High Frequency of Double Mutations in RYR2 and Genes Related to Long QT Syndrome in Patients with Severe Cardiac Symptoms

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Introduction: Long QT syndrome (LQTS) is a disease characterized by QT prolongation and ventricular tachycardia. The main cause of LQTS is mutations in KCNQ1, KCNH2, and SCN5A. Some patients diagnosed with LQTS show severe phenotype compared to those with the same mutation. One of the reasons is an additional mutation related to arrhythmias, especially in RYR2 which is the major causative gene for catecholaminergic polymorphic ventricular tachycardia (CPVT). We aimed to clarify the characteristics of double mutation carriers.

Methods: The study cohort consisted of 160 probands diagnosed with inherited primary arrhythmia syndrome and carrying RYR2 mutations. We performed genetic analysis for LQTS-related genes in addition to RYR2.

Result: We identified 5 probands (2 male) with double mutations in RYR2 and LQTS-related genes; 3 KCNH2, 1 KCNQ1, and 1 SCN5A (Table). They all had symptoms and 3 probands suffered cardiopulmonary arrest. Their mean age at the onset was 9.8 ± 4.9 years old. Four probands (Proband 1, 2, 4, 5) experienced symptoms during exercise, and 3 of them were clinically diagnosed with CPVT. Remaining 1 proband (Proband 3) suffered CPA in the early morning and was clinically diagnosed with LQTS. The QTc interval of probands clinically diagnosed with LQTS (n=2) was longer than that with CPVT (450.5 ± 30.5 vs 395.7 ± 0.6 ms).

Conclusion: Our study implied that LQTS patients carrying double mutations frequently suffered severe symptom. Therefore, cardiologists should be in mind that the patient may carry not only a mutation in a LQTS-related gene but also another mutation in other genes, even if the QT interval is prolonged.