Clinical and genetic profile of congenital long QT syndrome in Hong Kong: a 20-year experience in paediatrics

SY Kwok, Anthony PY Liu, Cindy YY Chan, KS Lun, Jasmine LF Fung, Christopher CY Mak, Brian HY Chung *, TC Yung

ABSTRACT

Introduction: Congenital long QT syndrome (LQTS) is a genetically transmitted cardiac channelopathy that can lead to sudden cardiac death. This study aimed to report the clinical and genetic characteristics of all young patients diagnosed with LQTS in the only tertiary paediatric cardiology centre in Hong Kong.

Methods: This is a retrospective review of all paediatric and young adult patients diagnosed at our centre with LQTS from January 1997 to December 2016. The diagnosis of LQTS was established with a corrected QT interval (QTc) ≥480 ms, Schwartz score of >3 points, or the presence of a pathogenic mutation.

Results: Fifty-nine patients (33 males) from 52 families were included, with a mean age of 8.17 years (range, 0.00-16.95 years) at presentation. Five patients had concomitant congenital heart diseases. The mean follow-up duration was 5.33 ± 4.65 years. The mean QTc in the cohort was 504 ± 47 ms. They presented with syncope and convulsion (49%), cardiac arrest (10%), bradycardia and neonatal atrioventricular block (12%). Fifteen (25%) patients were asymptomatic at diagnosis. Thirty-eight (64.4%) patients were confirmed to have a pathogenic mutation for LQTS genes. Forty-five (76.3%) patients received beta blocker therapy. Thirteen (22.0%) patients required implantable cardioverter defibrillator. There was no mortality in the study period. The 1-, 5-, and 10-year breakthrough cardiac event–free rates were 93.0%, 80.7%, and 72.6%, respectively.

Conclusion: Identification of the disorder, administration of beta blockers, and lifestyle modification can prevent subsequent cardiac events in LQTS. Genotyping in patients with LQTS is essential in guiding medical therapy and improving prognosis.

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New knowledge added by this study

- Two-thirds of young long QT syndrome patients in Hong Kong carry pathogenic mutations. Concomitant congenital heart disease is present in 8.5% of these patients.
- The current treatment strategy for young long QT syndrome patients in Hong Kong includes lifestyle modification, beta blocker therapy, implantation of a cardioverter defibrillator, and sympathectomy.
- Young long QT syndrome patients in the present study have good prognosis. No mortality was reported in the medium-term follow-up.

Implications for clinical practice or policy

- Genetic testing should be performed for all patients with clinical diagnosis of long QT syndrome, to facilitate timely genotype-guided therapy and early detection of affected family members.
- The diagnosis of long QT syndrome should be considered in young patients presenting with syncope and convulsions, as well as those with bradycardia and atrioventricular block in early infancy.
- Sudden cardiac death associated with long QT syndrome is preventable. Facilities for genetic testing and inherited arrhythmia assessment are recommended.

Introduction

Congenital long QT syndrome (LQTS) is a life-threatening cardiac arrhythmia syndrome, which leads to sudden death in young people.[1] Congenital LQTS is characterised by prolonged QT interval (QTc) on electrocardiogram (ECG) and occurrence

香港先天性長QT綜合症的臨床和遺傳特徵：20年兒科經驗

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引言：先天性長QT綜合症（LQTS）是遺傳性心臟病，可導致心臟性猝死。本研究旨在報告於香港唯一的三級兒科心臟科中心確診LQTS所有年輕患者的臨床和遺傳特徵。

方法：這項回顧性研究分析1997年1月至2016年12月期間在本中心確診LQTS的所有兒科和年輕患者，並基於經調正QT間期達480 ms或以上、Schwartz評分3分以上，或存在致病突變診斷LQTS。

結果：納入52個家庭共59名患者（33名為男性），確診或病發時平均年齡為8.17歲（年齡介乎0.00至16.95歲）。5名患者伴有先天性心臟病。平均隨訪時間為5.33 ± 4.65年，平均QTc間期為504 ± 47 ms。患者曾出現暈厥和驚厥（49%）、心臟驟停（10%）、心搏過緩和新生兒房室傳導阻滯（12%）。15名（25%）患者在診斷時並無症狀。確認38名（64.4%）患者具有LQTS基因的致病突變。45名（76.3%）患者接受β受體阻滯劑治療。13名（22.0%）患者需要植入式心律轉復除顫器。研究期間沒有死亡病例。1年、5年及10年無隨後的心臟事件發生率分別為93.0%、80.7%和72.6%。

結論：鑑定疾病、使用β受體阻滯劑和改變生活方式可預防LQTS隨後的心臟事件。LQTS患者的基因分型對於指導藥物治療和改善預後至關重要。

of syncope or cardiac arrest. During the past two decades, there have been major advancements in the understanding of the genetic factors underlying the clinical manifestations, prognosis, and subtype-specific therapy of LQTS.[1-3] Seventeen disease-causing LQTS genes have been identified, each of which can lead to dysfunction in the potassium, calcium, or sodium cardiac ion channels.[4] In this study, we review the clinical characteristics, genetic profile, management strategy, and outcome of our local LQTS paediatric patients.

Methods

Study population

Our study included all children, adolescents, and young adults diagnosed with congenital LQTS from January 1997 to December 2016 in the Department of Paediatric Cardiology, Queen Mary Hospital, which is the only tertiary paediatric cardiology referral centre in Hong Kong. All except three patients were Chinese. Diagnosis of congenital LQTS was reviewed with reference to the 2015 European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[5] Long QT syndrome was diagnosed with either corrected QTc ≥480 ms in repeated 12-lead ECG measurements or LQTS risk score >3 points, as proposed by Schwartz et al.[6] The presence of a confirmed pathogenic LQTS mutation, irrespective of the QTc, was also used for diagnosis of LQTS. Secondary causes of LQTS were excluded.

Demographic data, clinical presentation, family history, QTc at presentation, and genetic tests were retrospectively reviewed. Clinically important presentation was defined as clinical symptoms or rhythm disturbances that warranted concern. Incidental findings of isolated prolonged QTc were not regarded as clinically important presentation.

We reviewed the treatment modalities, including beta blocker therapy, implantable cardioverter defibrillator (ICD), permanent pacemaker, and left cardiac sympathetic denervation. Clinical outcomes up to December 2016 were summarised. Syncope, seizure, aborted cardiac arrest, appropriate ICD shock, or sudden cardiac death after diagnosis of LQTS were considered as breakthrough cardiac events.

Genetic test

Genetic tests were offered to all patients after informed consent was provided by their parents or guardians. Blood samples were sent to the Molecular Genetics Laboratory of Victorian Clinical Genetic Services, Melbourne, Australia, for genetic testing. Before 2014, six common LQTS genes were tested (*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2*) by sequencing of the entire coding region of all known transcripts of the genes. Multiplex ligation-dependent probe amplification analysis was performed on five genes (*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2*) to detect deletions or duplications. After 2014, next-generation sequencing was used to identify mutations in an arrhythmia gene panel to replace sequencing of the six LQTS genes (details of the arrhythmia full panel can be found at http://www.vcgs.org.au/tests/cardiac-gene-panels). Before referral to our unit, 13 patients had genetic tests performed by local or overseas genetic testing centres.

Mutations in the LQTS loci classified as pathogenic or likely pathogenic were considered as genotype positive in our cohort. Cascade testing was offered to first-degree relatives of patients identified as genotype positive.

Statistical analysis

Statistical analysis was performed with the SPSS (Window version 17.0; SPSS Inc, Chicago [IL], United States). Continuous variables were expressed as mean ± standard deviation, median and range. We used the standard *t* test for comparisons of continuous data. The $P<0.05$ were deemed statistically significant. Kaplan-Meier survival curves were created with censoring at first breakthrough cardiac event or last follow-up, and analysis was made using the log rank test.

Results

Demographics and clinical characteristics

During the study period, 59 patients (33 males) in 52 families were identified who fulfilled the diagnostic criteria as described. Nine individuals were diagnosed by ECG screening of our index cases including a 25-year-old young adult. The mean follow-up duration of the cohort was 5.33 ± 4.65 years. Four patients were lost to follow-up, but no death was reported in the territory-wide Hospital Authority electronic patient record. Five patients were under the care of adult cardiologists at the follow-up.

Table 1 shows the characteristics of our patients. The mean age at diagnosis was 8.12 ± 5.19 years (range, 0-25 years). For those patients who had clinically important presentation, the mean age at presentation was 8.75 ± 5.12 years (range, 0.00-16.95 years). Boys were younger than girls at presentation (6.39 ± 5.00 years vs 10.51 ± 4.55 years, P=0.016).

The mean QTc of the cohort was 504 ± 47 ms. The median Schwartz score was 4 points (range, 1-6 points). Index patients had longer mean QTc (512 ± 46 ms) when compared with screened family members (462 ± 25 ms, P=0.002).

Five (8.47%) patients had congenital heart defects: secundum atrial septal defect (n=1; genotype negative), ventricular septal defect (n=1; LQTS type 2 [LQT2]), tetralogy of Fallot (n=2; LQT2 and LQTS type 8 [LQT8]), and transposition of great arteries (n=1; genotype negative). One patient had bilateral sensorineural hearing loss and was subsequently confirmed to have LQTS type 1 (LQT1).

Mode of presentation

Figure 1 illustrates the mode of initial presentation of our patients. Forty-four patients had clinically important presentation at diagnosis. Syncope without convulsion was the most common mode of presentation (37.3%), among which around 40% of cases were stress-related. Convulsion was also a common symptom (12%). Aborted cardiac arrest occurred in six (10.2%) individuals.

Three patients presented with sinus bradycardia, one of whom was detected prenatally. Four patients, including three infants, had 2:1 atrioventricular (AV) block at diagnosis. A significant proportion of patients with LQTS (25.4%) did not have clinically important presentation at diagnosis; most of them had incidental ECG findings of prolonged QTc during medical check-ups or were identified by family cascade screening.

Treatment and outcome

The clinical outcomes of patients with LQTS in our cohort with clinically important presentation are summarised in Figure 2.

Beta blocker

All patients were offered beta blocker therapy. However, 14 patients refused beta blocker (11 patients had clinically important presentation). Seven patients were on beta blocker but stopped subsequently.

Metoprolol was the initial choice of beta blocker for most of our patients (n=27), whereas 10 patients had atenolol as initial choice. Propranolol was used in eight infants. Eight patients receiving metoprolol, atenolol, or propranolol later changed to nadolol to enhance compliance or for better control of breakthrough symptoms. Mexiletine was added as an adjuvant therapy for five patients with LQTS type 3 (LQT3) who were symptomatic. Among the 31 patients with an initial history of convulsion, syncope, or dizziness (mean follow-up duration, 4.81 ± 3.84 years), 21 became asymptomatic after medication and/or lifestyle modification. Two patients who had recurrent symptoms after initial beta blocker therapy became event-free after a change from metoprolol/atenolol to nadolol. Patients without clinically important presentation at

TABLE 1. Cohort characteristics of patients with LQTS

	Entire cohort (n=59)	Presentation positive* (n=44)	Presentation negative* (n=15)	P value	LQTS type 1 (n=10)	LQTS type 2 (n=12)	LQTS type 3 (n=7)	P value
Male, No. (%)	33 (55.9%)	25 (56.8%)	8 (53.3%)	NS	9 (90.0%)	8 (66.7%)	3 (42.9%)	NS
Age at diagnosis, mean ± SD (years)	8.12 ± 5.19	8.75 ± 5.12	9.27 ± 7.43	NS	7.15 ± 3.30	8.84 ± 6.25	7.50 ± 6.41	NS
QTc at diagnosis, mean ± SD (ms)	504 ± 47	514 ± 48	476 ± 27	0.005	499 ± 50	518 ± 39	506 ± 68	NS
Schwartz score, median (range)	4 (1-6)	4 (3-6)	3 (1-4)	<0.001	5 (3-5.5)	5 (3-6)	4 (1-5)	NS
Proband, No. (%)	50 (84.7%)	43 (97.7%)	7 (46.7%)	-	9 (90.0%)	11 (91.7%)	5 (71.4%)	NS

Abbreviations: LQTS = long QT syndrome; NS = not statistically significant; QTc = QT interval; SD = standard deviation

* 'Presentation' refers to clinically important presentation

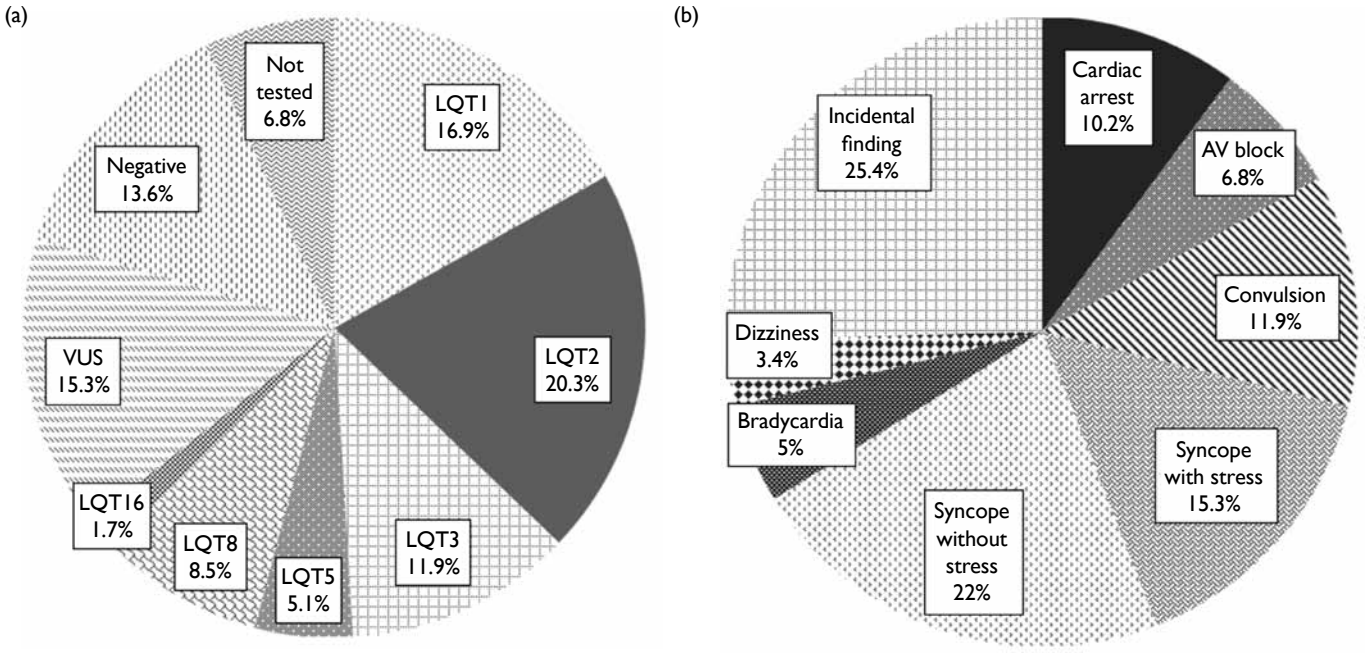

FIG 1. Genotypes and clinical presentations of our cohort of patients with long QT syndrome (n=59). (a) Genotypes and (b) clinical presentations of patients with long QT syndrome

Abbreviations: AV block = atrioventricular block; LQT = long QT syndrome; VUS = variants of unknown significance

diagnosis remained asymptomatic with or without beta blocker therapy, irrespective of presence of documented pathogenic mutation.

Implantable cardioverter defibrillator

Implantable cardioverter defibrillator was implanted in 13 patients, whose mean QTc was 501 ± 42 ms. Six of these patients had initially presented with aborted ventricular tachycardia (VT)/ventricular fibrillation (VF) arrest. Five patients received ICD implantation because of recurrent symptom or subsequent VT/VF despite beta blocker therapy. Two of these five patients experienced appropriate shocks after ICD implantation. One patient with pathogenic *KCNE1* mutation had syncope due to sinus arrest with long pauses; ICD was offered for primary prevention of sudden death in addition to pacing therapy. One patient who had AV block at birth developed subsequent unprovoked syncope at aged 6 years despite medical treatment and his pacing system was upgraded to ICD. In total, four patients experienced appropriate ICD shocks despite beta blocker treatment. There were no more ICD shocks after reinforcement of medication compliance, adjustment of dosage, and in one patient switching of metoprolol to nadolol.

Left cardiac sympathetic denervation

Left cardiac sympathetic denervation was performed via video-assisted thoracoscopic approach in two patients, together with ICD therapy. Both of them were free of cardiac events on follow-up.

Pacemaker

Pacemakers were implanted in five patients. Four of these five patients had functional AV block due to prolonged QTc. Normal AV node conduction recovered with time in these four children. The fifth patient had complete heart block after surgical repair of congenital heart condition (transposition of great arteries with ventricular septal defect).

The Kaplan-Meier survival curve is shown in Figure 3. Overall, the breakthrough cardiac event–free survival was 93.0% ± 0.034% at 1 year, 80.7% ± 0.065% at 5 years, and 72.6% ± 0.080% at 10 years for the entire cohort. Patients who had clinically important presentation at baseline had a higher risk of developing breakthrough cardiac events (P=0.048) compared with those who did not. There was no mortality during the study period.

Genotype

All but four patients underwent genetic testing. Testing was not possible in two patients owing to loss to follow-up before genetic testing could be offered; these two patients were strong phenotypes of LQTS with Schwartz scores of 4 and 5 points, respectively. The other two patients were first-degree relatives of

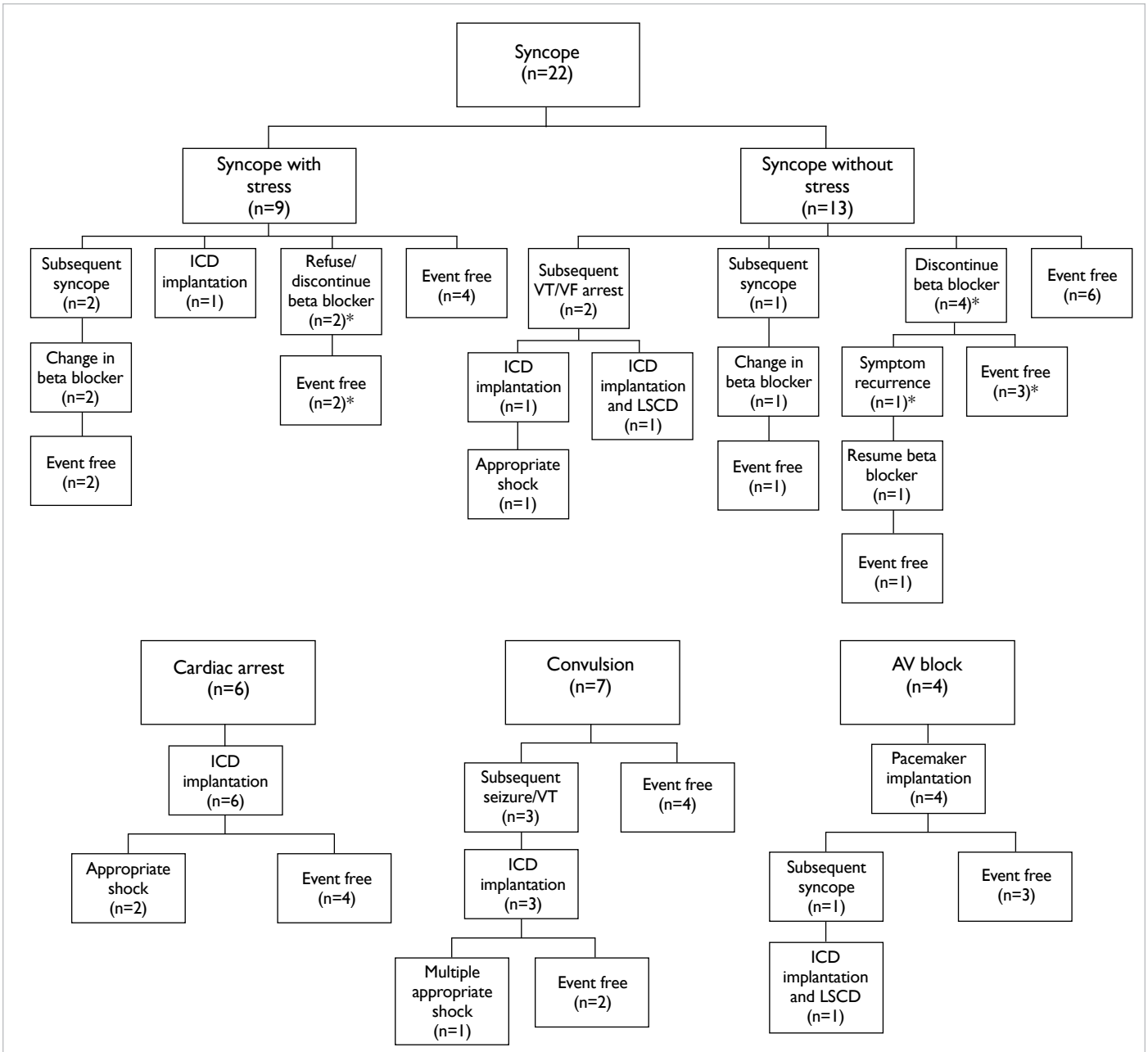

FIG 2. Outcomes of patients with long QT syndrome with clinically important presentation

Abbreviations: AV block = atrioventricular block; ICD = implantable cardioverter defibrillator; LCSD = left cardiac sympathetic denervation; VF = ventricular fibrillation; VT = ventricular tachycardia

* Patients were not on beta blocker therapy

confirmed genotype-positive patients.

Seven patients were genotype negative. Four of them were tested before 2014. Nine patients had their mutated genes classified as variants of unknown significance. We also included three patients (LQT1, n=2; LQT2, n=1), reported by Mak et al,[7] whose genetic tests were performed in a local laboratory.

Thirty-eight (69.1%) patients among those tested were confirmed to have pathogenic mutations for LQTS (Table 2). Eight mutations were novel (8/33, 24.2%). Most of the pathogenic mutations were missense mutation (30/33, 90.9%). Ten (16.9%) patients had LQT1 (*KCNQ1*). Twelve (20.3%) patients had LQT2 (*KCNH2*), whereas seven (11.9%) patients had LQT3 (*SCN5A*). Three patients had LQTS type 5 (*KCNE1*). There were five patients (three families) with LQT8 resulting from a rare pathogenic mutation in *CACNA1C*. LQT8 is linked

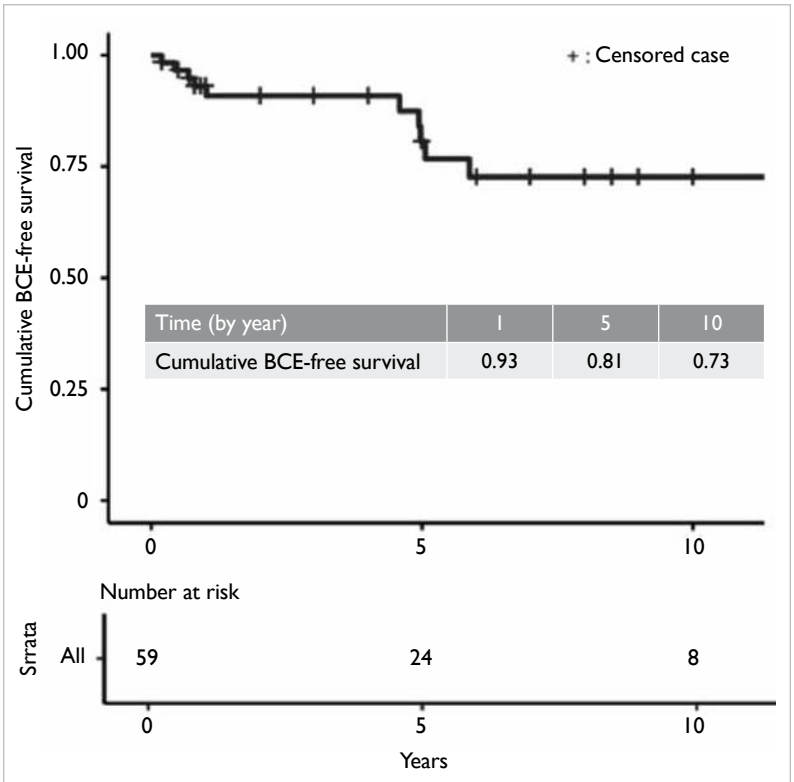

FIG 3. Breakthrough cardiac event (BCE)–free survival in treated long QT syndrome patients

to Timothy syndrome with multiple extracardiac manifestations. Only one of our patients with LQT8 had classical features of Timothy syndrome, with syndactyly, developmental delay, and congenital heart defect (tetralogy of Fallot). One patient had LQTS type 16 (*CALM3*). Figure 1 shows the details of the genotype information of LQTS genes identified.

Clinical characteristics of patients with LQT1, LQT2, or LQT3 are detailed in Figure 4. Syncope with stress was the predominant presentation in patients with LQT1 (60%). In contrast, syncope without stress was the main form of presentation in patients with LQT2 (41.7%). In patients with LQT3, around 30% had an initial presentation of aborted VF cardiac arrest. A high proportion (50%) of patients with LQT3 developed subsequent VT/VF despite medical therapy, compared with 14.3% in patients with LQT1 and 28.6% in patients with LQT2.

Nine patients were identified to have LQTS during family screening of index patients. Two patients had strong phenotypes but did not have genetic tests. Five patients had LQTS phenotypes with confirmation by genetic testing. Two asymptomatic children in the same family were referred to us and were identified by cascade screening of their father's pathogenic mutation.

Discussion

Long QT syndrome is a rare inherited disorder associated with an increased propensity to polymorphic VT/VF, syncope, and sudden cardiac death. In this report, we describe the clinical features and genetic profile of 59 LQTS paediatric patients managed in the only tertiary paediatric cardiology referral centre in Hong Kong over 20 years.

Long QT syndrome diagnosis

The prevalence of childhood LQTS was estimated to be 1:2000 in an Italian birth cohort.[8] In a recent Japanese study, the estimated probability of diagnosing LQTS was 1:3300 in children aged 6 years and 1:1000 in those aged 12 years.[9] Our results indicate that the prevalence of diagnosed LQTS in Hong Kong children was less than 1:10 000, suggesting an underdiagnosis of the condition. This is likely due to under-recognition of symptomatic LQTS in young patients who were treated for recurrent seizure and unexplained syncope. Without an ECG screening programme, many asymptomatic LQTS children also remain undiagnosed.

The lack of comprehensive screening for family members of adult LQTS probands is another reason for underdiagnosis, as only two children from a single family were referred to us from adult cardiologists over the 20-year study period. In addition, a 5-year-old child of a mother with known LQTS was not referred until he presented with convulsions.

Molecular autopsy for young victims of sudden cardiac death is not implemented in Hong Kong. In many developed countries, affected family members of LQTS sudden death victims are identified early through this pathway to prevent sudden cardiac death. We believe that the total number of symptomatic and asymptomatic young patients with LQTS in Hong Kong is much higher than what we have studied in our single tertiary referral centre.[10,11]

Long QT syndrome presentation

Congenital LQTS is usually diagnosed in patients presenting with syncope, unexplained seizure, and aborted cardiac arrest. The mean QTc of our patients was 504 ± 47 ms, and median Schwartz score of the entire cohort was 4 points (range, 1-6 points). This indicates that the patients that were referred to our centre were patients with more severe symptoms, resulting in a higher likelihood of a diagnosis of LQTS, based on clinical criteria.

Previous reports have shown that the risk of clinical events in boys (aged <15 years) with LQTS is significantly higher than that in girls with LQTS.[12] In our cohort, we also confirmed that symptomatic boys were significantly younger than girl at diagnosis or presentation.

TABLE 2. Genetic information of our LQTS cohort (33 mutations in 38 patients)

Nucleotide	Classification of mutation	Clinical implication	Coding effect	Protein position	Novel mutation
Mutation in KCNQ1 (LQTS type 1) (NM_000218.2)					
c.532G>A	Missense	Likely pathogenic	p.(Ala178Thr)	S2/S3	
c.683G>T	Missense/splicing	Likely pathogenic	p.(Arg228Met)	S4	Y
c.782A>G	Missense/splicing	Likely pathogenic	p.(Glu261Gly)	S4/S5	Y
c.845T>C	Missense	Pathogenic	p.(Leu282Pro)	S5	
c.965C>T	Missense	Pathogenic	p.(Thr322Met)	Pore/S6	
c.973G>A	Missense	Pathogenic	p.(Gly325Arg)	Pore/S6	
c.1018T>C	Missense	Pathogenic	p.(Phe340Leu)	S6	
c.1032G>A	Synonymous/splice	Pathogenic	p.(Ala344=)	S6	
c.1831G>A	Missense	Pathogenic	p.(Asp611Asn)	SAR	Y
Mutation in KCNH2 (LQTS type 2) (NM_000238.3)					
c.211G>T	Missense	Pathogenic	p.(Gly71Trp)	N-terminus	
c.316T>C	Missense	Likely pathogenic	p.(Phe106Leu)	N-terminus	Y
c.1501G>A	Missense	Pathogenic	p.(Asp501Asn)	S3	
c.1682C>T	Missense	Pathogenic	p.(Ala561Val)	S5	
c.1714G>A	Missense	Pathogenic	p.(Gly572Ser)	S5/pore	
c.1750G>C	Missense	Pathogenic	p.(Gly584Arg)	S5/pore	
c.1810G>A	Missense	Pathogenic	p.(Gly604Ser)	S5/pore	
c.1810G>C	Missense	Pathogenic	p.(Gly604Arg)	S5/pore	
c.2233_2365del	Deletion/frameshift	Pathogenic	Unknown	CNBD	Y
c.3094C>T	Missense	Likely pathogenic	p.(Arg1032Trp)	C-terminus	
c.3102_3103dupCC	Duplication/frameshift	Pathogenic	p.(Arg1035Profs*23)	C-terminus	
Mutation on SCN5A (LQTS type 3) (NM_001099404.1)					
c.1201T>C	Missense	Likely pathogenic	p.(Ser401Pro)	DI-S6	Y
c.1231G>A	Missense	Pathogenic	p.(Val411Met)	DI/DII	
c.3575G>A	Missense	Pathogenic	p.(Arg1192Gln)	DII/DIII	
c.5287G>A	Missense	Pathogenic	p.(Val1763Ile)	DIV-S6	
c.5296A>C	Missense	Likely pathogenic	p.(Met1766Leu)	DIV-S6	
c.5347G>A	Missense	Pathogenic	p.(Glu1783Lys)	C-terminus	
c.5350G>A	Missense	Pathogenic	p.(Glu1784Lys)	C-terminus	
Mutation in KCNE1 (LQTS type 5) (NM_000219.5)					
c.242A>G	Missense	Pathogenic	p.(Tyr81Cys)	C-terminus	
c.292C>T	Missense	Pathogenic	p.(Arg98Trp)	C-terminus	
Mutation in CACNA1C (LQTS type 8) (NM_199460.3)					
c.1186G>C	Missense	Pathogenic	p.(Val396Leu)	DI-S6	Y
c.1216G>A	Missense	Pathogenic	p.(Gly406Arg)	DI/DII	Y
c.2573G>A	Missense	Pathogenic	p.(Arg858His)	DII/DIII	
Mutation in CALM3 (LQTS type 16) (NM_005184.3)					
c.286G>C	Missense	Likely pathogenic	p.(Asp96His)	EF-hand 3	

Abbreviation: LQTS = long QT syndrome

Sinus bradycardia and functional AV block are well reported in perinatal LQTS.[13-15] The youngest patient in our group presented with fetal bradycardia. We also noted 2:1 AV block in three infants at presentation. Their AV conduction normalised with a significant decrease in QTc during follow-up. Paediatricians or family doctors should suspect LQTS in young infants with slow heart rates.

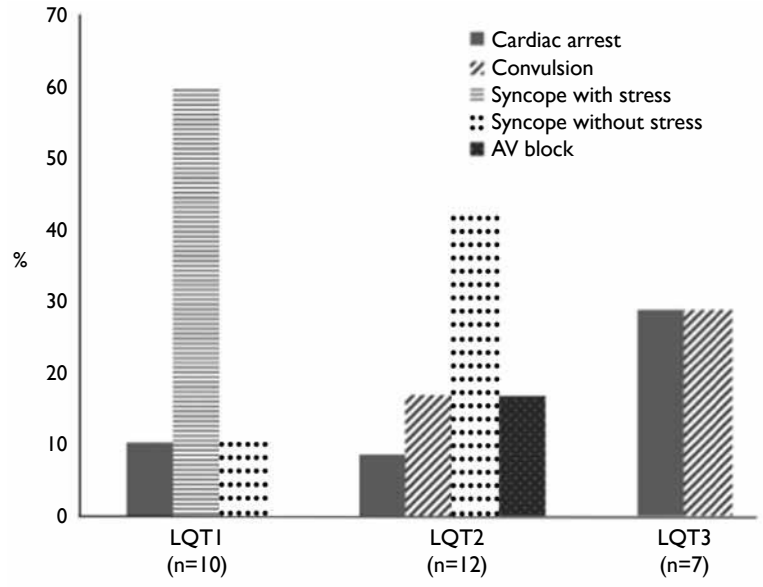

FIG 4. Clinically important presentation of patients with LQT1, LQT2, and LQT3
Abbreviations: AV block = atrioventricular block; LQT = long QT syndrome type

Long QT syndrome and structural congenital heart disease

Few links between LQTS and congenital heart disease have been reported, apart from Timothy syndrome. A recent single-centre review of 49 LQTS genotype-positive patients identified 11 (22%) cases with concomitant conotruncal anomalies and/or aortic arch anomalies.[16] In our cohort, five (8.5%) patients with LQTS had concomitant congenital heart disease. Two cases were diagnosed in the perioperative period. Prolonged QTc in the context of congenital heart disease can be confounded by several factors, including postoperative electromechanical factors, intrinsic, or postoperative QRS abnormalities. Therefore, the diagnosis of LQTS could be masked in patients with congenital heart disease. We suggest that ECG of patients with congenital heart disease should be evaluated carefully for QTc.

Long QT syndrome genotype

Throughout the world, 75% to 80% of patients with LQTS have identifiable genetic mutations, with LQT1, LQT2, or LQT3 accounting for 90% of cases. Pathogenic LQTS genetic mutations were identified in 69.1% of the patients in our cohort who were tested, which is comparable with other LQTS cohorts.[17] Similarly, we had predominant genotypes of LQT1 (10/59, 16.9%), LQT2 (12/59, 20.3%), and LQT3 (7/59, 11.9%). In a recent single-centre study of LQTS in China, LQT2 was also the most common genotype.[18] We also identified five (8.5%) patients with rare *CACNA1C* (LQT8) mutations, all of whom were Hong Kong Chinese. Without a study of a large Chinese population in the past 5 years for cross reference, we cannot be certain whether LQT8 is more prevalent in Chinese than in other ethnic groups.

Long QT syndrome management and outcome

Beta blockers are the mainstay of treatment for all LQTS genotypes. In a registry of 1530 patients with LQTS, all beta blockers seemed equally effective in reducing risk of a first cardiac event after beta blocker initiation. For patients with LQT1, no single type of beta blocker has been found superior, although nadolol was found to be superior for patients with LQT2.[19] However, another study suggested that symptomatic LQT1 and LQT2 patients on metoprolol had a higher rate of recurrence of cardiac events.[20] In the present study, 21 patients were prescribed metoprolol, two of whom required switching to another beta blocker due to recurrent symptoms. Because of the relatively short follow-up duration and small number of patients in our cohort, it is impossible to conclude on the efficacy of each beta blocker for patients with each genotype. Genotype-guided therapy is advocated in contemporary management in LQTS. Based on the available evidence, we are inclined to use nadolol as our first choice in symptomatic LQT2 patients. In symptomatic LQT3 patients, dual therapy using beta blockers and mexiletine are used. Mexiletine is a sodium channel blocker shown to shorten QTc in LQT3 patients.[21,22]

In addition to medical therapy with beta blockers, treatment of LQTS can also include lifestyle modifications, sympathetic denervation, and device therapy. With a multi-modality management strategy and genotype-guided therapy, outcome of LQTS have improved markedly over the past decades. The event-free survival was 96% at 1 year, 93% at 5 years, and 90% at 10 years, as reported recently in a large single-centre study which included 83% asymptomatic probands.[23] In the present study, the breakthrough cardiac event-free survival was 93.0% at 1 year, 80.7% at 5 years, and 72.6% at 10 years (Fig 3). The event rate in the present study is likely higher than that of the abovementioned study because we have a higher proportion of probands (85%), of whom 88% were symptomatic at presentation. Breakthrough cardiac events were mainly related to non-compliance to our treatment advice.

Study limitations

Our study was based on single-hospital data and referral bias is expected. We may have received referral of patients with LQTS with more severe symptoms. In addition, a short duration of follow-up in our patients (mean 5.3 years) may have led to underestimation of clinical cardiac events and mortality.

Future perspectives

Our study demonstrated the high yield of genetic testing and the importance of genetic information in predicting the prognosis of patients with LQTS and guiding their treatment. Early identification of affected family members through cascade screening of mutated gene was also demonstrated. We hope that public genetic services can continue to develop, to enable genetic testing to be offered to all patients with suspected channelopathies. We also advocate the establishment in Hong Kong of inherited arrhythmia clinics or cardiac genetic clinics in the public sector, as implemented in many other countries. Such clinics have proven effectiveness in reducing sudden cardiac death associated with inherited arrhythmia syndrome.[24]

Conclusion

Our study provides insight into the clinical and molecular profiles of young patients with LQTS in the only tertiary paediatric cardiology referral centre in Hong Kong. The LQT1, LQT2 and LQT3 genotypes are the most common in mutation-positive patients. Early identification of LQTS, administration of beta blocker therapy, device therapy, and lifestyle modifications can prevent sudden cardiac death. However, the breakthrough cardiac event survival was only 72.6% at 10 years. Further optimisation of the treatment strategy by genotype-guided therapy may reduce recurrent symptoms and improve prognosis.

Author contributions

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Declaration

All authors have disclosed no conflicts of interest. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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Ethical approval

This study received ethics approval from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong Western Cluster.

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