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Mutation specific clinical characteristics in long QT syndrome type 8; severe phenotype in Timothy syndrome patients

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Background: Long QT syndrome type 8 (LQT8) caused by mutations in CACNA1C has been classified as a very rare and severe type of long QT syndrome accompanied with Timothy syndrome (TS) with extra-cardiac phenotype. Recently, various mutations in CACNA1C have been identified in non-TS patients. However, mutation specific severity in LQT8 has not been elucidated yet, especially for non-TS patients.

Purpose: We aimed to clarify the clinical characteristics of LQT8 patients.

Methods: The study consists of 26 LQT8 patients (21 probands and 5 family members). We evaluated their phenotype.

Results: Table summarizes the clinical characteristics of LQT8 patients. TS patients diagnosed in younger age than those of non-TS. Four TS and one non-TS patients were diagnosed at the age of 0, though the non-TS patient was a son of a patient and asymptomatic. Nine patients suffered symptoms including 7 with cardiac arrest. We identified three TS mutations; classical p.G406R in two and p.G402S in two, and a new TS mutation, p.412M in one. Four of TS patients were symptomatic and two died suddenly at the age of 4 and 5. In contrast, no one died in non-TS patients. Five non-TS patients suffered symptoms in the age of 4,9,15,54 and 64, and the mutations were p.S643F, p.R858H (2 patients), p.K1518E and p.K1591T.

Conclusions: Although TS patients showed severe phenotype, most of the non-TS patients were asymptomatic. The phenotype in LQT8 are diversely different depend on the mutations, especially between patients with TS and non-TS.

Characteristics of TS and non-TS patient

	TS	Non-TS	P
N (male)	5 (2)	21 (9)	
Age (range)	0 (0–7)	12 (0–64)	0.004
Symptom			
Syncope	4	5	0.034
CPA	3	4	0.101
ECG characteristics			
QT interval	603±40	507±14	0.011
T wave alternans	5	2	<0.001
AV Block	4	1	0.002
Therapy		(4 unknown)	
Beta-blocker	4	7	0.311
Mexiletine	3	1	0.024
ICD implantation	2	2	0.21