Corrected QT interval (QTc) prolongation and syncope associated with pseudohypoparathyroidism and hypocalcemia

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An adolescent presented with exercise-associated syncope and electrocardiographic corrected QT interval (QTc) prolongation. Pseudohypoparathyroidism-induced hypocalcemia was diagnosed. The QTc (485 to 505 milliseconds) shortened during normalization of calcium levels, and syncope has not reoccurred. (J Pediatr 2000;136:404-7)

Electrocardiographic corrected QT interval prolongation signifies abnormalities in ventricular repolarization, which are associated with a risk of polymorphic ventricular tachycardia. Clinically, polymorphic ventricular tachycardia can manifest as syncope, seizure, or sudden death. Although QTc prolongation caused by primary or inheritable long QT syndrome has received considerable attention in the medical literature, acquired or secondary QTc lengthening occurs much more frequently.[1,2] Pharmacologically induced QTc lengthening by antiarrhythmic drugs such as quinidine and sotalol predominates in the adult population.[3] In children and adolescents, other drugs such as cisapride,[4] terfenadine,[5] and erythromycin[6] may be more often implicated. Metabolic abnormalities such as hypocalcemia are routinely mentioned in reviews of QTc prolongation etiologies. However, primary reports of hypocalcemia-induced QTc prolongation are rare and generally involve iatrogenic causes such as aggressive diuretic or dialysis use.[7] There are no previous reports of children or adolescents with QTc prolongation associated with syncope and caused by a primary calcium metabolism abnormality. In this report, we describe a child who developed QTc prolongation and syncope as a result of pseudohypoparathyroidism-induced hypocalcemia.

Case Report

A 12-year-old girl with recurrent exercise-induced syncope was referred to Children's Hospital and Regional Medical Center. She had experienced 3 syncopal episodes in the preceding half year. Each witnessed episode occurred with exertion. No seizure-like activity was observed. The first episode occurred immediately after running to first base during a softball game. On reaching the base, she became dizzy and passed out. No medical consultation was sought. Six months later, she experienced sudden collapse without premonition, while running during a soccer game. A physician bystander could not palpate any pulse. She remained unconscious for about 2 minutes and recovered spontaneously without resuscitation. She was then transported to a nearby hospital, where an electrocardiogram revealed a prolonged QTc of 485 milliseconds. Electrolytes were normal, with a sodium concentration of 139 mmol/L and a potassium concentration of 4.3 mmol/L. She was then referred to Children's Hospital and Regional Medical Center for cardiac evaluation. Another similar syncopal episode during running occurred before this evaluation and after discharge from the referring hospital.

ECG	Electrocardiographic
QTc	Corrected QT interval

She had otherwise been healthy except for seizures at 1 year of age, which were believed to be febrile in origin. She had never received any medications. Review of systems revealed the presence of intermittent paresthesias in her legs over an 18-month period. The patient has 2 healthy siblings, aged 4 and 8 years. Both her parents are alive and well, and electrocardiograms

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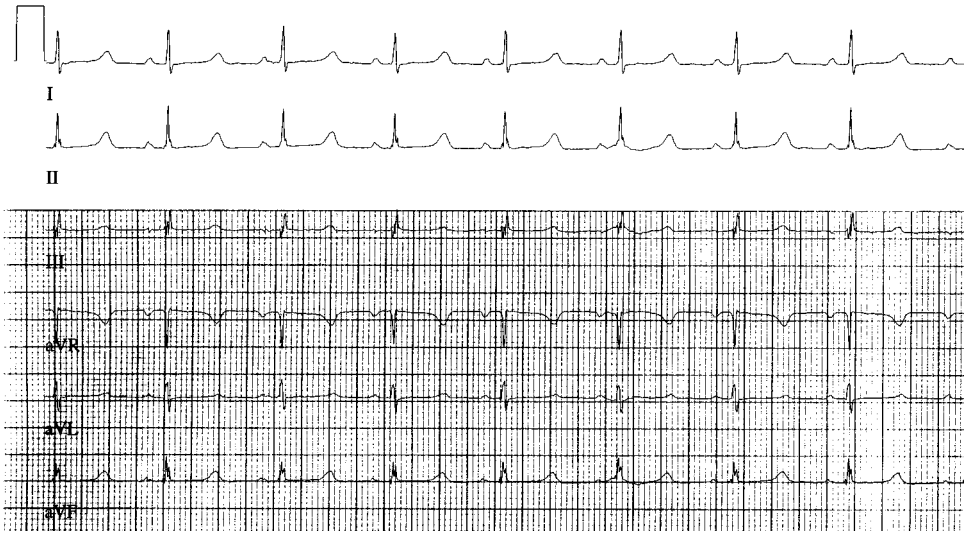

Fig 1. Electrocardiogram, limb leads, at initial examination; paper speed, 25 mm/sec. Sinus rhythm with QTc = 0.504 seconds.

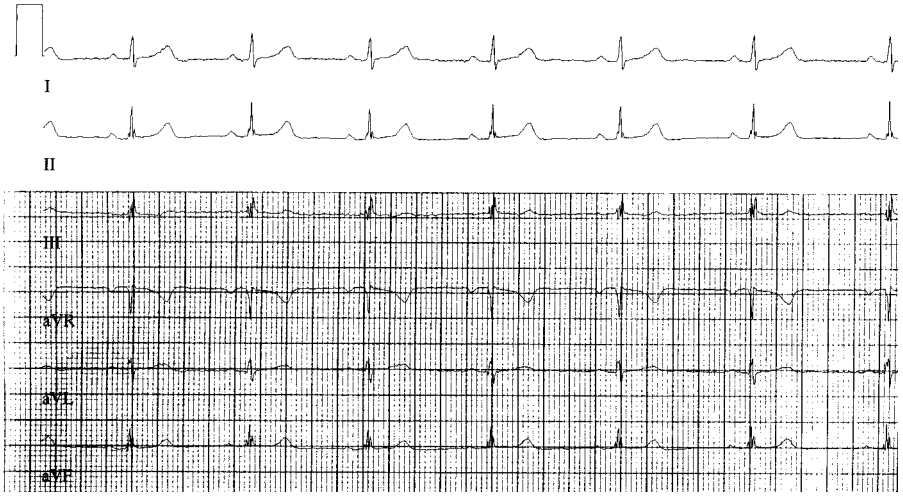

Fig 2. Electrocardiogram 18 months later. Calcium levels were normal. Sinus rhythm with QTc = 0.408 seconds.

demonstrated corrected QT intervals less than 400 milliseconds. There have been no unexplained sudden deaths in the family, which is large on both sides. However, endocrine disorders are present in several family members on both sides. A paternal uncle, paternal aunt, paternal grandmother, and one of the father's cousins have diabetes type II. Also, a paternal uncle and paternal aunt have had goiters and exophthalmus. Additionally, a maternal aunt and uncle have type II diabetes, and another maternal uncle has hyperthyroidism.

Initial physical examination showed her height at 147 cm (3rd percentile or 2 SDs below the mean) and weight at 41 kg (30th percentile for age). The patient was not short, when compared with her parents' stature. Heart rate was 87 beats/min, and blood pressure was 111/74 mm Hg. Findings on physical examination were normal. An exercise test was performed. She completed a total of 8 minutes of exercise (5th percentile for age and gender) on the treadmill using the Bruce protocol. She had a blunted heart rate response with a maximal heart rate at 133 beats/min. The test was terminated because of fatigue. At rest, her QTc was prolonged at 504 milliseconds with prolongation of the ST segment and normal-appearing T waves (Fig 1). During exercise and recovery, the QTc remained prolonged (range, 485-525 milliseconds). Absolute QT interval decreased from 440 milliseconds to 360 milliseconds. No bizarre T-wave changes were observed, and no arrhythmias were induced.

The patient was initially admitted to the hospital for monitoring and management of a presumed long QT syndrome. No arrhythmias were noted during inpatient monitoring. However, laboratory tests revealed abnormally low serum values for ionized calcium

(0.83 mmol/L; normal, 1.16-1.45 mmol/L), total calcium (4.1 mg/dL; normal, 8.2-11.2 mg/dL), and magnesium (1.1 mg/dL; normal, 1.8-2.4 mg/dL) and an elevated phosphorus concentration (7.0 mg/dL; normal, 4-6 mg/dL). Serum concentrations of glucose, urea nitrogen, creatinine, albumin, and electrolytes were within normal limits; complete blood count and urinalysis were unremarkable.

During subsequent endocrinology consultation, Tanner stage III breast development and pubic and axillary hair were noted. A positive Chvostek test response could be elicited. The patient also had shortening of the ring finger metacarpal, which was confirmed by bilateral x-ray films of the hand. Serum thyroxine, triiodothyronine, free triiodothyronine, thyroid-stimulating hormone, and albumin levels were normal. The serum immunoreactive parathyroid hormone level was 246 pg/mL (normal range, 10-65 pg/mL). Vitamin D level was normal.

We concluded that she had pseudohypoparathyroidism. The patient received 10% calcium gluconate (1 mL/kg), administered intravenously over a 10-minute period, followed by continuous infusions (100 mg/kg/d) and magnesium sulfate infused at a dose of 2 g intravenously to correct her hypomagnesemia. She then received orally administered calcium and vitamin D supplementation, which gradually elevated the serum calcium level and normalized the QT interval. At the time of discharge, her serum total calcium concentration was 7.3 mg/dL, and ionized calcium value was 0.95 mmol/L. Magnesium and phosphorous levels were within normal ranges. The QTc normalized (QTc = 397 milliseconds). After 18 months, her serum calcium and magnesium levels were maintained within normal ranges, although the parathyroid hormone level remained elevated. The ECG QT interval was still within normal limits (Fig 2). There were no syncopal episodes during that period.

DISCUSSION

Syncope and QTc prolongation represent major features of this patient's clinical presentation. Hypocalcemia-induced ECG abnormalities have been previously described, although they have not been associated with syncope.[8] Reported causes of hypocalcemia-induced QT prolongation include vitamin D–dependent rickets, aggressive diuretic use, and renal dialysis. This electrolyte disturbance causes ST segment and QT interval prolongation.[7,9] Many texts and reviews[10,11] indicate that this QTc prolongation occurs without the alterations in T-wave morphology associated with polymorphic ventricular tachycardia and frequently noted in pharmacologically induced or inherited types of long QT syndrome. However, Bronsky et al[8] have reported T-wave inversions and bizarre morphology in patients with hypocalcemic hypoparathyroidism or pseudohypoparathyroidism. Concurrent magnesium levels were not reported in those patients. Thus the contribution of hypomagnesemia in generating such ECG abnormalities was not clarified. This patient exhibited abnormally low calcium and magnesium serum levels, as well as hyperphosphatemia. Considerable debate has occurred in the past regarding the importance of hypomagnesemia in generating clinically relevant ECG abnormalities[12] or arrhythmias. Although no clear consensus is apparent, most ECG abnormalities in the clinical setting of hypocalcemia and hypomagnesemia are attributed to the former. Because these abnormalities were corrected concurrently in this patient, we cannot definitively eliminate hypomagnesemia as a cause of QTc prolongation.

Pseudohypoparathyroidism refers to a heterogeneous disorder, characterized by hypocalcemia and supranormal plasma parathyroid hormone levels. These findings indicate end-organ resistance to parathyroid hormone. This entity can occur in association with other endocrine abnormalities in the family. This patient presented with clinical features and laboratory data consistent with pseudohypoparathyroidism. Diagnostic criteria included a positive Chvostek sign, an indicator of tetany. Additionally, this patient had disproportionate foreshortening of the fourth metacarpals, a characteristic but inconsistent sign of pseudohypoparathyroidism and the Albright hereditary osteodystrophy phenotype.[13] Management of pseudohypoparathyroidism is directed toward normalization of electrolyte abnormalities. The urgency of treatment is usually directed by findings of tetany. QTc prolongation with clinically important syncope in this patient highlights the need for rapid correction.[14] Although torsade de points was not documented, the combination of exercise-related syncope, pulselessness, and QTc prolongation is highly suggestive that this dangerous ventricular arrhythmia occurred on 3 occasions.

The differential diagnosis for syncope and QTc prolongation includes a broad range of disorders including inheritable or new ion channel mutations, as well as pharmacologic or toxic agents, which alter ventricular repolarization. This clinical scenario emphasizes the importance of searching for metabolic disorders such as hypocalcemia after presentation of symptoms and laboratory features mimicking inherited or other acquired forms of long QT syndrome. Rapid normalization of serum electrolytes results in shortening of the QT interval and reduction of the risk for a life-threatening arrhythmia.

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