Syncope

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Case Presentation

A 45 year old white female rising from her seat to give a lecture at the Philadelphia Convention Center suddenly collapsed and lost consciousness. An automated external defibrillator device, on hand at the conference, demonstrated her rhythm to be in ventricular fibrillation. She was subsequently defibrillated and intubated in the field yet was unresponsive on arrival. Her husband related that his wife's past medical history was significant for hypothyroidism and a questionable diagnosis of lupus. Her medications included levothyroxine and Pycnogenal, a popular herbal supplement. She had no known drug allergies. The patient had no known tobacco, alcohol, or illicit drug abuse and works as an employee of federal government.

Hemodynamic vitals were stable. Cardiac exam revealed a regularly regular rhythm with normal heart sounds, and no jugular venous distention. Lungs were clear to auscultation and the abdomen was completely benign. The patient was warm with good distal pulses bilaterally and withdrew to pain and noxious stimuli though a complete neurologic exam was difficult to obtain at the time of admission.

Laboratories were significant for a potassium of 2.7 mEq/mL. The remaining electrolytes were normal. Her complete blood count, urine drug screen, and cardiac enzymes were within normal limits. Head CT demonstrated no intracranial abnormalities. An echocardiogram demonstrated normal left and right ventricular systolic size and function, though a small pericardial effusion was noted. Her initial EKG demonstrated a prolonged QT interval with a corrected QT value (QT_c) of 510 ms.

Discussion

The differential diagnosis of syncope in the younger adult differs slightly from that of the more classic presentation of syncope in the older adult (Table 1).[1] However, in both age groups one must consider both cardiac and non-cardiac causes. Arrhythmias and structural abnormalities figure prominently, though in these patients greater consideration must be given to congenital anomalies. In this particular case, the differential is narrower still, as the patient suffered sudden cardiac death (SCD). The differential of this condition includes: Congenital and Acquired Long QT syndrome, Wolff-Parkinson-White syndrome, idiopathic ventricular fibrillation, and coronary artery spasm.[1] In light of the patient's EKG findings, the diagnosis of prolonged QT syndrome was given and what follows is a discussion of this condition.

Long QT syndromes (LQTS)

Prolonged QT syndrome is defined as QT_c > 440 ms in men or >460 ms in women.[2] This is based upon the QT interval as measured in lead II. The Bazett correction formula ($QT_c = QT \times RR^{1/2}$) is frequently used to calculate the corrected QT interval. In acquired LQTS, an increase of greater than 25% from baseline is considered to be significant.[2] The condition is thought to be caused by lengthening of the repolarization phase of the ventricular action potential. It is a disease of ion channels due to mutation of genes encoding for transmembrane Na^+ and K^+ ion channel proteins. LQTS is hypothesized to be due to either a slowing of inward depolarizing Na^+ currents or slowing of outward repolarizing K^+ currents.[2]

Two forms of the condition have been described, congenital LQTS and an acquired form. Congenital LQTS is an inherited disease which presents with sudden cardiac death in patients with structurally normal hearts.[3] It is an autosomal recessive condition and mutations in 7 genes have been identified accounting for ~60% of families affected. The precise incidence of LQTS is unknown, although it is estimated to be 1 in 7,000 to 10,000 in the US.[2] It is more prevalent in Utah and Finland. LQTS is thought to cause 3000-4000 sudden deaths in children and young adults in the USA.[3] Untreated, it is a lethal condition with a 10 year mortality rate being between 50-70%.[3]

Risk factors for acquired QT prolongation

Several factors related to medication use lead to QT prolongation. This includes: the use of medications that prolong the QT interval (Table 2), concurrent use of medications that prolong the QT interval; the use of medications that slow drug metabolism due to inhibition of hepatic cytochrome P450 enzymatic system; impaired hepatic or renal function; dose and or concentration dependent response; the rate of medication infusion; and certain recreational drugs such as cocaine, amphetamines, and methadone.[4] It is believed that low potassium levels, low magnesium levels and other electrolyte disorders can causes acquired form of the condition.[4]

Cardiac risk factors for QT prolongations include structural heart disease and recent conversion from atrial fibrillation. While bradyarrhythmias can lead to QT prolongation this is usually related to taking antiarrhythmic medications and therefore is not necessarily an independent risk factor. Neurologic risk factors include stroke and subarachnoid hemorrhage. HIV infection can lead to QT prolongation due to a number of factors such as myocarditis, subclinical cardiomyopathy, and autonomic neuropathy. Eating disorders can also lead to electrolyte disorders leading to conduction disturbances. Connective tissue disorders with anti-RO/SSA antibodies are additional risk factors for QT prolongation. Finally, the condition is more common in females compared to males, an association thought to be an estrogen mediated effect.[4]

There is some controversy as to whether acquired LQTS is, in fact, its own distinct entity. Some schools of thought maintain that there is only a congenital form of LQTS that remains undetected until it is unmasked by one of the above mentioned factors. Of note, in patients with drug induced LQTS almost

all have blockade of the Ikr current which is mediated by the K^+ channel encoded by the HERG gene. The same channel is involved in LQT2, raising the question of whether these patients have a genetic predisposition to developing the condition.[4] Additionally, one study of 817 family members of patients with documented congenital LQTS by genetic testing yielded an average penetrance of 60%.[4]

Work-Up

As with any other condition, the first step in diagnosis is a thorough history. Approximately 60% of patients with familial LQT are symptomatic.[3] Palpitations are an uncommon finding because torsades usually are too fast to support any circulation. Rather patients might give a personal history of syncope or seizure-like activity especially with activity or severe stress. Each of the congenital forms possess their respective triggers. For example in LQT1, cardiac events are frequently associated with vigorous physical activity especially with diving and swimming. In LQT2 the patients are sensitive to sudden arousal such as sudden loud noises. On the other hand, LQT3 patients frequently experience events during rest or sleep. Asymptomatic patients come to medical attention after an affected family member or a prolonged QT_c is identified on an ECG obtained for some other reason.[3] Data from the International Registry demonstrated that by age 40, cardiac events (syncope, SCD, or cardiac arrest) occurred in 17% of family members overall, and in 26% of those with a prolonged QT interval.[5] First-degree relatives had a higher incidence of cardiac events by age 40 than second-degree relatives (26% vs 10%). Additionally, a detailed family history should be obtained to determine if there are any relatives with a history of sudden death in infancy or young adulthood during nocturnal, startle, or athletic activity, near-drowning, or any family history of SIDS.[3] In general, the physical exam does not provide any specific findings.

Of course, an EKG must be obtained in all patients suspected of having the condition to assess the QT interval. However, data from the International Registry for LQTS showed that 5% of 1345 family members presented with cardiac arrest had a normal QTc. In fact, only 70% of gene carriers have a prolonged QT_c[5]. Some additional ECG findings in this condition include notched T waves noted during the recovery phase of exercise testing suggestive of LQTS and T-wave alternans noted during physical or emotional stress. Ten typical ST-T patterns have been described in LQTS. The QT dispersion in a 12-lead ECG (QT_c max-QT_c min) should also be noted.[5] An EKG obtained during an acute event demonstrates either Torsades des Pointes or ventricular fibrillation with a short-long-short sequence being the hallmark of LQTS. Repeat EKG testing is necessary in patients with a high clinical suspicion as normal QT_c and normal T wave morphology do not exclude the disease. It can be helpful to obtain an ECG from immediate family members for comparison.

Additional testing modalities have been examined for diagnostic purposes. Exercise stress testing can be used to detect the condition in patients with borderline length QT intervals, as an ECG obtained post-exertion may show QT prolongation. However, pharmacologic provocation studies have not been well studied. Holter monitoring can also be utilized to detect intermittent QT prolongation, bradyarrhythmia, T wave alternans, and notched T-waves. EP testing though, is not diagnostic of the condition. Finally, genetic screening may be useful in families with known genotype, however it is mainly used for research purposes.

Complications

The main concern in this patient population is the development of Torsades de Pointes and ventricular fibrillation. Sudden death is the only event in 30-40% of patients. Untreated symptomatic patients with LQTS have a greater than 20% mortality rate in the first year after an initial syncopal episode.[3]

Management

In the short term, immediate cardioversion to terminate arrhythmias is frequently required. This is usually followed by withdrawal of offending agents if present and correction of electrolyte abnormalities. Magnesium is effective in suppression of short term recurrences of torsades irrespective of baseline magnesium levels. A single bolus of 2 g of magnesium should be given over 2-3 minutes followed by an intravenous infusion of 2-4mg/min. A second 2 g bolus should be administered either 15 minutes later or immediately if torsades recur while the magnesium is being infused.[6] Potassium is used as an adjunct to intravenous magnesium. In pts with LQT2 some evidence to suggest maintaining high normal levels (4.5-5.0) of potassium may be beneficial.[6] However there is no evidence of any effect on preventing or reversing torsades. Temporary transvenous cardiac pacing to a rate of 100 beats per minute can be used in patients who fail magnesium therapy. This has been demonstrated to be beneficial regardless of baseline heart rate. Isoproterenol can also be used as it controls short term recurrence of torsades by increasing heart rate. An initial dose of 2 mcg/kg/min is given and then titrated to heart rate of 100 bpm. Of note, isoproterenol cannot be used in pts with congenital LQT because of adrenergic stimulating effects.[6]

In terms of long term management, it is clearly agreed upon that all symptomatic patients should be treated. Conversely, it is unclear as to whether other groups of asymptomatic patients should be treated. Prophylactic treatment is recommended in all intermediate and high risk patients. In patients with LQT1 this means male and female patients with QTc >500ms. In LQT2 this includes male patients with a QTc of > 500ms and all females. All patients with LQT3 should be treated prophylactically. Asymptomatic patients who should be treated include all patients with congenital deafness, neonates and infants, affected siblings of children who have died suddenly, patients with documented T-wave alternans and patients with very long QT (>600ms).

Table 1. Differential Diagnosis of Syncope in a Younger Adult	
Cardiac syncope	**Noncardiac syncope**
Arrhythmia Ventricular arrhythmias Ventricular tachycardia Torsade de pointes Supraventricular tachyarrhythmias Bradyarrhythmias Sinus bradycardia High-grade atrioventricular blocks Pacemaker malfunction	Vasovagal response to pain Situational syncope (Micturition, defecation, tussive, and carotid sinus syncope) Autonomic dysfunction
Low flow states Advanced cardiomyopathy Congestive heart failure Valvular insufficiency	Neurovascular causes Volume depletion – dehydration, hemorrhage Addison's disease
Cardiac outflow obstruction Aortic stenosis Hypertrophic obstructive cardiomyopathy Mitral stenosis Pulmonary stenosis Pulmonary embolus Left atrial myxoma Pericardial tamponade Acute MI Aortic dissection Primary pulmonary hypertension	Psychiatric disease incl cardiac manifestations of anorexia nervosa Hypoglycemia

Table 2. Drugs That Prolong the QTc Interval	
CNS	ziprasadone, thioridazine, risperidone
Antibiotics	clarithromycin, ketoconazole, fluconazole, moxifloxacin
Neoplastic Agents	arsenic, tamoxifen
Anti-rejection	tacrolimus
Class I and III Antiarrhythmic Agents	quinidine, sotalol, amiodarone, dofetilide
For complete list: www.qtdrugs.org, www.torsades.org	

Beta-blockers are the first line therapy in symptomatic patients. Approximately 75% of cardiac events are precipitated by adrenergic stimuli. As a result beta blockers reduce mortality from 71% to 6%, however syncope and other events recur in approx 25% of treated patients.[5] Maximal beta blockade should be implemented to a target of <130 bpm at maximal heart rate. There have been no studies comparing different agents but agents with longer half-life are preferable secondary to non-compliance. Commonly used agents include propanolol at a dose of 2-3 mg/kg and nadolol dosed at 1 mg/kg.[5] Pacemakers are used as an adjuvant to beta blockers in patients with bradycardia or AV node blockade.

Left cardiac sympathetic denervation has been attempted in patients who failed beta blocker therapy. The largest study to date looked at 123 patients and demonstrated a decrease in the number of cardiac events from 99% to 45%, with a 5 year survival rate of 94%.[7] AICD devices are first line therapy for any patient surviving a sudden cardiac arrest. They are also commonly used in patients who fail all other therapies. However AICD devices, especially if they misfire, can produce emotional distress triggering arrhythmias and shocks, therefore one should continue adjuvant therapy with beta blockers. Finally the long term efficacy of ablation remains unknown.

Current therapies under investigation include: Na^+ channel blockers such as mexiletine, flecainide, lidocaine, pentisomide, and phenytoin; K^+ channel activators such as nicorandil, pinacidil, and cromakalim; alpha-adrenergic receptor blockers; calcium channel blockers; atropine; and protein kinase inhibitors.[7]

Monitoring of these patients includes a baseline EKG with follow-up EKG's on treatment with QT prolonging medication. Also, patient education is paramount. Patients need to be instructed to report any symptoms including palpitations, pre-syncope or syncope. Patients and physicians must be cautious with any new medications. Patients should also report clinical changes and side effects that may signal hypokalemia such as gastroenteritis. It is important for these patients to avoid activities that can act as trigger events. Finally, screening of family members is necessary to pick up subclinical cases.

References

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