Published in final edited form as:

Heart Rhythm. 2005 March ; 2(3): 304–306.

Congenital long QT syndrome aggravated by salt-wasting nephropathy

Dawood Darbar, MD^a, Saba Sile, MD^{a,c}, Frank A. Fish, MD^b, and Alfred L. George Jr, MD^{a,c}

^a From the Departments of Medicine,

^b Pediatrics, and

^c Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee.

Abstract

Long QT syndrome (LQTS) is characterized by episodes of fainting or by sudden death as a result of torsades de pointes (TdP). In both the congenital and acquired forms of the syndrome, symptoms often become manifest upon exposure to additional clinical stressors of repolarization, such as drugs or hypokalemia.

We report here the case of a patient with congenital LQTS in a 6-year-old boy who manifested symptoms only in the presence of electrolyte abnormalities associated with the inherited salt-wasting renal disorder Gitelman syndrome. In this case, a second distinct congenital disorder modified the clinical presentation of LQTS.

Keywords

Congenital long QT syndrome; Gitelman syndrome; Repolarization; Failure

Case report

The proband is a 6-year-old boy who first presented in March 2002 with a syncopal episode after a flu-like illness. At age 3 years, the patient had presented with a viral illness and was found to have severe hypokalemia (1.6 mEq/L). Additional clinical evaluation revealed a history of lethargy, growth failure, normal blood pressure, hypomagnesemia (0.70 mEq/L), hypocalciuria (12.8 mEq/day), and urinary potassium wasting (94.4 mEq/L). A presumptive diagnosis of Gitelman syndrome, an inherited salt-wasting nephropathy, was made. The patient's growth improved dramatically after potassium and magnesium supplementation was started. However, at age 4 years, the patient began to experience syncopal episodes often associated with intercurrent illnesses and hypokalemia. The short-lived syncopal episodes usually occurred during vigorous play. The patient's mother (a nurse) described a single "gasping" breath followed by apnea, cyanosis, and ashen appearance associated with a "very rapid and irregular pulse." However, an ECG tracing was never successfully recorded during a syncopal episode. Evaluation at age 6 years after one such episode revealed serum potassium 3.2 mEq/L, magnesium 1.9 mEq/L, and prolonged corrected QT interval (QTc) 500 ms (Figure 1). Failure of QTc to shorten despite potassium repletion (serum potassium 4.5 mEq/L associated with QTc 490 ms) prompted referral of the patient to a cardiologist. The patient had

Address reprint requests and correspondence: Dr. Dawood Darbar, Division of Cardiovascular Medicine, Vanderbilt University School of Medicine, Room 383, Preston Research Building, Nashville, Tennessee 37323-6602. E-mail address: dawood.darbar@vanderbilt.edu..

This work was supported by NIH Grants HL68880 to Dr. George and UO1-HL65962 and a National Kidney Foundation research fellowship to Dr. Sile.

a family history of syncope (mother, maternal uncle, and maternal grandfather) and congenital LQTS (maternal cousin). Since starting nadolol, in conjunction with potassium chloride, magnesium, spironolactone and amiloride, the proband has been syncope-free over 12-month follow-up.

Although the proband's 34-year-old mother denied a recent history of syncope, she had lost consciousness many times while playing high-school basketball. The episodes were preceded by her feeling light-headed and dizzy and aware that her heart was racing. She also recalled a syncopal episode that occurred while she was swimming, which required family members to pull her out of the water. These spells were attributed to epilepsy, but no antiepileptic medication was ever prescribed. Her medical history was significant for asthma, which was treated with an albuterol inhaler. Results of physical examination, echocardiogram, and serum and urine biochemistry were unremarkable. However, ECG revealed QTc of 500 ms (Figure 2A). On treadmill exercise testing, she managed 10:43 minutes (82% of predicted heart rate), but QTc failed to shorten with increased heart rate (Figure 2B). She and the proband subsequently were treated with nadolol.

Failure to adapt the QT interval for heart rate and for exercise- or swimming-induced syncope is consistent with the LQT1 form of congenital LQTS. The diagnosis was confirmed in the proband and mother by finding a T-to-C mutation in *KCNQ1* that resulted in a leucine-to-proline change at position 266 in the fifth transmembrane-spanning segment of the ion channel.

Hypokalemic alkalosis, hypomagnesemia, and hypocalciuria are consistent with a diagnosis of Gitelman syndrome, but an early age of onset and growth retardation are observed more often in Bartter syndrome, a related inherited renal tubulopathy. Mutations in the renal sodium chloride cotransporter gene *SLC12A3* have been associated with typical cases of Gitelman syndrome,¹ whereas mutations in the *CLCNKB* gene encoding a renal chloride channel are found in cases with mixed features of Gitelman and Bartter syndromes.^{2,3} Both of these disorders are transmitted by autosomal recessive inheritance. A systemic search for mutations in *SLC12A3* was negative, but two novel *CLCNKB* missense variants (M176I in exon 5, R544H in exon 15) were identified in the proband.

Discussion

Although the proband's corrected QT interval remained prolonged in the absence of hypokalemia or hypomagnesemia, syncope occurred only in the presence of hypokalemia. In this subject, recurrent hypokalemia was secondary to the inherited salt wasting nephropathy Gitelman syndrome. Thus, two distinct genetic defects, one affecting cardiac potassium channels and the other serum potassium, appear to act in synergy to reduce repolarization reserve in the proband, giving rise to syncope.

Although TdP can occur in many settings (e.g., heart block, as originally described), it usually is seen in patients with congenital LQTS or in association with drug therapy. Acquired LQTS is a more prevalent disorder and often is caused by several drugs that preferentially block the rapid component of the delayed rectifier K⁺ current (I_{Kr}).⁴ Although risk factors for acquired LQTS have been developed, such as high drug doses, bradycardia, and hypokalemia, predicting development of TdP, particularly in the absence of high doses or plasma concentrations, can be problematic.^{5,6} Consequently, the unifying concept of "reduced repolarization reserve" has been proposed to explain the variable risk.⁷ This framework suggests that, in the normal ventricle and conducting system, multiple mechanisms exist that affect rapid and normal repolarization. Indeed, the normal function of the delayed rectifier potassium currents I_{Kr} and I_{Ks} is a major contributor to such stable repolarization or a large repolarization reserve and subclinical loss of function of one of these may be well tolerated until a second insult is

superimposed. Examples of loss of function include ion channel mutations⁸ or polymorphisms,⁹ hypokalemia (which reduces I_{K_r} ¹⁰), or bradycardia.¹¹ In the present case, however, reductions in I_{K_s} and I_{K_r} , brought about by a mutation in *KCNQ1* and hypokalemia, respectively, apparently combined to reduce repolarization reserve and precipitate syncope.

In the proband, congenital LQTS became apparent only in the presence of hypokalemia associated with an inherited salt-wasting nephropathy. Congenital LQTS also may be unmasked by hypokalemia caused by diuretics or intercurrent illness (e.g., gastroenteritis). Temporal association of syncopal episodes with physical activity and hypokalemia in the proband make arrhythmia a likely etiology of these events.

Although hypokalemia and hypomagnesemia can cause QT interval prolongation, only one study has evaluated QT interval in patients with Gitelman syndrome. Bettinelli et al¹² demonstrated prolongation of the QT interval in more than 40% of untreated patients with Gitelman syndrome. However, no studies have evaluated QT intervals in patients with Gitelman syndrome who receive adequate electrolyte replacement. Furthermore, arrhythmias or syncopal episodes in patients with Gitelman syndrome (or other inherited normotensive–hypokalemic nephropathies) are surprisingly unusual despite hypokalemia.^{13,14}

No correlation was demonstrated between serum potassium or magnesium levels and QTc in the proband. Furthermore, failure of the QTc to shorten with potassium supplementation prompted referral to a cardiologist for suspected congenital LQTS. Although a report suggests that potassium supersupplementation may reduce QTc to near-normal levels in patients with LQT2, whether this therapy proves to be effective in improving repolarization reserve in LQT1 remains to be determined.¹⁵

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Figure 1.
ECG recorded from the proband showing prolonged QTc (500 ms).

Figure 2. ECGs before and after exercise in the proband's mother. Baseline corrected QT was prolonged (500 ms) (**A**) and failed to shorten with exercise (520 ms) (**B**).