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유전적으로 확인된 선천성 QT 연장증후군 환자의 장기 경과에 대한 연구

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The outcome of genetically defined Long QT syndrome

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Abstract

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Background: Long QT syndrome (LQTS) is a potentially fatal hereditary ionic channelopathy which characterized by the ventricular arrhythmia, and sudden cardiac death with prolonged ventricular repolarization time. To date, the molecular genetic studies confirmed that relevant mutations of 17 genes have been implicated in LQTS. Clinical characteristics of LQTS are diverse from symptomless to sudden cardiac death while related the genotype-phenotype correlation.

Objective: This study evaluated the genetic diagnosis, the fulfillment of current treatment strategies and the overall outcomes of 105 LQTS patients and their families from a single center in Korea.

Methods and Results: We conducted a retrospective investigation on 105 Korean LQTS patients (female 48; 45.7%). A median age of first symptom was 10.5 years (0.00 – 80). The first symptom was syncope or seizure in 38 (54.3%), aborted cardiac arrest in 21 (30%), and fetal arrhythmia in 3 (4.2%). The LQTS was diagnosed at their median age

of 11 years (0.003 – 80). In 90 of them, genotype was performed: LQT1 (27.8%), LQT2 (12.2%), LQT3 (15.6%), LQT 4-8 (6.6%), JLNS (5.6%) and VUS (7.8%). Three of them (3.3%) showed multiple mutations. The 72 LQTS probands and the 18 genetically proven family members were evaluated. Over the family group, the penetrance of LQTS genetic mutation was 51 %. The QTc interval was significantly longer in symptomatic group (533.5ms, 505ms, p=0.003). Patients with JLNS had a significantly younger median age of diagnosis compared with the rest (p=0.011). Over the median follow-up of 6.75 (1.5-20.0) years, 81 (77.1%) patients have not experienced an LQTS-triggered BCE. During median 6.67 years follow-up in symptomatic group, the treatment composed no therapy in 10 (14%), β-blockers in 56 (80%), and implantable cardioverter defibrillators (ICD) in 25 (35%, median 14.8 years, 2.25 – 80). Flecainide or mexiletine was added in 4 of LQT3, 2 of LQT4-7 patients. The left cardiac sympathetic denervation (LCSD) was conducted in 5 LQT1 patients, 1 LQT3 patient and 1 LQT4 with concomitant RyR2 mutation. Among 25 patients who received an ICD, 14 patients confirmed the genetic findings (1 LQT1, 2 LQT2, 8 LQT3, 1 LQT7, and 2 LQTM). During the median post-ICD follow up 6.83 years (1.58 – 20.0), 13 patients (2 LQT2, 6 LQT3, 2 LQTM, 1 no test/Schwartz, high risk, and

2 G(-)/P(+)) experienced an appropriate, life-saving therapy and all survived except one LQT3 patient with cardiomyopathy.

Conclusion: Recently, with the progression of genotype in LQTS, the recognition of the molecular pathogenesis and the genetically tailored therapy are fostered. Devastating cardiac events was prevented with good long term outcome in the genetically confirmed and properly managed LQTS patients in this study. It may be the crucially important that the rigorous genetic analysis, the risk stratification, and the appropriate therapy based LQTS related individual phenotype.

Keyword : Long QT syndrome; Genetics; Death, sudden; Outcomes

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Chapter 1. Introduction

1.1. Study Background

The sudden death of a young and healthy person is the most devastating scenarios in clinical medicine. While coronary artery disease and acute myocardial infarction are the major causes of sudden cardiac death (SCD) in older populations, inherited cardiac disorders are comprised of the substantial proportion of SCD cases aged 40 years and less. These primary arrhythmogenic ionic channelopathies are the long-QT syndromes (LQTS), short-QT syndromes, catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), idiopathic ventricular fibrillation (IVF), and inherited cardiomyopathies, namely hypertrophic cardiomyopathy. Among these cardiac channelopathies, the LQTS is the leading contributors of sudden unexplained death in the young [1, 2]. The LQTS is characterized by the delayed ventricular repolarization as manifestation on electrocardiogram (ECG) as QT prolongation. Lengthening of the QT interval has increased the propensity to syncope or seizure, ventricular tachycardia, torsades de pointes, and sudden cardiac arrest. Hereditary LQTS is a familial ion channelopathy with variable penetrance, including the relatively common Romano-Ward syndrome as autosomal dominant (or sporadic) and the rare Jervell and Lange-Nielsen syndrome as autosomal recessive trait (or sporadic). After first descripted the LQTS with congenital deafness in 1957 [3], there have growing the interest in hereditary arrhythmogenic diseases. Over 20 years ago, the genetic and molecular biology were broken new ground by the identification of the culprit genes causing the LQTS [4-6]. To date, the molecular genetic studies confirmed that relevant mutations of seventeen genes have been implicated in LQTS [7]. The major causative genes as KCNQ1, KCNH2 and

SCN5A, which associated with LQTS type 1 to 3, are constituted over 75–80% [8–10]. The estimated prevalence is approximately 1:2000 [11, 12]. The criteria for diagnostic LQTS relied on the Schwartz score (revised 2011, [13]), which giving different weight on the ECG findings (resting and during exercise), the clinical history, and family history. The patient keeps the score over 3.5 points, which implied that he (or she) is high probable LQTS. Clinical characteristics of LQTS are diverse from symptomless to sudden cardiac death because of variable penetrance, and related the genotype–phenotype correlation. In general, most studies recommend that the treatment of LQTS consists of pharmacotherapy (such as beta–blockers), device implantation, and/or left cardiac sympathetic denervation surgery based on the risk stratification [14–19]. To date, the therapy has to be compounded of not only evidence based treatment considering of conventional risk but also personalized treatment on phenotype.

1.2. Purpose of Research

We, therefore, sought to: (1) characterize populations of LQTS in the clinical and genetic aspect; (2) determine overall outcome of LQTS and individualized treatment approaches among LQTS registered at a single tertiary center.

Chapter 2. Materials and methods

2.1. Subject

We conducted a retrospective review of the electronic medical records of 105 patients who were diagnosed and treated the long QT syndrome patients and their families defined molecularly between 2000 and 2016 at Seoul National University Hospital (SNUH). For all patients, the data were collected for gender, age at initial symptom (if had symptom), clinical presentation, age at diagnosis, current age, follow-up duration, treatment, occurrence of cardiac event after treatment, results of genetic studies, family history, and ECG data (resting ECG, 24hour holter monitoring, epinephrine challenging test, or treadmill test). The Schwartz score was calculated with data for each patient. The patient who presented the symptom showed a syncopal event, palpitation, bradycardia, fetal arrhythmia, or cardiac arrest. A syncopal event means the arrhythmogenic syncope, dizziness, or seizure, which excluded vasovagal syncope (aggravated by abrupt positional change, or heat, dehydration) and focal, febrile, or acquired seizure. The inclusion criteria were the LQTS, who met the diagnostic criteria: 1) proven pathogenic mutation patients either who presented suspicious clinical symptoms or no obvious clinical presentation with normal ECG, 2) at least one of their serial ECG documented prolonged QTc interval (by Bazett formula) longer than 0.47 sec or the Schwartz score of 3.5 points and over.

2.2. Statistical analysis

All statistical analyses were conducted using the SPSS statistical package (version 19.0; SPSS, Chicago, IL). Continuous variables are expressed as mean ± SD or median (min, max) when appropriate. Using student's t-test for

continuous variables and the chi-square test for nominal variables applied. Variable Differences between groups were examined using the Mann-Whitney test. Frequencies with proportions were determined for categorical variables. Survival analysis was performed by the Kaplan-Meier estimation, for the comparison of subgroup survival mantel-cox log rank analysis was performed. A p-value less than 0.05 was considered statistically significant.

The institutional review board for clinical research at Seoul National University Hospital approved the use of medical records for this study (IRB H-1705-140-859).

Chapter 3. Results

The characteristic demographic data of entire cohort the 105 LQTS patients (female 48; 45.7%) is demonstrated in Table 1. The median age of diagnosis is 11.0 (0.003–80) years of age in total cohort, while in symptomatic group the first symptom developed at median 10.5 years of age (0.00–80), median age of diagnosis is 11.1 year–old (0.003–80). Among the symptomatic group, the presentations of first symptom are syncope or seizure (n=38, 54.3%), aborted cardiac arrest (n=21, 30%), palpitation (n=5, 10%), fetal arrhythmia (n=3, 4.2%), bradycardia (n=2, 2.8%), and dystonia (n=1, 1.4%). Significantly, the median QTc interval in symptomatic group is longer than in asymptomatic group (533.5ms, 505ms; p=0.003). The overall treated follow–up duration is 6.75 (1.5–20.0) years. Although there are small cases, the symptomatic group has a significantly larger proportion of patients who had a family history of SCD (15.5%, 12.1%; p<0.001) when compared with the asymptomatic group. The mode of initial presentation symptom in symptomatic group demonstrated in Figure 1.

3.1. Phenotype

In symptomatic group, the thirty–eight patients (54.3%, of 70) suffered the initial symptom as syncope or seizure. The syncope attacks during stress situation are found in twenty–four patients, more detail during exercise in 23 (68%), during emotional challenging in 1 (3%). The syncope episodes at the resting situation like sleeping, or being in class occur in ten patients (29%). The aborted cardiac arrest as the initial symptom had been experienced in 21 patients. The situation at the cardiac arrest enumerates at exercise in 6, at emotional stress (such as getting a scolding) in 4, at sleep in 4, at postpartum 1, at general anesthesia induction or light sedative

procedure in 3, and at unidentified 3 patients (Figure 1). Among the patients initially classified as asymptomatic group, some events such as syncope and seizure had occurred in a few cases during follow-up observations. This will be described later on a case by case basis.

The age and gender distribution of symptomatic group showed in Figure 2. Though there are no statistically significant differences in gender distribution (p=0.397), symptomatic presentation patients with older age were more likely to be female.

The congenital sensory nerve hearing loss as a combined anomaly presented all 5 patients as Jervell and Lange-Nielsen syndrome (JLNS). Among these 5 patients, 4 patients was initially presented no syncopal or seizure like motion which we defined as asymptomatic, whereas the other presented syncope with stress (exercise like jumping up steps) initially. To describe the patient in more detail, the patient's chief complaint was recurrent syncope. This 5-year-old patient had loss of consciousness with seizure like movement such as tonic-clonic feature and eye ball deviation two years before he first visited the hospital. The symptoms usually appeared when walking or exercising, and the duration was several seconds to several minutes. His medical history revealed that he had undergone cochlear transplantation because of congenital sensorineural deafness. His resting 12 lead ECG showed a markedly prolonged QTc (590ms) and the treadmill test revealed T wave alternans. There was no specific familial history. The diagnostic criteria of LQTS were satisfied, and the molecular genetic analysis presented the compound heterozygous mutations in the KCNQ1 gene. More details of genetic mutation will be given later. While he was taking medication, there was no syncopal event. But at his 13 year-old age, he fainted during playing basketball. Then we decided that the left cardiac sympathetic denervation surgery (LCSD) was necessary and more effective

treatment. He underwent the LCSD at his 13 year-old. There was no acute complication and the patient is event-free for 4 years of follow-up. One of the initially asymptomatic patients developed syncope with stress during follow-up duration. This 14-month-old patient was visited the otolaryngology due to hearing loss and was referred to our clinic for an abnormal ECG for pre-operative evaluation. There was no syncopal event at his past medical history previously, but his older brother presented a syncope history during running in playground. After receiving the consent form, the blood of the patient and the patient's family was collected and examined for the KCNQ1 gene. More details of genetic mutation will be given later. After the diagnosis, the patient was prescribed a beta blocker. But he had a syncope event while taking medication, and received the left cardiac sympathetic denervation surgery at the age of 31-month-old because of recurrent syncopal events despite having kept medication adjustment. During the last 5 years of follow-up, he is well controlled without any more syncopal event.

By familial screening genetic study in JLNS patients, 9 patients, including confirmed JLNS patients, confirmed the KCNQ1 gene impairment.

The Andersen-Tawil syndrome, classified as LQTS type 7, is characterized by the pathognomonic clinical features: periodic paralysis or muscle weakness, distinctive facial and skeletal dysmorphism (low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, scoliosis and a broad forehead), and ventricular arrhythmia [20, 21]. Of four patients confirmed as the Andersen-Tawil syndrome, two patients classified as symptomatic group that one showed dizziness and the other complained several syncopal events. Three patients showed combined symptoms as periodic paralysis and weakness. Two out of three were siblings (brother and sister), and the other one is sister whose mom is same but has different father. And another who

diagnosed the Andersen-Tawil syndrome showed typical features as low-set ears, triangular face and micrognathia with left 5th finger clinodactyly. The patient had several syncopal events during exercise (like a swing) and resting. The 24hour holter ECG showed non-sustained ventricular tachycardia, and treadmill test revealed ventricular premature beats and several bigeminies. The molecular gene study was performed. At age of 13 year-old, the patient got the implantable cardioverter defibrillator.

The Timothy syndrome, also known as LQTS type 8, is multi-organ system disorder that associates cardiac arrhythmia, heart defect, developmental delay, and anomaly of hands and feet, especially associates with syndactyly [22]. In our group, two patients confirmed LQT8. One patient has typical features frequently found in the Timothy syndrome as dysmorphic face (round face, bald at birth, and small teeth) and syndactly, who showed first presentation as ventricular fibrillation under the general anesthesia induction for syndactly repair operation(third, fourth, and fifth digits). After resuscitation, sinus rhythm was recovered, and the resting electrocardiogram showed a prolonged QT interval (QTc 587ms). The 24hour holter ECG showed T wave alternans and functional 2:1 AV block. A β-blocker (propranolol) was administered and mexiletine added during the age of his 4 to 7 year-old. At age of 10 year-old, the short acting propranolol converted to long acting atenolol. Another patient who had a ventricular septal defect at birth showed typical prolonged QTc but there are any other extra-cardiac symptoms.

The first symptom which was presented under the 1 year old age showed in 7 patients including 3 with fetal arrhythmia. More detail descripted about fetal arrhythmia, 1 who showed fetal tachycardia presented neonatal ventricular tachycardia after birth and the patient was confirmed LQT2. Other 2 patients were showed fetal tachycardia with premature

ventricular beats, and were genetically verified LQT 2 and 3, respectively.

3.2. Genotype

The genetically verified test was performed in 90 patients (of 105 patients, 85.7%). The type of genetic test composed with LQT1 (n=30, 33.4%; Jervell Langel-Nelson Syndrome (n=5, 5.6%)), LQT2 (n=11, 12.2%), LQT3 (n=14, 15.6%), LQT7 (n=4, 4.4%), LQT8 (n=2, 2.2%) and 3 (3%) of multiple LQTS-associated mutations (LQTM) (Figure 3). The phenotype according to the genotype demonstrated in Table 2. Although not statistically significant (because of small cases), the syncopal events were manifested younger in the JLNS group than in the LQT1 group (mean age 2.58 year-old vs. 6.0 year-old; p=0.307). In LQT3 group, there were more people who showed cardiac arrest than in LQT1 group (RR 8.0, p=0.043). In our study, Although not statistically significant, there was a tendency for more frequently syncopal events which occurred during resting or sleep situation to occur in LQT3 patients than in LQT1 patients (p=0.2). Patients with JLNS had a significantly younger median age of diagnosis compared with the rest (p=0.011). The proportion of patients with a ICD insertion of LQTS was significantly more in those patients in LQT3 compared with all other LQTS group (p=0.004). In aspects of the association between genotype and phenotype, the genotype in the group showing cardiac arrest is as Figure 4. LQTM (multiple LQTS-asssociated mutations) composed 3 patients. One was found to carry a likely pathogenic variant, TAZ, while assessing the evaluation of cardiomyopathy. The other who presented first clinical feature as syncope at nodding off at 16 year-old was found the KCNH2 and SCN5A mutation. The β-blocker was prescribed and maintaining the medication for 2 years, the syncope during walking had occurred and the

implantable cardioverter defibrillator (ICD) was inserted for the purpose of primary prevention. During the 3.42 year follow-up period, the patient was treated appropriately shock therapy by ICD. The other who showed severely tragic clinical course was harbored the ANK2 variant which associated LQT4 as well as the RYR2 variant which could have caused catecholaminergic polymorphic ventricular tachycardia (CPVT). First of all, the β-blockers (propranolol, bisoprolol) were applied, the flecainide was added and the patient should be disqualified from all competitive sports. Nevertheless, the symptoms continued and the ICD was implanted. After ICD implantation, the electrical storm bothered the patient and the left cardiac sympathetic denervation surgery (LCSD) was performed. Maintaining the medication in post-LCSD state, the patient is doing well during the 9.92 years follow-up after ICD implantation.

Jervell and Lange-Neilsen (J-LN) syndrome (JLNS, Autosomal Recessive trait), associated with congenital deafness was diagnosed in 5 patients. Of the five patients, two are brothers. Molecular genetic analysis of each patient revealed as follows : 1) KCNQ1 exon 11 deletion 2) KCNQ1 exon 1-16 combined heterozygous (i) c.828-830delCTC, p.S277del deletional mutation ii) c.921G>A, p.V307V splicing mutation), 3) KCNQ1 exon 7-10 large deletion and c.1893dup frame shift mutation, 4) KCNQ1 exon 8-11 large deletion and c.684-2A>G(IVS4) mutation.

LQT7 which identified with pathogen in KCNJ2 come out 4 patients. LQT8 which was found variant in CACNA1C gene are confirmed 2 patients. One who has typical features frequently found in Timothy syndrome confirmed the point mutation c.1216G > A in exon 9 in CACNA1C.

3.3. Treatment

During median 6.67 years follow-up in symptomatic group, β-blockers were taken by 56 out of 70 (80%), Figure 5. Four of LQT3 took mexiletine as only or additionally. One of LQT7, and one of LQTM have flecainide as only or additionally. β-blockers were not completely effective on the symptomatic patients with SCN5A, ANK2 and KCNJ2. Most of the patients diagnosed with the LQTS were taking the medication. When the syncopal event occurred during follow-up, other medications were added or the procedure/surgical treatments were considered. During the follow-up, there were twenty-four patients who suffered the syncopal event like a syncope or cardiac arrest. Among them, twenty-three patients were classified as initially symptomatic group, and the rest one patient was initially asymptomatic. He who diagnosed as JLNS was initially presented abnormal ECG for pre-operative evaluation to surgical treat for his deafness. There was a significant difference in breakthrough cardiac event (BCE)-free survival by genotype (p=0.012), as shown in Figure 6. One-year and 10-year BCE-free survival was highest in patients with LQT1, whereas one-year BCE-free survival was lowest in patients with LQT3. This trend is similar to the paper published in Mayo clinic in 2017 for 166 LQTS patients [23].

Thirty patients were operated on ICD Implantation or LCSD. 26 patients had indication of ICD implantation, but one patient refused. Total 25 patients who underwent ICD implantation followed up for median 6.83 years (1.58-20.0). The first ICD implantation included in this study was performed in September 2005, and the last was performed in October 2016. Table 3 presents characteristics and proven genotype in ICD recipients. Among patients, the median age of ICD implantation is 14.8 years old (2.25-80). Our study on ICD showed that female (17, 65%) and LQT3 (44% of performed gene study) patients had a disproportionately high probability of being implanted with an ICD. Among 25 ICD recipient patients, there was a statistically

significant more proportion as LQT3 (31%) than as LQT1 (4%) among the individuals who confirmed the genotype (p=0.011). All patients were symptomatic prior to ICD implantation. Seven patients (28%) received ICD treatment as primary prevention, while 18 patients (72%) as secondary prevention. Twelve patients suffered from aborted sudden cardiac arrest as an initial presentation. Six patients had cardiac arrest under medication maintaining during follow-up period. Among seven patients for primary prevention, there were one of LQT2, 3 of LQT3, 2 of all LQTM, and one of genotype (negative for evaluation about LQT1, 2, 3)/phenotype (positive). All of them suffered intractable syncope or seizure despite medication. Fourteen patients were applied β-blocker at pre-ICD state, and among them, 6 patients experienced arrest event during β-blocker treatment. The age at ICD implantation was distributed differently in each of the LQTS (**Figure 7**). Relatively, there showed that LQT3 implanted ICD more younger age. During a follow-up of 6.83 years, at least 1 appropriate shock was received by 52% (13/25) of the patients. Thirteen patients (2 LQT2, 6 LQT3, 2 LQTM, 1 no test/Schwartz, high risk, and 2 G(-)/P(+)) with ICD experienced an appropriate, life-saving therapy. **Figure 8** presents the Kaplan-Meier analysis of the clinical risk factor characteristics related to appropriate shock. The LQTS type as clinical risk factor presented statistically significant differences. According to the LQTS type, LQT2 genotype notably predicted those ICD recipients most likely to receive an appropriate shock therapy.

Left cardiac sympathetic denervation surgery (LCSD) was applied 7 patients. There are 5 patients in LQT1 (Among them, 2 patients in JLNS), 1 patient in LQT3, and 1 in LQT4 with concomitant RyR2 mutation. Only LCSD underwent for 2 LQT1 and 2 JLNS. One patient who was diagnosed as LQT1 maintaining the beta-blocker experienced syncope during

riding a bicycle. So the LCSD was done, but after LCSD maintaining medication the arrest event during playing soccer occurred. Then the patients got ICD. The rest 2 patients who underwent ICD implantation presented intractable ICD inappropriate shock and planned LCSD was done.

Among total cohort, all survived except one LQT3 patient with cardiomyopathy. The patient was confirmed with SCN5A p.R1193Q polymorphism. Ion channel dysfunction associated with the SCN5A gene showed mixed phenotype, including LQT3, sinus node dysfunction, and dilated cardiomyopathy [24]. He treated by implantation of ICD at the age of 27 month-old. Although he received two appropriated shock for ventricular fibrillations, the patient eventually died of dilated cardiomyopathy progression.

Chapter 4. Discussion

Since the LQTS was first described 60 years ago, the pathogenesis, diagnostic method and treatment have advanced respectively. However because of low prevalence of LQTS and the clinical heterogeneity, the reports of overall outcomes are sporadic. With the establishment of an international LQTS registry, there are extensive clinical and molecular studies. Accordingly, the risk stratification and individual tailored therapy have been shown to improve the outcome. Because there are the variable strategies for stratified risk evaluation and individual treatment between institutions, there are too complicated to generalize. LQTS directed treatment options are presented as the optimal approach in individualized plan, considering of risk-benefit about life style modification, application of medication (like beta-blockers), ICD Implantation, LCSD, procedure side effects, and patient's compliance. We investigated the genotype-phenotype, therapeutic plan and outcomes of LQTS in single center who evaluated and treated using clinical materials.

Among total cohort, the median age of diagnosis is 11.0 (0.003-80) years of, while in symptomatic group the first symptom developed at median 10.5 years of age (0.00-80), median age of diagnosis is 11.125 years-old (0.003-80). There have been other studies that described the median age of initial symptom as childhood or early adulthood [25, 26]. *Rohatgi at al. (2017, [23])* reported the 606 patients with LQTS in Mayo clinic, and the median age of diagnosis was a similar age comparing our cohort. For 60 years, getting more perception among clinicians and developing of molecular studies, the approach to the patients was accuracy. In symptomatic group, there was statistically significant longer QTc than in asymptomatic group, and it showed the prolongation of QTc was a good predictor for clinically significance. In many studies,

there have been consistent data which show baseline QTc interval ≥ 500 ms is associated with a high risk of cardiac events [27-29].

For LQTS is an autosomal dominant or recessive inheritance trait, there is no gender difference in patient population. In this cohort, there was no significant difference in gender either and no significant gender difference in diverse clinical manifestations. However, when divided into two groups by the age of 13 years-old of initial presentation, male was predominant in younger group and female in older group. Several studies demonstrated the similar results and this risk associated with gender difference is coming from hormonal effects [28, 30-32].

The 90 patients were genetically verified. Multiple LQT associated mutations was found in 3 patients. One who was found to carry TAZ mutation presented cardiomyopathy. The pathogenic variant in TAZ is known as the causative substrate of infantile cardiomyopathy [33, 34]. The patient had a brother who died of similar clinical features. As known pathogenic variants at 17 genes including the three major LQT related genes (KCNQ1, KCNH2, and SCN5A) were confirmed in contemporary era. Sometimes clinically suspicious, but if there are no abnormalities found in conventional genetic testing, a comprehensive cardiac-related multi-gene panel sequencing can be used to find the alleged pathogen. Because genetic testing is a significant reference for treatment, accurate diagnosis is important.

Management modalities consist of life style modification, beta blocker, left cardiac sympathetic denervation (LCSD), and implantable cardioverter defibrillator (ICD) implantation [14, 17, 18, 35-37]. Among treatment modalities, beta blockers are reducing significantly in cardiac event in LQTS patients and affected familial members [38]. Untreated asymptomatic patients with genetic proven have high risk about cardiac event.

As the LQTS patients had prescribed beta blocker, the beta blockers are extremely effective [15, 39, 40]. Regrettably, cardiac events persist to present while the patients are taking the prescribed beta blockers [38]. Among LQT3 patients who were verified SCN5A gene mutation, 4 patients had prescribed sodium channel blockade, “mexiletine” [14, 41, 42]. Two in four patients got ICD implantation under maintaining medication. Another sodium channel blockade, “flecainide” applied 2 patients who are composed 1 LQT7 and 1 LQTM. The Andersen-Tawil syndrome patient who was found the pathogenic variant in KCNJ2 is controlled using propranolol and flecainide [43-45].

Of those patients in our study with an ICD, nearly 28% received their device as primary prevention (If including ICD indication but patient refused case, almost 31%). *Horner et al (2010, [46])* reported that the proportion of primary prevention is nearly 85% patients among 51 patients. It comes from different enroll cases demographic data (our study investigated more young patients). In our study, 52% of ICD recipients had received the appropriate shock. Importantly, family history of sudden cardiac death is a powerful factor that influences the decision making process for an ICD indication. However, lots of combining influence are complicating, an ICD decision based solely on a positive family history should be discouraged in the management of LQTS patients.

Life-style modification, β-blockers, LCSD, and ICD implantation are important therapeutic modalities in proper management of patients with LQTS. Prudent consideration is needed before making a decision according to evidence-based and individualized therapeutic approaches. Therefore, here we proposed the management strategy in LQTS (**Figure 9**).

There are some limitations in our study. The most important limitation is the small sample size. Because LQTS is a group of heterogeneous clinical characteristics and genetic disorder, the

sample size is not enough to compare with each clinical or genetic subgroup. And our study has a retrospective design, there were some cases that the items for data analysis were omitted on medical records. These made our studies incomplete.

Chapter 5. Conclusion

Recently, with the progression of genotype in LQTS, the recognition of the molecular pathogenesis and the genetically tailored therapy are fostered. Devastating cardiac events was prevented with good long term outcome in the genetically confirmed and properly managed LQTS patients in this study. It may be the crucially important that the rigorous genetic analysis, the risk stratification, and the appropriate therapy based LQTS related individual phenotype. Here, based our data, we proposed the management strategy in LQTS.

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Tables and Figures

Table 1. Total cohort characteristics and Comparisons between asymptomatic patients and symptomatic patients.

	Entire cohort (N=105)	**Asymptomatic** (n=35, 33.3%)	**Symptomatic** (n=70, 66.7%)	**P Value**
Female	48 (46)	11 (33)	37 (51)	NS
Age of diagnosis, yrs	11.00 (0.003-80.0)	10.0 (0.005-53.0)	11.125 (0.003-80.0)	NS
Median QTc interval, ms *	525 (422-693)	**505 (442-600)**	**533.5 (422-693)**	**0.003**
Symptomatic	70 (67)	0	70 (100)	
Syncope/Seizure	38 (54.3)	NA (Not applicable)	38 (54.3)	
Syncope with stress	24 (34.3)	NA (Not applicable)	24 (34.3)	
Fetal arrhythmia	3 (4.2)	NA (Not applicable)	3 (4.2)	
Pt with Sx presentation<1yr	7 (9.7)	NA (Not applicable)	7 (9.7)	
Cardiac arrest	21 (30.0)	NA (Not applicable)	21 (30.0)	
Family history of SCD *	15 (14.3)	**4 (12.1)**	**11 (15.3)**	**<0.001**
Family history of LQTS	41 (39.0)	22 (66.7)	19 (26.4)	NS
LQTS genotype testing	90 (85.7)	31 (93.9)	59 (81.9)	
Treated follow-up, yrs	6.75 (1.5-20.0)	7.0 (1.58-12.41)	6.67 (1.5-20.0)	NS

Figure 1. The mode of initial presentation in symptomatic group

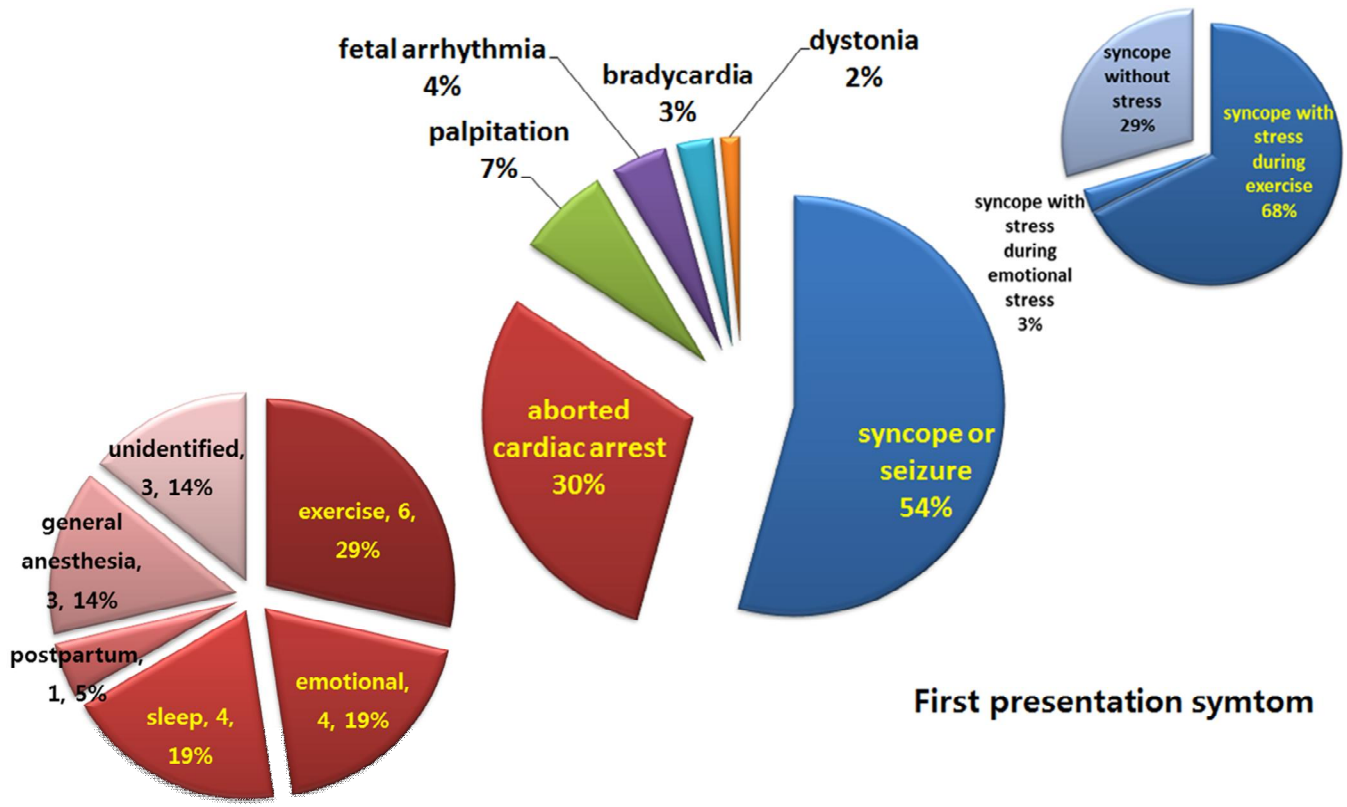


Figure 2. The sexual distribution depending on the initial presentation age

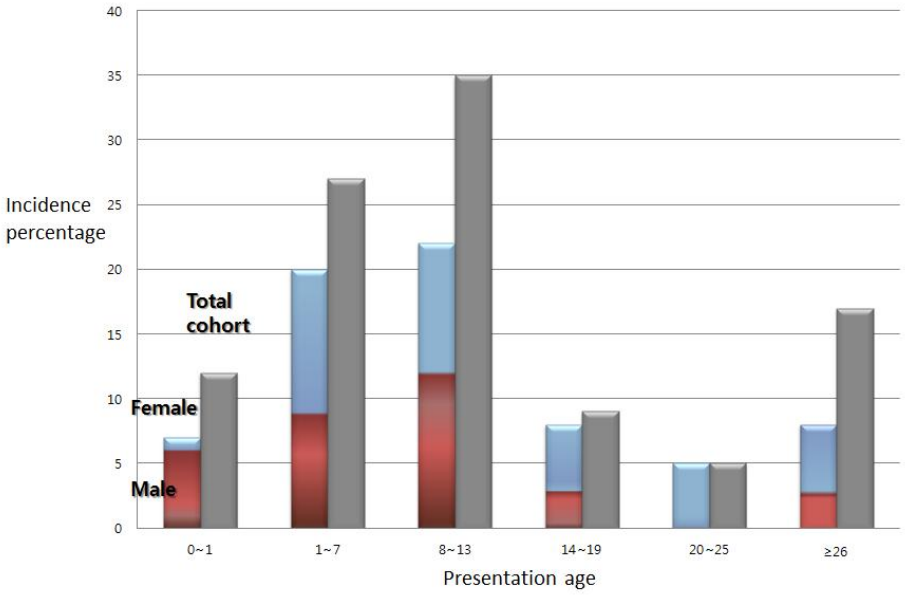


Figure 3. The distributions of genetic mutation confirmed in the genetically verified group

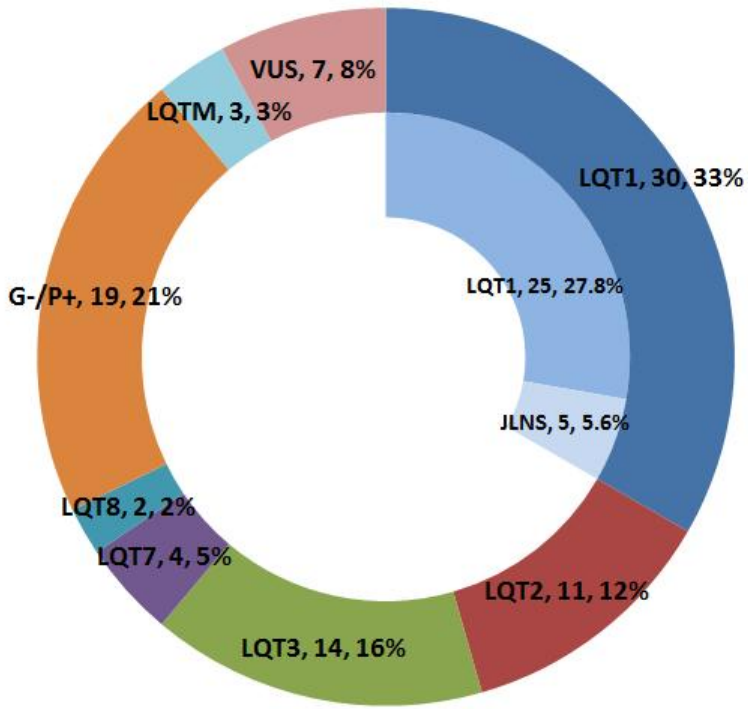


Table 2. Cohort characteristics and comparison by LQTS

	LQT1	LQT2	LQT3	LQT7	LQT8	JLNS	LQTM	VUS	G-/P+
	n=25	n=11	n=14	n=4	n=2	n=5	n=3	n=7	n=19
Female, n(%)	8 (32.0)	6 (54.5)	7 (50)	3 (75)	0 (0)	2 (40)	1 (33)	2 (28.6)	12 (63.2)
Age of diagnosis	9.0 (0.006-53.0)	10.0 (0.005-43.0)	9.5 (0.003-51)	10 (5-13)	1.5 (0.003-3)	**1* (0.083-5.16)**	4.0 (1.25-16.0)	10.0 (4.0-15.0)	13.0 (0.5-58)
Median QTc interval	512 (442-679)	554 (452-682)	518.5 (442-644)	507 (460-537)	581 (572-590)	530 (442-625)	526.0 (494-590)	525.0 (481-596)	534 (422-693)
Symptomatic	10 (40.0)	6 (54.5)	12 (85.7)	2 (50.0)	1 (50.0)	1 (20.0)	2 (66.7)	6 (85.7)	17 (89.5)
Cardiac arrest (initial)	0 (0)	3 (27.2)	**5 (35.7)†‡**	0 (0)	1 (50)	0 (0)	0 (0)	1 (14.3)	3 (15.8)
Family history of SCD	3 (12.0)	2 (18.2)	4 (28.6)	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	3 (15.8)
Family history of LQTS	**18 (72.0)§**	8 (72.7)	8 (57.1)	3 (75)	0 (0)	3 (60.0)	0 (0)	0 (0)	0 (0)
ICD insertion	1 (4.0)	2 (18.2)	**8 (57.1)** ‖	1 (25)	0 (0)	0 (0)	2 (66.7)	0 (0)	4 (21.1)
LCSD done	3 (12.0)	0 (0)	1 (7.1)	0 (0)	0 (0)	2 (40.0)	1 (33.3)	0 (0)	0 (0)
Treated follow-up	7.75 (2.67-19.67)	7.75 (1.58-12.83)	6.46 (1.75-12.92)	9.41 (6.9-10.58)	9.58 (5.9-13.25)	5.0 (3.75-11.41)	4.83 (4.5-20.0)	7.92 (1.67-13.17)	6.16 (1.5-17.8)

* Patients with JLNS had a significantly younger median age of diagnosis compared with the rest (p=0.011)

† Patients with LQTS 3 were significantly more cardiac arrest presentation compared with the rest (p=0.003)

‡ In LQTS 3 group, there were more people who showed cardiac arrest than in LQT 1 group (RR 8.0, p=0.043), by Fisher's exact test.

§ The proportion of patients with a family history of LQTS was significantly more in those patients in LQTS 1 compared with all other LQTS group (p<0.001)

‖ The proportion of patients with a ICD insertion of LQTS was significantly more in those patients in LQTS 3 compared with all other LQTS group (p=0.004)

*, †, §, ‖ Bonferroni correction was applied to reduce type I error.

Figure 4. The genetic distribution of the initial presentation as “abort cardiac arrest”

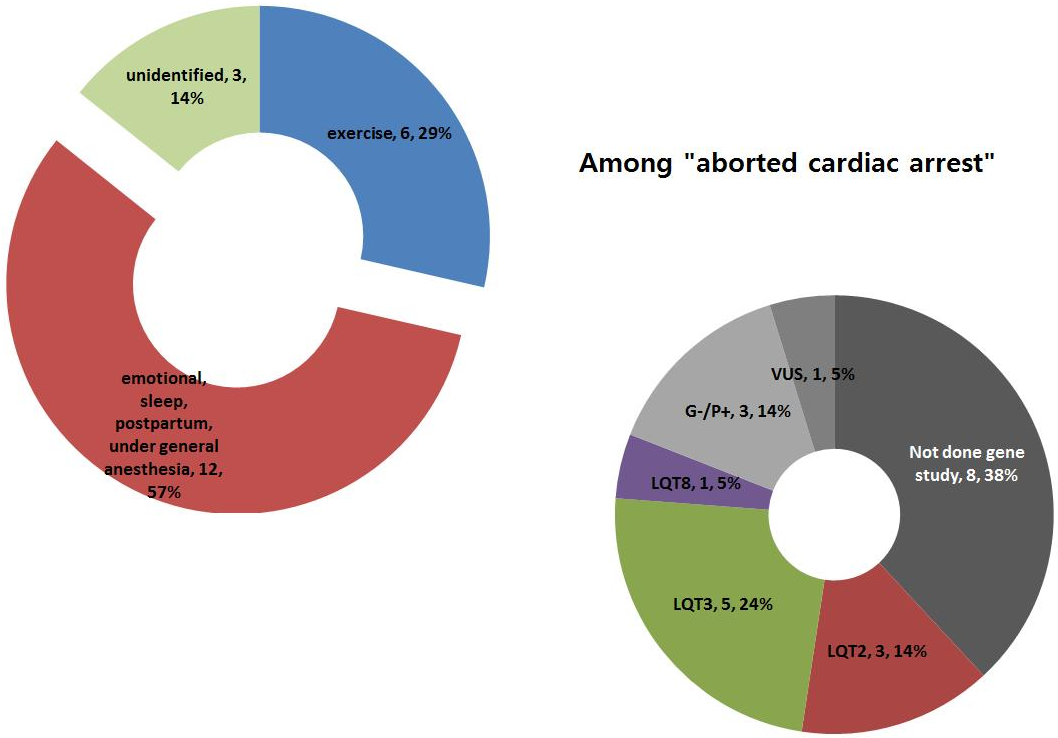


Figure 5. The treatment modalities in symptomatic group

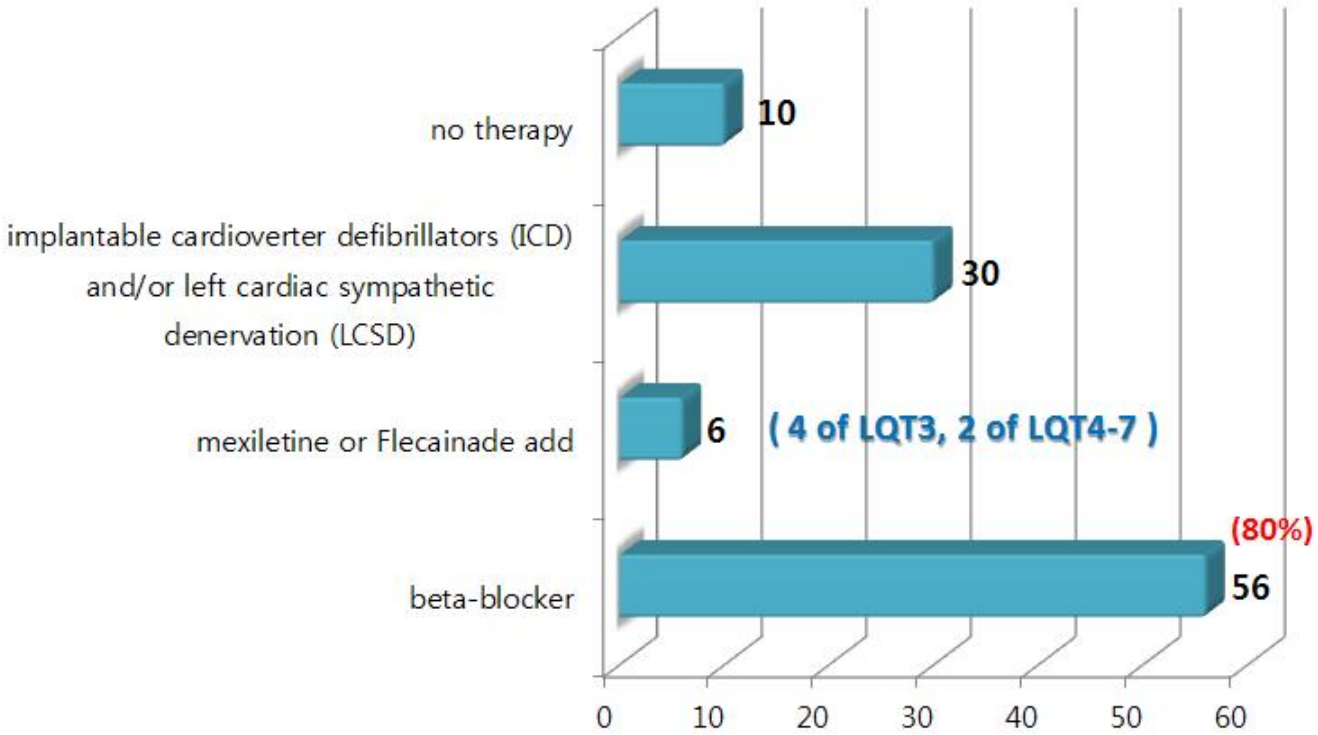


Figure 6. Breakthrough cardiac event-free survival curve for entire genetic verified long QT syndrome.

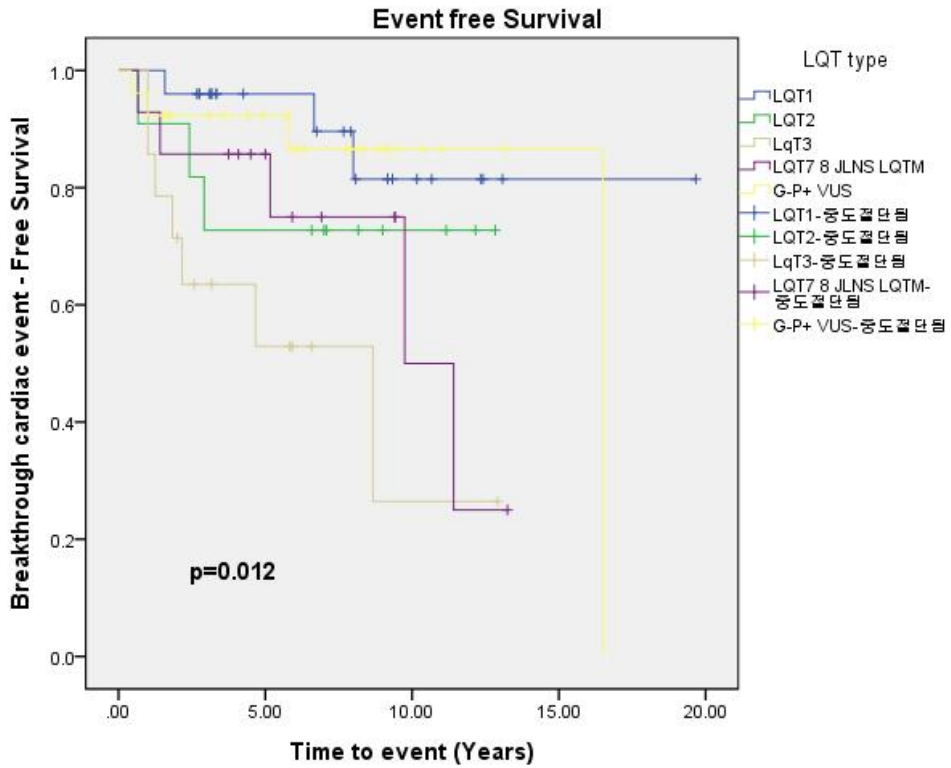


Table 3. Clinical characteristics among 25 patients with LQTS and ICD treatment

Characteristics	**Cases; n (%)**
Median age, years (range)	**14.8** (2.25-79.9)
Median follow-up, years (range)	**6.83** (1.58-20)
Sex, Female	**17 (65)**
Symptom, First presented	26 (100)
Syncope/Seizure	14 (54)
Aborted cardiac arrest	**12 (46)**
Beta-blockers (at pre-ICD state)	14 (54)
Genotype-positive	
LQT1	1 (4)
LQT2	2 (8)
LQT3	**8 (32)**
LQT7	1 (4)
LQTM	2 (8)
Genotype-negative	
G (-)/P (+)	4 (15)
no test/Schwartz, high risk	7 (28)
LCSD prior to ICD	1 (4)

Figure 7. Age at ICD implantation in patients with LQT type.

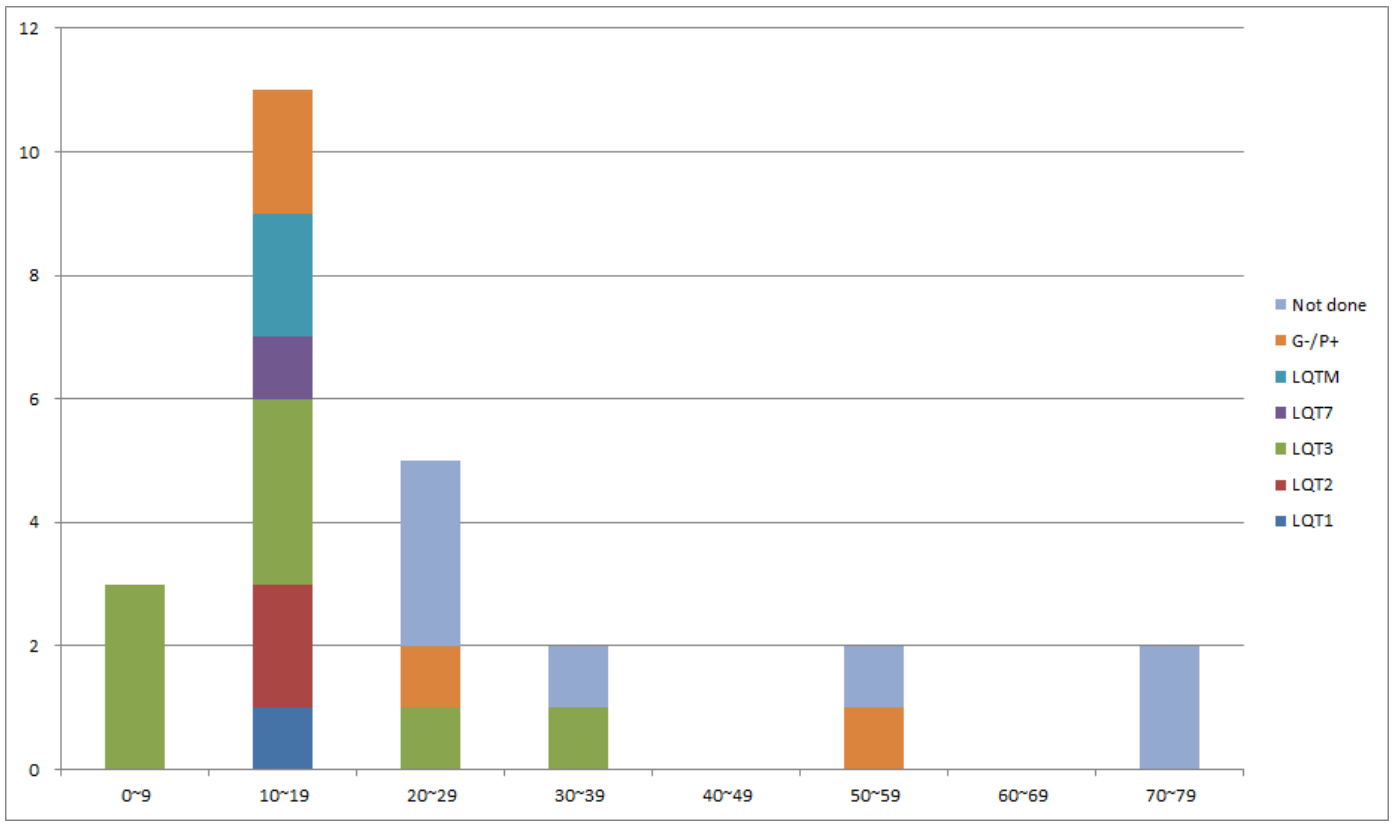


Figure 8. Individual/cumulative risk factors of an appropriate ICD shock

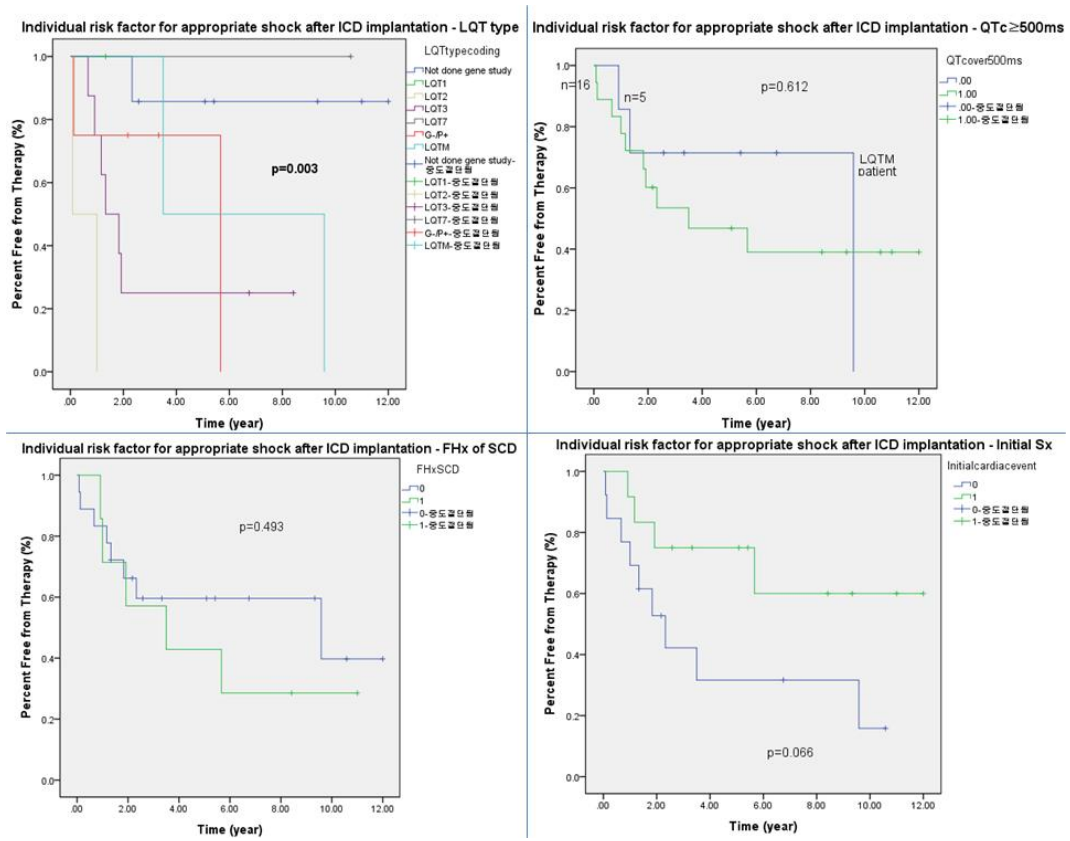
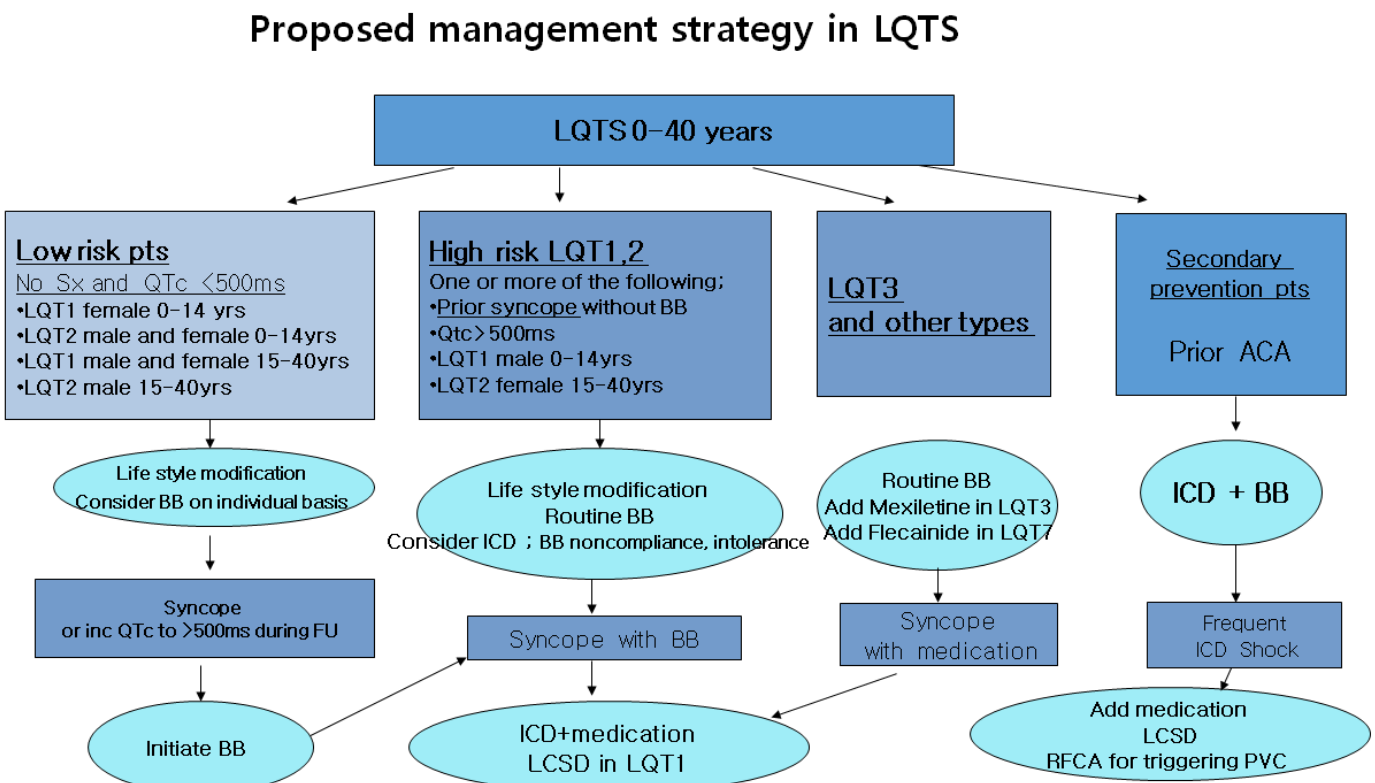


Figure 9. Proposed management strategy in LQTS



Abbreviations and Acronyms

ACA : aborted cardiac arrest

BCE: breakthrough cardiac event

CPVT: catecholaminergic polymorphic ventricular tachycardia

ECG: electrocardiogram

G(−)/P(+): genotype(negative for evaluation about LQT1, 2, 3)/phenotype(positive)

ICD: implantable cardioverter−defibrillator

JLNS: Jervell Langel−Nelson Syndrome

LCSD: left cardiac sympathetic denervation

LQTM: multiple long QT syndrome−associated mutations

LQTS: long QT syndrome

ms: milli−second

QTc: corrected QT interval (using *Bazett's formula*)

SCD: sudden cardiac death

TdP: torsades de pointes

VUS: variant of uncertain significance

국문초록

배경: 선천성 QT연장증후군은 치명적인 유전적 이온 채널병증으로 심실성 부정맥을 특징으로 하며, 이는 심실 재분극 시간의 비정상적인 연장을 야기하여 급성 심정지로 인한 사망을 야기한다. 최근에, 유전학적으로 선천성 QT연장증후군과 관련된 17개의 유전자 변이를 확인하였다. 선천성 QT연장증후군은 유전자형-표현형의 연관성에 따라, 전혀 증상이 없는 환자부터 급성 심정지로 인한 사망까지 그 임상상이 다양하다.

목적: 본 연구는 한국의 한 단일 기관에서 진단되고 치료받고 있는 105명의 QT연장증후군 환자들의 유전학적 진단과 현재 치료지침, 임상상의 경과를 연구하였다.

방법 및 결론: 우리는 105명의 선천성 QT연장증후군 환자들(여성은 48명; 45.7%)를 대상으로 후향적 연구를 하였다. 첫 증상이 나타난 중간 나이는 10.5세 (0.0-80.0) 이었다. 첫 증상으로는 쓰러지거나 경기와 같은 정신을 잃는 증상을 38명 (54.3%), 21명 (30%)에서 명백한 심정지로, 3명 (4.2%)에서 태내 부정맥을 보였다. 선천성 QT연장증후군으로 진단된 중간 나이는 11세 (0.003-80) 이었다. 105명 중 90명에서 유전적인 검사를 진행하였으며, 그 구성은 선천성 QT연장증후군 1형 (27.8%), 2형 (12.2%), 3형 (15.6%), 4-8형 (6.6%), JLNS (5.6%), 그리고 VUS (7.8%) 이었다. 유전학적 검사를 시행한 90명의 환자들 중에 2개 이상의 복합적인 문제 유전자가 확인된 환자가 3명 (3.3%)이었다. 72명의 선천성 QT연장증후군 관련 문제 유전자를 갖는 환자들과 그 환자들의 가족 중 문제 유전자가 확인된 18명의 가족 구성원이 연구에 포함되었다. 환자와 가족 구성원간의 연구를 통하여, 선천성 QT연장증후군 문제 유전자의 유전투과도는 51%이었다. 첫 발현으로 증상을 보였던 그룹에서 증상이 없었던 그룹에 비하여 통계적으로 유의하게 QTc 간격이 길었다. (533.5ms, 505ms, p=0.003). 저벌-

랑게 닐슨 증후군 (JLNS)으로 진단된 환자들이 다른 선천성 QT연장증후군 아형보다 통계적으로 유의하게 어린 연령에 진단되었다 (중간 나이 1세, p=0.011). 전체 연구된 환자들의 중간 추시기간은 6.75년 (1.5-20.0)으로, 이 기간동안 77.1%인 81명에 있어 추시기간동안 어떠한 선천성 QT연장증후군에 의한 심장성 이벤트 (예를 들면, 실신이나 정신소실, 또는 심정지) 를 경험하지 않았다. 첫 발현으로 증상을 보였던 그룹에서 중간 추시기간인 6.67년 동안, 10명 (14%)에서는 환자 순응도 관련되어 치료 하지 않았고, 56명인 80%에서는 베타차단제를 처방하였으며, 25명 (35%, 제세동기 삽입시 중간 나이 14.8세, 2.25-80)에서는 제세동기를 삽입하였다. Flecainide 또는 Mexiletine은 4명의 3형, 2명의 4-7형으로 분류된 환자들에게 적용되었다. 좌심성교감 신경절제 수술 (LCSD)은 총 7명의 환자에게서 시행되었다. 선천성 QT연장증후군 1형에서 5명, 3형에서 1명, 복합 선천성 QT연장증후군 관련 유전 변이를 보인 환자에서 1명이 시행받았다. 제세동기를 삽입한 25명의 환자 중에서, 14명의 유전학적 검사를 확인하였고, 1형 1명, 2형 2명, 3형 8명, 7형 1명, 복합 선천성 QT연장증후군 2명이 포함되었다. 제세동기 삽입후 중간 추시기간 6.83년 (1.58-20.0) 동안, 13명이 생명을 위협하는 부정맥에 대하여 삽입된 제세동기에 의한 적절한 치료로 생명을 구했다. 전 연구에 포함된 환자들 중에서 3형으로 진단된 심근병증을 동반한 1명을 제외하고 나머지는 모두 생존하여 있다.

결론: 최근에 선천성 QT연장증후군에 대한 유전학적인 진단이 비약적인 발전을 거듭하면서, 유전학적인 인식과 함께 그 병인론에 따른 유전학적 맞춤형 치료가 발전하고 있다. 본 연구에서는 선천성 QT연장증후군 환자들에게 유전학적인 확진과 함께 적절한 치료를 함으로써 끔찍한 심장성 이벤트를 예방하고, 좋은 장기예후를 보일 수 있음을 확인하였다. 유전형을 확인하기 위한 적극적인 유전학적 분석, 위험 층화를 통한 위험도 평가, 그리고 각 환자 개개인의 개별

적인 표현형에 관련된 근거 중심의 적절한 치료가 매우 중요하다.

주요어 : 선천성 QT증후군; 유전학; 급성 심정지; 예후

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