Persistent QT Prolongation in a Child with Gitelman Syndrome and SCN5A H558R Polymorphism

Takashi Tsukakoshi, MD, Lisheng Lin, MD, Takashi Murakami, MD, Junko Shiono, MD, Iisho Izumi, MD and Hitoshi Horigome, MD

Summary

Gitelman syndrome (GS) is an inherited renal tubular disorder characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and low urinary calcium excretion. While it is considered a benign disease, severe ventricular arrhythmia and sudden cardiac death related to the prolongation of the QT interval have been reported in rare cases. Herein we report a 13-year-old girl with GS who presented with persistent prolongation of the QT interval, even after being treated for hypokalemia and hypomagnesemia. Genetic analysis identified SCN5A H558R polymorphism, which modulates the function of myocardial sodium channel, and SLC12A3 A588V mutation, which causes GS. The SCN5A polymorphism and GS-related electrolyte disturbance might have contributed to the persistent QT prolongation in this patient. Although no ventricular arrhythmias were recorded in this case, careful cardiac surveillance should be applied for avoiding life-threatening cardiac events.

Key words: QT interval prolongation, SCN5A polymorphism, Gitelman disease, Sudden cardiac death, SLC12A3

Gitelman syndrome (GS) is an inherited renal tubular disorder caused by mutations in the SLC12A3 gene, which encodes thiazide-sensitive sodium-chloride cotransporter (NCC). GS is characterized by hypokalemic metabolic alkalosis in combination with hypomagnesemia and low urinary calcium excretion. It is usually considered a benign disease with mild symptoms and good prognosis. Although the incidence is low, severe ventricular arrhythmia or sudden cardiac death caused by QT interval prolongation has been reported.

Here, we report a girl who presented with persistent QT prolongation on the electrocardiogram (ECG) and was diagnosed with GS combined with SCN5A H558R polymorphism by genetic analysis. While the effect of SCN5A H558R polymorphism on the QT interval remains to be explored, it possibly modulates the function of a myocardial sodium channel.

Case Report

A 13-year-old girl was found to have QT interval prolongation on ECG screening conducted at a heart check program in school. She had no history of ventricular arrhythmias or syncope, and the family history was negative for long QT syndrome (LQTS), sudden cardiac death, or congenital deafness. The ECG demonstrated sinus rhythm with a QT interval prolongation (QT 0.48 seconds, QTc 0.49 seconds) (Figure 1). The longest QT interval was 0.50 seconds (QTc 0.52 seconds), but no other arrhythmias were recorded on Holter ECG. Treadmill exercise test did not induce any arrhythmias. The QT intervals (QTc) at rest, peak exercise, and 4 minutes post-exercise were 0.44, 0.47, and 0.51 seconds, respectively (Figure 2).

Laboratory tests showed hypokalemia (2.7 mEq/L), hypomagnesemia (1.5 mg/dL), low urinary calcium excretion (U-Ca/U-Cr 0.0028), and high serum bicarbonate (28.3 mEq/L). These findings suggested an inherited renal tubular disorder. A diuretic loading test showed a decrease in distal fractional chloride reabsorption after furosemide administration but not after thiazide, thus establishing the clinical diagnosis of GS. Treatment commenced with potassium gluconate, magnesium sulfate, and potassium sparing diuretics (spironolactone) to maintain a normal level of serum electrolytes. The prolongation of the QT interval persisted despite treatment and subsequent correction of hypokalemia and hypomagnesemia (Figure 3).

After obtaining an informed consent from the parents, genetic analysis of GS and LQTS-related genes (LQTS 1-13) was performed at the age of 16 years.
SLC12A3 A588V mutation and SCN5A H558R polymorphisms were identified. No other mutations of LQTS 1-13 genes, which have already been confirmed to be pathogenic, or reported variants that relate to the QT interval, were identified.

**Discussion**

Patients with GS tend to present with low levels of serum potassium and magnesium, which contribute to QT interval prolongation. Although the clinical manifestations of GS are usually mild with good prognosis, life-threatening events are known to occur, although rarely. Scognamiglio, et al. reported a GS patient who experienced aborted sudden cardiac arrest with a QTc value of 0.45 seconds on the ECG (0.52 seconds on Holter ECG). It is important to monitor and correct serum electrolyte disturbances to prevent ventricular arrhythmia and sudden death in GS patients. Furthermore, the risk factors of acquired LQTS such as certain antiarrhythmic agents, antiinfective drugs, and psychotropic drugs should be avoided.

Our patient exhibited persistent QT prolongation, even after being treated for hypokalemia and hypomagnesemia. Other potential factors that affect the QT interval, in addition to electrolyte disturbances, were therefore suspected.

The SCN5A gene encodes an α-subunit of the cardiac voltage-gated sodium channel (Nav 1.5). Mutations in SCN5A result in various cardiac diseases, including Brugada syndrome, dilated cardiomyopathy, sick sinus syndrome, atrial fibrillation, and LQTS. Amino acid change of histidine with arginine at codon 558 (SCN5A H558R) is a polymorphism located in the sodium channel I-II interdomain cytoplasmic linker. Its allele frequency accounts for 29%, 20%, and 9% in African Americans, Caucasians, and Asians, respectively. This relatively common single-nucleotide polymorphism is reportedly associated with longer QT intervals in the general population.

Although H558R polymorphism reportedly has no independent functional effects on sodium channel in in vitro studies, it modulates the expression of various arrhythmogenic genotypes under specific conditions. For example, H558R polymorphism reduced the occurrence of ventricular fibrillation in patients with Brugada syndrome. On the contrary, it reportedly exhibited LQT3-like dysfunction when it coexisted with SCN5A A572D, another missense variant in healthy subjects.

The functional analysis of SCN5A-mutation-positive Brugada syndrome demonstrated that the polymorphism attenuates the slow inactivation of sodium channel, which is enhanced by the coexisting pathogenic mutation of SCN5A. Matsumura, et al. demonstrated that SCN5A H558R polymorphism modulated the clinical manifestations of Brugada syndrome. In their report, patients with H558R showed a lower methylation level of SCN5A promoter and expressed higher levels of SCN5A in right atrial sections compared with patients without H558R. H558R increases the expression level of sodium channel and may therefore affect the very early phase of the action potential.

While the effects of H558R polymorphism on the QT interval in the present case are unclear, the coexistence of GS-related electrolyte abnormalities and SCN5A H558R polymorphism might have increased the risk of acquired LQTS.

Although life-threatening arrhythmias have not oc-
curred in our patient thus far, we believe it is important to provide careful management and patient education for preventing potential lethal arrhythmias and sudden death.

Disclosures
Conflicts of interest: None.

References