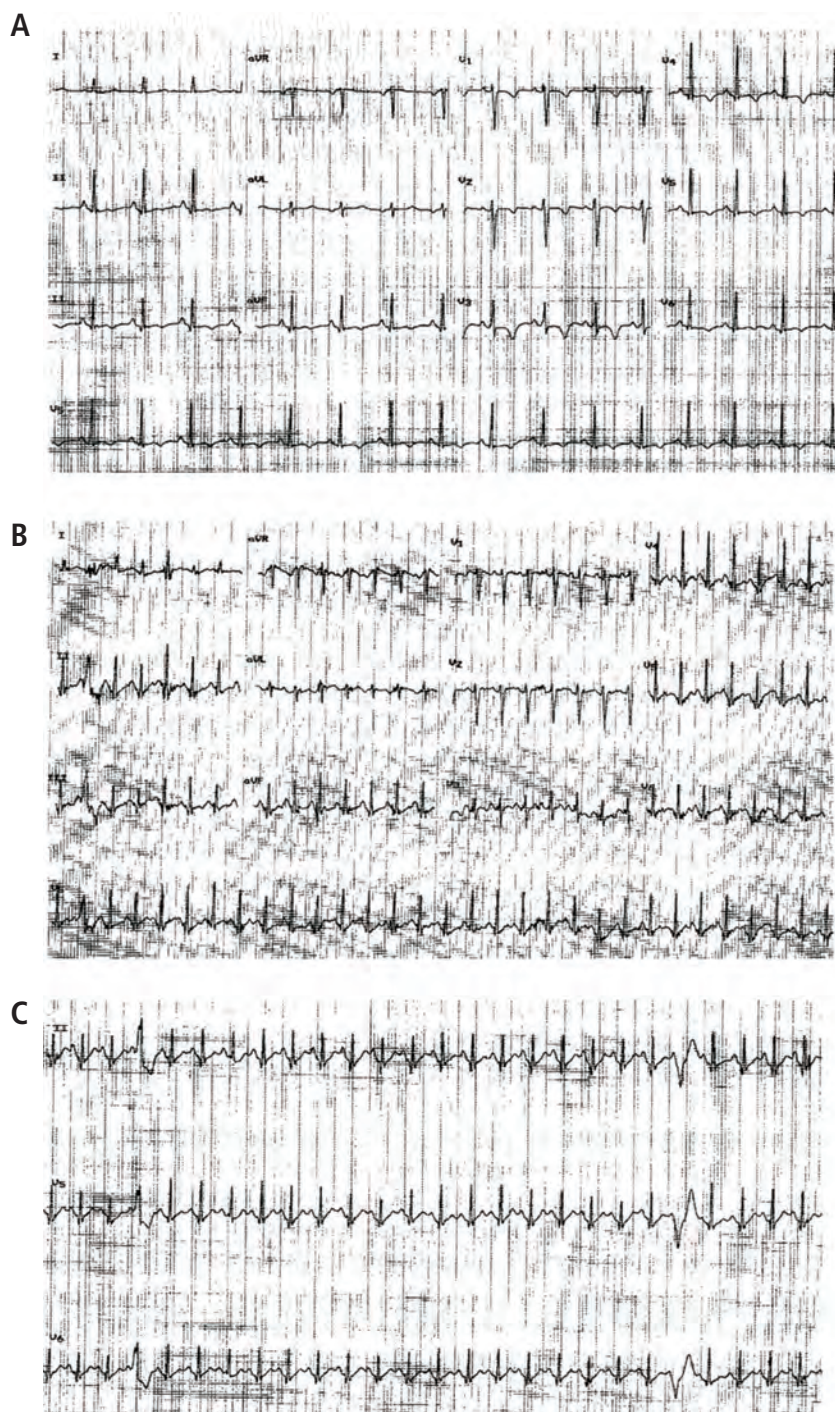


Figure 5. (A) Holter monitor recordings of the exercise stress test of Patient 2 during the resting phase. (B) Holter monitor recordings of the exercise stress test of Patient 2 at peak exercise. (C) Holter monitor recordings of the exercise stress test of Patient 2, at 1:29 minutes into recovery.

She had cardiac arrest while taking a college final examination; she was resuscitated but underwent prolonged resuscitation time (estimated at 45 min) and multiple shocks for VF. An echocardiogram done after the cardiac arrest showed severely decreased left ventricular (LV) systolic function

(ejection fraction 25%), a moderately dilated RV with thinning and hypokinesis of the RV free wall, and RVOT. Her hospital course following cardiac arrest was complicated by anoxic brain injury, clot embolization to the left lower extremity resulting in an ischemic leg necessitating a

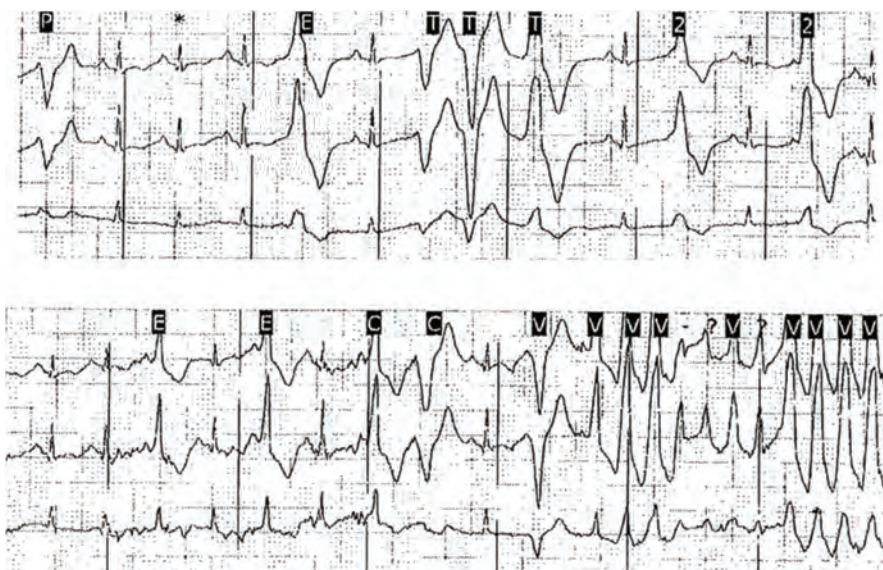
left below-knee amputation, acute renal failure, and shock liver. Subsequent echocardiography showed improvement in LV function; however, the RV remained dilated and hypokinetic. An ICD was placed prior to discharge following a prolonged hospitalization, and  $\beta$ -blocker therapy was reinitiated.

Patient 2 meets “definite” diagnostic criteria for arrhythmogenic RV cardiomyopathy (ARVC) based on the current 2010 Task Force criteria<sup>28</sup> with three major criteria (abnormal RV by echocardiograph, precordial T-wave inversions, NSVT with left bundle branch block morphology). She met “borderline” diagnostic criteria during her initial evaluation at age 16 with one major criterion (precordial T-wave inversions in  $V_1$ - $V_4$ ) and 1 minor criterion ( $>500$  VPCs on 24-hour Holter monitor).

Recurrent syncope resulting in traumatic injuries in the presence of these findings should have raised concern for a more malignant diagnosis than NMH. Instead, her clinical presentation was deemed to be most consistent with NMH and idiopathic RVOT VT. The disease process progressed over a 2-year period with an increase in symptoms and burden of ventricular ectopy. The last Holter tracing shown is also concerning, demonstrating very tight coupling intervals during runs of NSVT.

Patient 2 presented for further management of tachycardia pacing-terminated sustained VT by the ICD.  $\beta$ -blocker therapy was discontinued at that point, and sotalol and an angiotensin-converting enzyme inhibitor were added to her regimen. She has not had further VT. For the purpose of family screening, genetic testing was performed, which revealed a Class I deleterious mutation in *DSG2* Gln873Ter and a





deleterious splice mutation in *PKP2* IVS10-1G>C. Screening of all first-degree relatives was recommended, including mutation-specific genetic testing. This revealed one mutation from her mother and another from her father.

The patient presented with syncope resulting in physical trauma. The ECG revealed classic T-wave inversion in the precordial leads. The EP testing result was debatable but the information of an RVOT VT with classic T-wave inversions in the precordial leads substantiated the diagnosis of ARVD. At this point, the diagnosis was ARVD and further testing should have included genetic testing. magnetic resonance imaging (MRI) findings are helpful if the diagnosis remains an enigma.

autosomal dominant and recessive patterns of inheritance identified. Although predominance in men has been well described,<sup>11,29</sup> it has not been reported as an independent risk factor.

The diagnosis of ARVC is based on fulfilling specific diagnostic criteria that include ECG abnormalities, delayed potentials on signal-averaged ECG, presence of ventricular arrhythmias, structural abnormalities identified on imaging, and genetic and pathologic findings.<sup>28</sup> Studies have found various risk factors for SCD in these patients, including young age, history of syncope, hemodynamically unstable ventricular arrhythmia, and marked RV enlargement alone or in combination with LV involvement.<sup>30</sup> Prevention of SCD is the main

of  $\beta$ -blockers and antiarrhythmic agents are not well established at this point.<sup>32</sup>

### Take Home Points

This adolescent girl with ominous clinical presentation of recurrent syncope, and ECG and Holter findings raising a strong suspicion for ARVC, needed advanced imaging with cardiac MRI and genetic testing. The sequence of clinical events highlights the importance of identifying structural heart disease by echocardiography or cardiac MRI. Positive results of genetic testing would have solidified the diagnosis of ARVC. The final step would have been placement of an ICD for prevention of SCD. The importance of a careful clinical history, physical examination, ECG interpretation, and echocardiogram analysis cannot be overemphasized.

### Patient 3

A 24-year-old woman presented for the evaluation of recurrent syncope. She had a history of multiple episodes of syncope before the age of 2 years, described by her mother as periods of "passing out," that lasted seconds to minutes in duration. There were no obvious warning signs or residual symptoms afterward. After age 2 years she did not have these episodes until approximately 1 year earlier, at age 23. Since then, she has had approximately five to six episodes of syncope, which correlated with having blood drawn, at the sight of blood, and while having a radiograph taken of her leg. She is usually out for less than 1 minute and needs approximately 15 minutes to "gather herself" after regaining consciousness. She feels diaphoretic and dizzy prior to the episode, which lingers afterward and is often associated

*ARVC is a rare, inherited disorder characterized by fibrofatty replacement of RV myocardium leading to life-threatening ventricular arrhythmia and SCD.*

ARVC is a rare, inherited disorder characterized by fibrofatty replacement of RV myocardium leading to life-threatening ventricular arrhythmia and SCD. It has genetic origin with both

objective for treatment in patients with ARVC; ICD therapy is the most effective treatment. The success rate for catheter ablation is variable and related to disease severity.<sup>31</sup> The protective effects

with nausea. A typical episode was observed in clinic while she was having blood drawn.

In addition, she periodically has palpitations, which she first noticed at approximately age 12. Palpitations are the abrupt onset and termination of a rapid, racing heart, often associated with chest discomfort, shortness of breath, and slight dizziness. These generally last from 5 to 20 minutes, occur approximately once every few months, both at rest and with activity. Once she turned 21, the palpitations became less frequent. A particularly severe episode occurred while swimming a relay race in high school. During the race, she had sudden onset of palpitations and had to be pulled out of the pool. She did not experience loss of consciousness at that time. The palpitations terminated several minutes later, and after several additional minutes she felt “back to herself.”

More recently, she began having skipped beats associated with a squeezing sensation in her chest. This newest symptom is particularly bothersome to her and has affected her level of physical activity for fear that increased activity will make these symptoms worse.

Her maternal aunt has had multiple episodes of syncope, typically in the setting of either visualizing or undergoing venipuncture. There is no history of sudden death in her family. Her parents do not have history of syncope. She has a younger brother who is alive and healthy. Her medications include birth control pills and multivitamins. Results of her physical examination are unremarkable. Her baseline ECG is shown in Figure 7.

This young woman was diagnosed with NMS as the cause of recurrent syncope. She was advised to maintain adequate



Figure 7. Baseline electrocardiogram of Patient 3.

hydration, avoid caffeine and alcohol, and to assume a supine posture at the first sign of her symptoms. Her symptoms persisted despite these measures.

She underwent additional cardiac testing, including an echocardiogram, 24-hour Holter monitoring, and an ETT. The echocardiogram reportedly showed a structurally normal heart, with normal biventricular size and function, without wall motion abnormalities or valvular abnormalities. The 24-hour Holter monitor revealed sinus rhythm with sinus arrhythmia, heart rates ranging from 47 to 133 beats/min (Figure 8). Three isolated ventricular ectopic beats and 18 supraventricular ectopic beats were recorded without any symptoms. Two brief (>2 sec) pauses were observed following nonconducted supraventricular ectopic beats. The patient did not have any symptoms during this recording. The patient exercised for 11.45 minutes on standard

was 187 beats/min (95% of maximum predicted). There was no evidence of ischemia or arrhythmias. Select ECG tracings are shown in Figure 9.

Because the patient did not have symptoms while wearing a Holter monitor, 30-day event monitoring was pursued. This showed sinus rhythm, sinus arrhythmia with a heart rate ranging from 50 to 124 beats/min, and one 3-beat run of VT (Figure 10), which was associated with symptoms of skipped beats.

The patient's clinical history had many features suggesting NMS, but the Holter monitor was suspicious for LQTS, with QTc intervals ranging from 435 to 520 msec on the surface ECG. Genetic testing was pursued, and she was found to have a Class I deleterious mutation for LQTS (*KCNQ1* Arg518Ter). She was started on  $\beta$ -blockers and has not had any new episodes of syncope, but continues to have intermittent palpitations. Screening of all first-degree relatives with surface

*Congenital LQTS is an inherited disorder most commonly involving mutations in the delayed rectifier channel ... or the sodium channel...*

Bruce protocol, achieving a peak workload of 13 METS before stopping for fatigue and dizziness. Her maximum heart rate

ECGs and thorough history was recommended.

Congenital LQTS is an inherited disorder most commonly





Figure 8. Holter monitor recordings of Patient 3.

involving mutations in the delayed rectifier channel (slow component— $I_{Ks}$ —in LQT1, and rapid component— $I_{Kr}$ —in LQT2) or the sodium channel (*SCN5A* in LQT3). As previously reported, boys carry a greater risk of cardiac events prior to puberty. However, at adolescence the risk reverses and women carry a greater risk than men through age 40 and into menopause.<sup>33,34</sup> LQTS, both acquired and congenital, must remain part of the differential diagnosis in all young women with recurrent syncope even when the diagnosis of NMS seems likely.

Medication-induced or so-called acquired LQTS is also more frequently observed in

women. Inhibition of the rapid component of the delayed rectifier potassium channel ( $I_{Kr}$ ) is the most common cause of medication-induced QT prolongation. Remarkably, 70% of subjects that develop torsades de pointes from drug-induced QT prolongation are women.<sup>35</sup>  $I_{Kr}$  inhibition by low-dose  $17\beta$  estradiol may help explain these findings in women.<sup>36,37</sup>

### Take Home Points

This young woman is a challenging case as she had many features raising a suspicion of NMS, and she may have two different etiologies to

her syncope. The critical take home point is the importance of analyzing the ECG carefully for elusive etiologies for syncope (Table 2).

## Conclusions

Syncope is common in children, adolescents, and teenagers. It is usually attributable to neurally mediated reflex syncope, but the differential diagnosis includes potentially dangerous disorders such as cardiac rhythm disturbances secondary to ion channelopathies, or ventricular outflow tract obstruction, which are far less common in children than adults. The most important part of

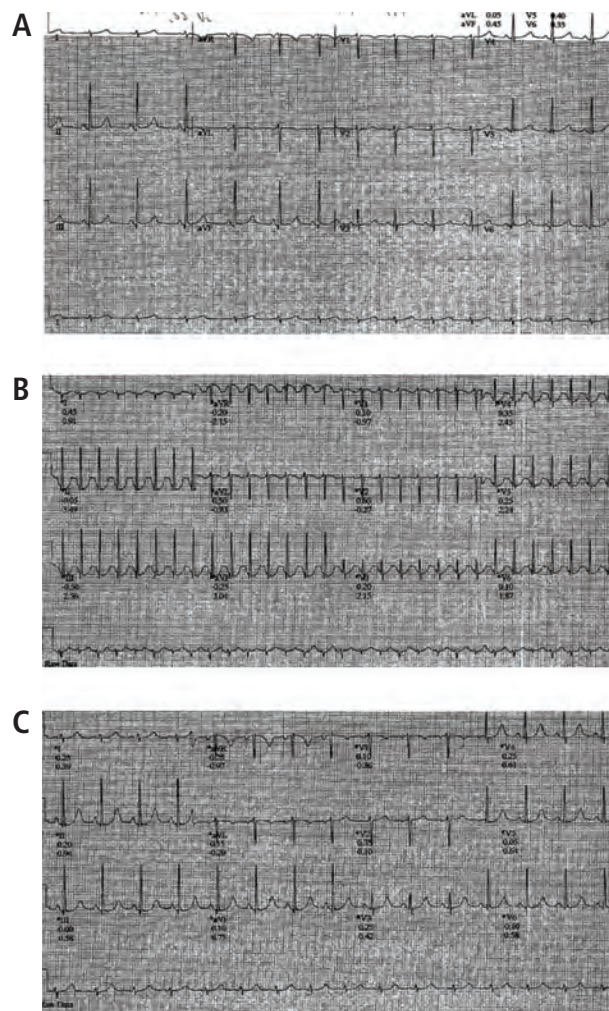


Figure 9. (A) Electrocardiographic tracings of the exercise stress test of Patient 3, at rest. (B) Electrocardiographic tracings of the exercise stress test of Patient 3, at peak exercise. (C) Electrocardiographic tracings of the exercise stress test of Patient 3, during recovery.



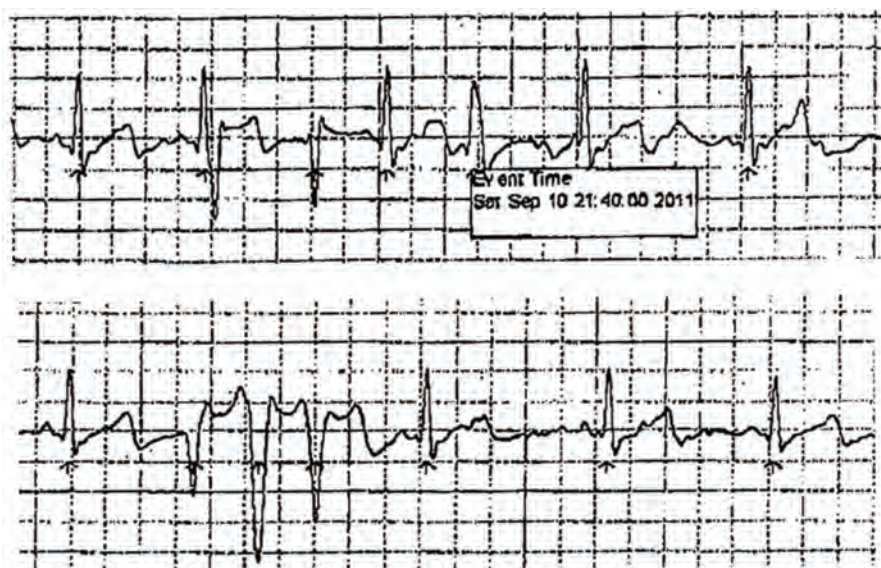


Figure 10. Event monitor recordings of Patient 3.

the diagnostic evaluation is taking a thorough history and performing a comprehensive physical examination. The patient's symptoms, before and after syncope, as well as any observer's description of the event, will help determine the cause in the vast majority of patients. The emphasis must be on a broad differential diagnosis considering all the orthostatic syndromes, the potential structural and electrical etiologies, and the associated genetic syndromes.

An ECG should be used as a screening tool for unusual cardiac causes. If there is doubt about the

diagnosis, cardiac causes must be ruled out; echocardiography and stress testing are crucial in determining structural and electrical etiologies. The mainstay of management of young patients with NMS consists of advice and education on the various factors that influence systemic blood pressure in conjunction with chronic expansion of intravascular volume.

Although NMS is a common diagnostic consideration in young, otherwise healthy girls and women, hereditary arrhythmias should always be considered even in the absence of significant

family history, particularly when the standard approach fails to make an impact on the patient's clinical status. The importance of a careful history, physical examination, ECG, echocardiography, stress testing analysis, and consideration of genetic testing cannot be overemphasized. Case #1 reveals recurrent syncope in a patient with normal physical examination, ECG, and echocardiography findings, with complex ventricular arrhythmias that should have raised a suspicion for one of the channelopathies. Case #2 emphasizes the importance of echocardiography and cardiac MRI to identify clinical and subclinical structural heart disease. Case #3 identifies the importance of careful ECG analysis in light of the clinical circumstance. Ongoing surveillance is also warranted to identify any concerning changes in clinical status that may herald more ominous disease processes.

Hereditary arrhythmia management extends beyond the diagnosis or prescription of medications for individual patients. Lifestyle modification, including exclusion from activities involving physical exertion, and consideration of an

## TABLE 2

### Take Home Points

#### Golden Rules of Syncope Evaluation

1. Detailed clinical history and physical examination
2. Electrocardiographic assessment for possible channelopathies
3. Treadmill testing and Holter monitoring to assess for rhythm disturbances
4. Echocardiography to assess systolic and diastolic function and identify any structural abnormalities
5. Magnetic resonance imaging assessment for structural abnormalities and delayed gadolinium enhancement
6. Genetic testing should always be considered

ICD, can be lifesaving measures in appropriately selected patients. Genetic counseling and testing of first-degree relatives should always be considered. These cases highlight the need for detailed assessment to exclude structural heart disease as well as channelopathies related rhythm disturbances as the etiology for recurrent syncope in young patients. This series also highlights the coexistence of NMH with potentially catastrophic cardiac disorder in patients who present with true syncope. ■

## References

- Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). *J Cardiovasc Electro-physiol.* 2009;20:352-358.
- Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res.* 2011;21:69-72.
- Singer W, Sletten DM, Opfer-Gehrking TL, et al. Postural tachycardia in children and adolescents: what is abnormal? *J Pediatr.* 2012;160:222-226.
- Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc.* 2007;82:308-313.
- Alshekhlee A, Guersch M, Ridha F, et al. Postural tachycardia syndrome with asystole on head-up tilt. *Clin Auton Res.* 2008;18:36-39.
- Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc.* 2012;87:1214-1225.
- Oliphant CS, Owens RE, Bolorunduro OB, Jha SK. Ivabradine: a review of labeled and off-label uses. *Am J Cardiovasc Drugs.* 2016;16:337-347.
- Plum F, Posner JB. *The Diagnosis of Stupor and Coma.* 3rd ed. Philadelphia, PA: F.A. Davis; 1980.
- Benditt DG, Brignole M. Syncope: is a diagnosis a diagnosis? *J Am Coll Cardiol.* 2003;41:791-794.
- Kaufmann H. Neurally mediated syncope and syncope due to autonomic failure: differences and similarities. *J Clin Neurophysiol.* 1997;14:183-196.
- Grubb BP. Neurocardiogenic syncope and related disorders of orthostatic intolerance. *Circulation.* 2005;111:2997-3006.
- Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med.* 1997;336:775-785.
- Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. *Circulation.* 1982;65:384-398.
- Schwartz PJ, Priori SG. Long QT syndrome: genotype-phenotype considerations. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside.* 4th ed. Philadelphia, PA: WB Saunders; 2004:651-659.
- Brugada J, Brugada R, Antzelevitch C, et al. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation.* 2002;105:73-78.
- Jhanjee R, van Dijk JG, Sakaguchi S, Benditt DG. Syncope in adults: terminology, classification, and diagnostic strategy. *Pacing Clin Electrophysiol.* 2006;29:1160-1169.
- Wieling W, Ganzeboom KS, Saul JP. Reflex syncope in children and adolescents. *Heart.* 2004;90:1094-1100.
- Lombroso CT, Lerman P. Breathholding spells (cyanotic and pallid infantile syncope). *Pediatrics.* 1967;39:563-581.
- Driscoll DJ, Jacobsen SJ, Porter CJ, Wollan PC. Syncope in children and adolescents. *J Am Coll Cardiol.* 1997;29:1039-1045.
- Ganzeboom KS, Colman N, Reitsma JB, et al. Prevalence and triggers of syncope in medical students. *Am J Cardiol.* 2003;91:1006-1008, A8.
- Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet.* 1998;352:1970-1973.
- Grubb BP. Clinical Practice. Neurocardiogenic syncope. *N Engl J Med.* 2005; 352:1004-1010.
- Kosinski D, Grubb BP, Temeszy-Armos P. Pathophysiologic aspects of neurocardiogenic syncope: current concepts and new perspectives. *Pacing Clin Electrophysiol.* 1995;18:716-724.
- van Dijk JG, Sheldon R. Is there any point to vasovagal syncope? *Clin Auton Res.* 2008;18:167-169.
- Tea SH, Mansourati J, L'Heveder G, et al. New insights into the pathophysiology of carotid sinus syndrome. *Circulation.* 1996;93:1411-1416.
- Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the

## MAIN POINTS

- Syncope is defined as a sudden transient loss of consciousness (TLOC) with concomitant loss of postural tone followed by spontaneous recovery. It is a subset of a broader class of medical conditions, including postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, and neurally mediated syncope (NMS), that may result in TLOC. The overlap of these clinical conditions leads to confusion regarding syncope classification that can hinder evaluation strategies, and pose challenges for diagnosis and treatment, particularly in young women.
- Structural heart diseases can result in TLOC. Conditions include acute myocardial infarction, hypertrophic cardiomyopathy, acute aortic dissection, cardiac tamponade, severe pulmonary hypertension, and severe aortic stenosis. TLOC in patients with these conditions is relatively rare, but important to recognize, as they are potentially life threatening.
- The central nervous system rarely accounts for TLOC; however, various forms of bradycardia and tachycardia are common causes.
- NMS refers to a cluster of situations in which cardiovascular reflexes that normally control the circulatory responses become intermittently maladaptive in response to an environmental trigger, resulting in vasodilatation and/or bradycardia with a fall in systemic blood pressure and global cerebral perfusion.
- An electrocardiogram should be used as a screening tool for unusual cardiac causes. If there is doubt about the diagnosis, cardiac causes must be ruled out; echocardiography and stress testing are crucial in determining structural and electrical etiologies.
- Lifestyle modification, including exclusion from activities involving physical exertion, and consideration of an implantable cardioverter-defibrillator, can be lifesaving measures in appropriately selected patients. Genetic counseling and testing of first-degree relatives should always be considered.



- European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011; 8:1308-1339.
27. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106:69-74.
28. Wilde AA, Bhuiyan ZA, Crotti L, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med*. 2008;358:2024-2029.
29. van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: from bench to bedside. *Heart*. 2013;99:497-504.
30. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533-1541.
31. Baucé B, Frigo G, Marcus FI, et al. Comparison of clinical features of arrhythmogenic right ventricular cardiomyopathy in men versus women. *Am J Cardiol*. 2008;102:1252-1257.
32. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation*. 2003;108:3084-3091.
33. Dalal D, Jain R, Tandri H, et al. Longterm efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2007;50:432-440.
34. Marcus GM, Glidden DV, Polonsky B, et al; Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC registry. *J Am Coll Cardiol*. 2009;54:609-615.
35. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the international LQTS registry. *Circulation*. 1998;97:2237-2244.
36. Buber J, Mathew J, Moss AJ, et al. Risk of recurrent cardiac events after onset of menopause in women with congenital long-QT syndrome types 1 and 2. *Circulation*. 2011;123:2784-2791.
37. Kurokawa J, Tamagawa M, Harada N, et al. Acute effects of oestrogen on the guinea pig and human IKr channels and drug-induced prolongation of cardiac repolarization. *J Physiol*. 2008;586:2961-2973.