学 位 論 文 の 要 旨

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学 位 論 文 名　Clinical and Electrophysiological Features of Japanese Pediatric LQTS Patients With *KCNQ1* Mutations

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論文内容の要旨

INTRODUCTION

Congenital long QT syndrome (LQTS) is a hereditary disorder characterized by a prolonged QT interval on the electrocardiogram (ECG) and episodes of polymorphic ventricular tachycardia known as torsade de pointes (TdP), which may cause syncope and even sudden cardiac death. The cause of the LQTS is suspected dysfunction of several ion channels in the myocardial muscle cells, and seven candidate genes related to the syndrome have recently been identified. The mutation involving the *potassium voltage-gated channel, KQT-like subfamily, member 1* (*KCNQ1*) gene is believed to cause dysfunction of a slow activation element of the delayed K^+ current and to increase sensitivity to sympathetic stimulation compared with other types of LQTS. We studied the clinical and electrophysiological features in a group of Japanese pediatric LQTS patients with *KCNQ1* mutations (LQT1).

PATIENTS AND METHODS

Clinical study: We analyzed *KCNQ1* mutations in 13 Japanese pediatric patients with a long

QT interval on their ECG. We retrospectively investigated the clinical records of the LQT1 patients for their past and family histories of LQTS-related cardiac events, other complications, and the ECG findings at rest and during exercise (Ex).

Gene analysis: We obtained informed consent from the patients and/or their families for the genetic analysis. The *KCNQ1* gene was amplified by the PCR method using genomic DNA extracted from peripheral-blood lymphocytes as reported by Splawski *et al.*, and then analyzed by direct sequencing.

Baseline 12-lead ECG: The QT interval (QT) and the intervals of two consecutive R waves were manually measured in the resting ECG according to the methods of Takenaka *et al.* We then calculated ventricular heart rate (HR), and the corrected value of QT (QTc) according to Bazett *et al.*

Treadmill Ex testing: Graded Treadmill Ex testing using a stressing protocol was undergone for all the patients. We evaluated the presence or absence of TdP and T wave alternans (TWA) during Ex, recorded peak HR (pHR) and calculated the HR increase from rest to peak Ex (dHR). With ten age-matched pediatric patients served as non-LQTS controls; we compared pHR and dHR between the LQTS group with *KCNQ1* mutations and the control group.

Statistical analysis: Unpaired t-tests were used to compare the groups. Data are expressed as mean +/- standard deviation. A p value <0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

Mutation analysis of the KCNQ1 gene: Of the 13 pediatric patients tested, *KCNQ1* mutations were identified in eight (61.5%) patients from six unrelated families, two males and six females (mean age at first visit was 7.7 +/- 1.5, range 6.4 to 9.7 years). Four missense mutations of *KCNQ1* were found in seven patients, and an insertion/deletion in the remaining one. These findings suggested that *KCNQ1* mutation is most common in Japanese pediatric LQTS, and missense mutation is frequent in Japanese pediatric LQT1 patients. We identified a novel insertion/deletion mutation at the intron-exon border of exon 4 in a patient with a family history of LQTS-related cardiac events. This mutation was an inframe mutation resulting in Asp202Glu substitution, and two amino acid deletions

(Leu203 and Ile204). Asp202, Leu203, and Ile204 are highly conserved throughout several species; this region might have an important role for *KCNQ1* function.

Clinical features: Syncope occurred in two patients with transmembrane domain mutations before the age of seven years, but not in patients with C-terminal domain mutations until at least six years of age. In the family with the C-terminal domain mutation (Arg591His), the family members had syncope during their elementary school days, both were treated medically. Shimizu *et al.* reported a correlation between the genotypes and the risk of tachyarrhythmia attacks in adults; patients with transmembrane domain mutations had a higher risk of LQTS-related cardiac events compared with patients with C-terminal domain mutations. Our findings suggest that the risk of LQTS-related cardiac events might not differ between pediatric LQT1 patients with C-terminal domain mutations and those with transmembrane domain mutations.

ECG findings: The QTc in the resting ECG exceeded 450 milliseconds in all but one patient. No patient developed either TdP or TWA during Ex testing. Compared to the controls, pHR and dHR were significantly lower in the LQT1 group (LQT1 vs. control, 153 +/- 17 vs. 182 +/-13 beats per minute, $p<0.01$, 65 +/- 17 vs. 99 +/- 24, $p<0.01$, respectively), suggesting that pediatric LQT1 patients have chronotropic incompetence. Slow activation of the delayed rectifier potassium channel, defective due to a *KCNQ1* mutation may affect the sinus nodal cell. Sinus node dysfunction or a poor response to sympathetic stimulation have been suggested in pediatric LQT1 patients.

CONCLUSIONS

KCNQ1 mutation is most common in Japanese pediatric LQTS. The risk of LQTS-related cardiac events might not differ between pediatric LQT1 patients with C-terminal domain mutations and those with transmembrane domain mutations. Sinus node dysfunction or a poor response to sympathetic stimulation have been suggested in pediatric LQT1 patients. Further studies in a large population will be needed to further clarify the clinical and electrophysiological features of pediatric LQT1 patients.