Clinical Vignettes

A 26-Year-Old Woman with Recurrent Loss of Consciousness

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The case of a 26-year-old woman with congenital long QT syndrome and recurrent arrhythmic syncope which had been misdiagnosed as a seizure disorder is presented. Useful criteria for discriminating between loss of consciousness due to congenital long QT syndrome and loss of consciousness caused by seizure activity are discussed. The multiple potential causes and clinical implications of a prolonged QT interval, as well as the clinical features and management of congenital long QT syndrome are reviewed.

KEY WORDS: arrhythmias; syncope; seizure disorder.

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CASE

A 26-year-old woman presented to a general cardiology clinic with a chief complaint of palpitations. The palpitations had begun a few months prior and had been occurring with increased frequency in recent weeks. She characterized the episodes as a rapid heartbeat that alternated between a regular and irregular rhythm. She denied associated symptoms of chest discomfort or shortness of breath, but did experience lightheadedness. The palpitations lasted 30–60 seconds and occurred once or twice a week over the preceding two months. They seemed to occur at any time of day and without regard to physical activity, stress, or anything else she could identify. They had on occasion awakened her from sleep.

Her past medical history was notable for dyslexia and a complex-partial seizure disorder. She had a history of five seizures: a first seizure at age 15, a second at age 18, and a third at age 20, at which point carbamazepine treatment was initiated. Computed tomography and magnetic resonance imaging of the head was normal. An electroencephalogram was normal as well. Ten months previously carbamazepine was discontinued because she had been free of seizures for

several years. However, about two weeks prior to her cardiology appointment she had a fourth seizure, and treatment with topiramate was initiated. She had a fifth seizure a few days prior to her cardiology appointment.

The seizures always occurred when she was in a state between sleeping and wakefulness and were always precipitated by a loud noise, such as a ringing telephone. She experienced a prodrome of anxiety, lightheadedness and tachycardia. She would hyperventilate prior to losing consciousness. These events were witnessed by her mother, a registered nurse, who noted tonic and focal twitching movements of her daughter. Her mother also reported that her daughter was sometimes incontinent of urine and generally unresponsive for a few minutes during these episodes. When her daughter awakened she was immediately alert and did not feel fatigued or confused.

Family history was significant for premature coronary disease in her father, who had undergone coronary artery bypass grafting at 45 years of age. There was no family history of sudden death. Her only medication was topiramate 50 milligrams by mouth twice a day. She did not smoke tobacco, use any illicit drugs, or drink alcohol. She was an art student at a nearby university.

Her heart rate was 94 beats per minute and her blood pressure was 118/64 mm Hg. She was a very pleasant, slender young woman. The physical exam was entirely normal. Laboratory data included a normal complete metabolic profile (including normal potassium and calcium levels), a normal complete blood count, and a normal TSH level. A 12-lead resting electrocardiogram (ECG) showed normal sinus rhythm, a prolonged QT interval, shallow T wave inversion in the anteroseptal leads, and bifid T waves in the high lateral and anterolateral leads (Fig. 1).

Based on the prolonged QT interval, the history of palpitations, and the fact that episodes of loss of consciousness were provoked and not spontaneous, congenital long QT syndrome (LQTS) was suspected. Arrhythmic syncope was thought to be the etiology of her episodes of loss of consciousness. A magnesium level, an echocardiogram, and an event monitor were ordered. The patient was instructed not to drive or perform other activities that might place her or others at risk should she lose consciousness. An urgent evaluation by an electrophysiologist was scheduled.

The patient was seen the next day by an electrophysiologist. The magnesium level from the previous day returned at 2.2 milligrams/deciliter, within the normal range. An echocardiogram showed a structurally normal heart. Due to ensuing events an event monitor was never placed. A repeat ECG performed in electrophysiology clinic showed clear QT prolongation with bifid T waves (Fig. 2). The markedly prolonged QTc interval, bifid T waves, and the history of syncope triggered by a loud acoustic stimulus suggested a very high likelihood of LQTS, specifically the LQT2 variant. Implantable cardioverter-defibrillator (ICD) placement was recommended and the patient was admitted to the hospital. The morning after admission, she was awakened by

Key Points A history of syncope increases the risk for sudden death in patients with a prolonged QT interval.

Twitching, convulsive-type movements, and urinary incontinence are classic for seizure, but may be seen in syncope.

A careful history and physical examination are essential for the proper diagnosis of loss of consciousness.

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Figure 1. Initial ECG. The patient is in normal sinus rhythm. There is a nonspecific T wave abnormality characterized by flattened and poorly defined T waves. There is the suggestion of a bifid character to the T waves in the high lateral and anterolateral leads (arrows). The QT is prolonged, and was read by the instrument as 444 milliseconds (ms), with a corrected QT (QTc) of 509 ms. (A QTc above 480 ms for postpubertal females is considered prolonged.) However, the T wave morphology renders accurate measurement of the QT interval difficult.

Figure 2. Repeat ECG. The patient is in normal sinus rhythm, though the heart rate is slower than in the ECG shown in Fig. 1. The T waves are more distinct than in the previous ECG and the QT interval is clearly prolonged (QT/QTc 544/570 ms). The bifid character of the anterolateral T waves is more apparent as compared to the previous ECG (arrows).

a loud noise and had a two minute episode of polymorphic ventricular tachycardia (torsades de pointes) with syncope, from which she spontaneously recovered (Fig. 3). This episode—which was witnessed by her mother—was identical to the previous episodes which had been diagnosed as seizures.

DISCUSSION

Distinguishing between seizure and syncope can be quite difficult¹⁻³. Misdiagnosis of arrhythmic syncope due to LQTS as a seizure disorder has been reported previously^{4,5}. The tonic and twitching movements which occurred during this patient's syncopal episodes, as well as occasional urinary incontinence, may suggest seizure but are also seen in syncope¹. Such episodes are sometimes described as "convulsive syncope."² In these cases, loss of consciousness with absent muscle tone for some time prior to the onset of tonic-clonic movements can be a clue to the true nature of the event⁶. Auditory stimuli have been reported to precipitate seizures, though quite infrequent-

ly. A history of auditory triggers does not exclude seizure as a cause of loss of consciousness, but makes it less likely⁷. Postictal confusion is seen in approximately 25% of patients with syncope and greater than 70% of patients with loss of consciousness due to seizures. The absence of confusion argues in favor of a diagnosis of syncope⁸. Antecedent palpitations are more strongly associated with syncope than with seizure. One study examining factors predictive of seizure rather than syncope found antecedent palpitations to have a negative likelihood ratio for seizures of 0.116⁹.

Another possible cause of loss of consciousness is medications, some of which can predispose to arrhythmia and syncope. This patient had taken both carbamazepine and topiramate. Carbamazepine can cause heart block leading to syncope, but this is rare¹⁰. However, this patient's episodes did not correlate with carbamazepine treatment. Topiramate is not known to cause or exacerbate arrhythmias.

The absence of postictal confusion and the presence of auditory triggers were only suggestive but not diagnostic of syncope due to LQTS. The additional findings of a markedly prolonged QT interval and bifid T waves argued strongly in favor of LQTS as the basis of this patient's episodes of loss of

Figure 3. ECG recording at the onset of loss of consciousness. This recording shows torsades de pointes, a type of polymorphic ventricular tachycardia and the typical arrhythmia associated with LQTS. The recording first shows normal sinus rhythm, then the "long-short" interval which characteristically initiates torsades de pointes. The long cycle is initiated by a premature ventricular beat (left arrow). A compensatory pause follows the premature ventricular beat, creating a long cycle, which terminates with a sinus beat (middle arrow). This long cycle results in prolonged repolarization, and thus a prolonged QT interval, in the ensuing "short" cycle, and when the next QRS complex occurs—during repolarization—it precipitates torsades de pointes (right arrow).

consciousness. Finally, the witnessed episode correlating with torsades de pointes ultimately confirmed the diagnosis.

The QTc is considered prolonged if it is greater than 470 milliseconds (ms) in men or 480 ms in women¹¹. A prolonged QT interval can be either acquired or congenital, and generally predisposes to ventricular arrhythmias, which can be lethal. Acquired prolonged QT is far more common than congenital LQTS; overt congenital LQTS has a prevalence of about 1 in 5000.¹² Some experts believe that the prevalence of LQTS mutations is significantly higher and cases of apparent acquired long QT reflect an underlying genetic disorder that only becomes clinically manifest with exposure to an additional insult¹³. Common causes of an acquired prolonged QT interval include ischemia as well as electrolyte abnormalities, particularly depleted serum potassium, magnesium, or calcium levels (though hypocalcemia rarely predisposes to arrhythmias). A multitude of drugs can also cause a prolonged QT interval, including antibiotics, antiarrhythmics, and antipsychotics¹¹. Examples include clarithromycin, erythromycin, pentamidine, disopyramide, sotalol, quinidine, procainamide, haloperidol, chlorpromazine, and thioridazine. A comprehensive list of QT-prolonging drugs may be found at www.qtdrugs.org. Neither carbamazepine nor topiramate, the medications with which this patient was treated, prolongs the QT interval. Congenital LQTS is most frequently caused by mutations in potassium channels but can also be caused by mutations in calcium or sodium channels or by mutation of the ankyrin gene. While a multitude of genes have been found to cause LQTS, in more than ninety percent of cases where a responsible mutation is found the mutation is in one of the three genes responsible for variants LQT1-3¹⁴. In LQT1 and 2, the responsible genes encode potassium channels, and in the case of LQT3 the responsible gene encodes a sodium channel. Congenital LQTS is most commonly inherited in an autosomal dominant manner as the so-called Romano-Ward syndrome. It is also transmitted in an autosomal recessive pattern, as the rare Jervell-Lange-Nielsen syndrome, which is associated with congenital deafness¹⁵.

The ECG in LQTS usually shows a prolonged QT interval, although the QT interval can vary significantly on serial ECGs, thereby complicating the diagnosis¹². Depending on the specific genetic variant the T waves may have characteristic features. For example, bifid or notched T waves, as were seen in this patient's ECG, are typical of LQT2. Bifid T waves are thought to be caused by differential changes in action potential duration in distinct cardiac cell types all of which are affected by the ion channel mutation¹⁶. The T waves in LQT1 tend to be large and broad-based, while the T waves in LQT3 tend to be narrow-based and thus have a peaked appearance¹⁶.

Diagnostic criteria for congenital long QT syndrome have been codified in a scoring system (Table 1)¹⁷ which incorporates ECG findings (prolonged QT interval, T wave alternans and notched T waves), rhythm abnormalities (torsades de pointes or low heart rate for age¹⁸), syncope, congenital deafness, and a family history of LQTS or unexplained sudden death before 30 years of age. A score of four or greater suggests a high likelihood of LQTS. The patient described had a score of six (three points for a QTc interval greater than 480 ms, one point for notched Twaves in three leads, and two points for syncope in response to a loud acoustic stimulus). Her score remained the same after she had torsades de pointes in the hospital, because syncope and torsades are mutually exclusive in this scoring system.

Table 1. LQTS Diagnostic Criteria

	Points
ECG Findings*	
A. QTc	
480 ms or longer	3
460-470 ms	2
450 ms (in males)	1
B. Torsades de pointes	2
C. T Wave alternans	1
D. Notched T wave in three leads	1
E. Low heart rate for age#	0.5
Clinical History	
A. Syncope	
With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history†	
A. Family members with definite LQTS‡	1
B. Unexplained sudden cardiac death below age 30 among immediate family members	0.5

*In the absence of medications or disorders which affect these ECG features

|| Mutually exclusive

#resting HR below second percentile for age

†The same family member cannot be counted in A and B

‡Defined by LQTS score of 4 or greater

Scoring: 1 point or less, low probability of LQTS; 2-3 points, intermediate probability; 4 or more points, high probability.

(Table reproduced with permission from Wolters Kluwer Health.)

The arrhythmia responsible for symptoms in LQTS is torsades de pointes. Torsades de pointes is defined as polymorphic ventricular tachycardia occurring in the context of a prolonged QT interval. Typical symptoms of LQTS include palpitations, presyncope, syncope, and cardiac arrest. Triggers of these symptoms depend on the specific variant. Triggers in LQT1 and LQT2 are probably adrenergically mediated. The common arrhythmic trigger in LQT1 is physical exercise (especially swimming), while arrhythmia generally occurs during sleep or at rest in LQT3 patients^{19,20}. Precipitation of symptoms by sudden loud acoustic stimuli, as occurred in this patient, is most commonly seen in the LQT2 variant—in one study, 80% of such episodes occurred in LQT2 patients²¹.

Mortality of untreated symptomatic LQTS is high. In one study, mortality after a first syncopal episode was 26% at 3 years and 53% at fifteen years²². Onset of symptoms usually occurs early in life: 74% of males and 51% of females have a first event by age 15²³. Interestingly, there is a so-called "gender risk reversal" effect which takes place as LQT patients age: males are at higher risk of cardiac events before age 15, but after that age females are at higher risk¹². Females also seem to have a higher risk of untoward events associated with the use of QT prolonging medications²⁴. These gender-related differential effects are thought to be hormonal. In support of this notion, there is a reduced risk of arrhythmic events in LQT females during pregnancy but an increased risk in the 9 months after parturition²⁵. The increased risk postpartum is most evident in LQT2 females. The effects of pregnancy are likely multifactorial, and may include direct antiarrhythmic effects of estrogen and downregulation of adrenergic receptors by estrogen. These effects may be reversed in the postpartum state, when estrogen levels decline, particularly with breastfeeding. In addition, there may be increased adrenergic tone related to the stress of caring

for a newborn infant. The fact that beta blockers suppress the increased risk during the postpartum period supports a role for increased adrenergic tone as a mechanism of increased risk.²⁵

A first line treatment option for LQTS is beta blockers. Beta-blockers probably reduce arrhythmic events by reducing adrenergic triggers, which are primarily important in LQT1 and LQT2. Indeed, the demonstrated benefit of beta blockers is largely confined to LQT1 and LQT2 patients¹². Beta-blockers are effective in both males and females, and are most effective in the highest risk individuals²⁶. However, the recurrence rate for symptomatic patients who are placed on beta-blockers is as high as 32% at 5 years^{27,28}. Sympathetic denervation is rarely used and has a recurrence rate of 54% in symptomatic patients²⁹. A third treatment option is the ICD, for which small studies suggest excellent protective benefit^{30,31}. ICDs are best reserved for the highest risk patients, including females with LQT2^{32,33}. Risk factors for increased mortality have been identified, and differ according to age group. In adults aged 18–40, risk factors for increased mortality include QTc greater than 500 ms, prior syncope, and female gender¹².

This patient underwent ICD implantation and treatment with beta-blockers was initiated. Topiramate therapy was discontinued. She is doing very well several months after implantation and has had no recurrent symptomatic events. Genotyping (Familion protocol, PGxHealth, New Haven CT) showed a novel probable deleterious mutation (Asp501Glu) in the non-pore transmembrane region of KCNH2, the gene responsible for LQT2³⁴. Genotyping of her family is planned but has not yet been performed.

The evaluation of loss of consciousness should emphasize the unparalleled diagnostic yield of the history and of the physical examination¹. Diagnostic tests should take a secondary role and be selected in a thoughtful and focused manner. The case described illustrates how a carefully constructed history, along with limited appropriately selected tests, can serve to effectively exclude certain etiologies of loss of consciousness and point to the correct diagnosis.

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