Clinical and genetic spectrum of hereditary cardiac arrhythmia syndromes

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Clinical and Genetic Analysis of Long QT Syndrome in two Malay Children

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(submitted)
Clinical and Genetic Spectrum of Hereditary Cardiac Arrhythmia Syndromes
Abstract:
Long QT syndrome (LQTS) is predominantly a genetic cardiac arrhythmia disorder. We report clinical and genetic findings in two unrelated Malay children with LQTS. First child presented with intrauterine and neonatal bradyarrhythmia and a QTc of 530ms. Second child had bradyarrhythmia, 2:1 atrioventricular block and a QTc of 560 ms. We have found a Long QT, type 1 causal mutation, p.Ile567Thr in the \( KCNQ1 \) gene in the first child. A pathogenic mutation could not be detected in the second child, explaining the heterogeneity of this disease. We first report a genetic mutation causal to LQTS in a Malay child.

Introduction:
Congenital Long QT syndrome (LQTS) is an inherited cardiac arrhythmia disorder characterized by prolongation of the QT interval; patients are predisposed to ventricular tachyarrhythmias and fibrillation leading to recurrent syncope or sudden cardiac death. LQTS affects an estimated 1 in 2,000 people worldwide.\(^1\) LQTS in Malaysia was first reported in 1990 in a 26-year old woman, who presented with complete heart block and prolonged QT interval.\(^2\) At that time, the genetic pathophysiology of LQTS was still undiscovered. Later, in a report from Singapore, genetic clues causal to LQTS have been investigated in a family with several LQTS affected members but without any detectable genetic pathology.\(^3\) There have not been any further reports on LQTS since then from Malaysia or Singapore, despite LQTS being one of the significant causes of sudden unexplained deaths, both in adults and in children.\(^4\) 70% of the LQTS patients were reported to have a mutation in one of the presently known 12 LQTS causing genes; mutations in \( SCN5A \), \( KCNH2 \) and \( KCNQ1 \) comprise the 90% of the genotyped LQTS patients.\(^1\) Here, we report the clinical and genetic findings in two children with LQTS, native of Kelantan province of Malaysia.

Case report-1:
The neonate, now 7 weeks old, was detected perinatally to have a low heart (ranging between 100-110 bpm) rate in utero, and because of that, he was delivered via Cesarian section at 38th week due to fetal distress. The child remained asymptomatic at birth with a heart rate ranging from 66 beats/min during sleep to 110/min when fully awake and crying. An ECG performed on day 1 of life, displayed a prolonged QT, with a corrected QT (Bazett’s correction) of 530 ms, and bifid T waves in more than 3 leads (Figure 1). Investigations were carried out to rule out acquired causes of the LQTS, calcium and magnesium levels were normal as were glucose.

The child is now on β-blocker propranolol (0.3mg/kg/day) with recovery of his heart rate to be above 80/min and since then, he had become more active. Basal ECG of his mother is
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![ECG Child](image1)

![Exercise ECG Mother](image2)

![Rest ECG Mother](image3)
normal and she has no complaints pertaining to arrhythmias. We have performed an exercise ECG of the mother, at a heart rate of 128/min, her QTc was 510 ms (Figure 1), which returned to normal after the exercise. There is no known history of early deaths on the maternal side, although there is a history of premature death of a brother of the mother at young age without an obvious reason. On the paternal side there is history of hypertension and coronary heart disease, but no early deaths.

In the neonate, we have screened the main three LQTS (LQT1, LQT2 and LQT3) causing genes, $\text{KCNQ1}$ (NCBI ref: NM_000218), $\text{KCNH2}$ (NCBI ref: NM_000238) and $\text{SCN5A}$ (NCBI ref: NM_000335), respectively, as mutation in these three genes comprise 90% of the mutation positive LQTS patients.\(^3\) We have identified a pathogenic missense mutation p.Ile567Thr (c.1700T>C) (NCBI Ref. NM_000218) in exon 14 of the $\text{KCNQ1}$ gene in the neonate (Figure 1). No other mutation was detected in the $\text{KCNH2}$ and $\text{SCN5A}$ genes. Proband (neonate) inherited the p.Ile567Thr ($\text{KCNQ1}$) mutation from his apparently asymptomatic mother.

**Case report -2:**
Patient is an 18 months old boy, the younger of 2 siblings. He was admitted to University Sains Malaysia Hospital for acute gastroenteritis with moderate dehydration. He presented with history of diarrhoea and vomiting for 2 days which was associated with fever. However on hospital admission he was noted to have bradycardia with heart rate ranging from 40 to 62 per minute. He had no history of syncope or seizures, and had been born full term via spontaneous vaginal delivery with birth weight of 2.7 kg. Antenatal and postnatal history was uneventful. Physical examinations revealed no abnormalities. There was no facial dysmorphism. Cardiovascular examination was normal. His weight was 10 kg (10th percentile). Blood investigations did not reveal any abnormality in the potassium, calcium and magnesium levels.

His ECG showed bradycardia with various degrees of intermittent heart block and QTc of 560 sec (Figure 2). In addition there was also inverted T wave. He was given intravenous Lignocaine (infusion of 50 mg/kg/min) and subsequently prescribed propanolol 0.2 mg/kg/ dose b.d.s. However there was no improvement of heart rate. He has been discharged on
low dose propanolol, while awaiting surgical insertion of a pacemaker at the National Heart Institute, Kuala Lumpur. He continues to tolerate the low heart rate well. We also have performed ECG on both parents and his sister. Father and his sister’s ECG were normal but the mother’s ECG showed sinus rhythm with QTc of 480 ms (Figure 2). Both parents and his sister are doing well. The mother, father and the sister were 28, 36 and 5 years old respectively. There was no history of sudden death in the family, but his father has had many episodes of syncope (without cause) and has presently been referred to the National Heart Institute, Kuala Lumpur and is due for an electrophysiology study with tilt table testing.

We have screened the following LQTS causing genes in this child: *KCNQ1* (causal to LQT1; NCBI ref: NM_000218), *KCNH2* (LQT2; NM_000238), *SCN5A* (LQT3; NM_000335), *ANK2* (LQT4; NM_001148), *KCNE1* (LQT5; NM_000219), *KCNE2* (LQT6; NM_172201), *KCNJ2* (LQT7; NM_000891), exon-8 of *CACNA1C* (LQT8; NM_199460), *CAV3* (LQT9; NM_033337), *SCN4B* (LQT10; NM_174934), *AKAP9* (LQT11; NM_147185) and *SNTN1* (LQT12; NM_003098). A pathogenic mutation could not be detected in any of these LQTS causing genes. As the conventional PCR cannot identify a large genomic deletion/duplication, which in some instances were shown to cause LQTS,5 we have used Multiplex ligation-dependent probe amplification (MLPA) kits, P108 SCN5A and P114-A2 LQT (MRC Holland, Amsterdam) to exclude any large genomic rearrangements (deletion or duplication) in the following genes *KCNQ1, KCNH2, SCN5A, KCNE1* and *KCNE2*. We could not detect any rearrangement in any of these genes.

**Discussion and Conclusion:**

LQTS is a heterogeneous disease, mutations in one of the presently known 12 genes constitute 70% of the LQTS patients.1 We have found a LQTS causing pathogenic mutation p.Ile567Thr in *KCNQ1* gene in case one, which he inherited from his mother. His mother is devoid of any LQTS related symptoms, but, on exercise, her ECG showed a prolonged QTc (510 ms) (Figure 1), exercise is known to unmask the ECG phenotypes in LQTS mutation carriers.1 Variability in clinical penetrance is a well-known phenomenon in LQTS and ~50% of the LQTS causing mutation carriers are reported to be asymptomatic, which could explain why the proband’s mother does not have any symptoms despite having the identical pathogenic mutation.1 We were not able to investigate family members from the mother’s side, but there is no apparent history of SCD or syncope in her family members. LQTS causing mutation, p.Ile567Thr in *KCNQ1* gene detected in case-1 has been reported previously also in an Italian LQTS patient.6 As to the function, mutations in *KCNQ1* are known to reduce the slowly activating delayed rectifier outward K+ current (I\(_{Ks}\)) of the cardiac action potential, which in turn lengthens the QT interval in LQTS patients.1 In line with
In addition to the report of this mutation in the previously reported Italian patient and in this report in a Malay patient, we ought to consider that the p.Ile567Thr mutation in \textit{KCNQ1} a recurrent mutation in LQT1 pathology.\textsuperscript{6}

Patient mentioned in case report-1 harboured a mutation in \textit{KCNQ1}, who had bradycar-
dia during intrauterine stages and also postnatally. Lupoglazoff et al. (2004) reported 23 LQTS afflicted neonates for a causal genetic mutation, divided clinically in two different groups, a) LQTS with 2:1 atrioventricular block and b) LQTS with bradycardia. In the report by Lupoglazoff et al. (2004), neonates with LQTS and sinus bradycardia preferentially harboured a mutation in the \textit{KCNQ1} gene; LQTS with 2:1 AV block were preferentially associated with a mutation in \textit{KCNH2} gene. Concordant with the findings by Lupoglazoff et al. (2004), neonate with sinus bradycardia in our report (both gestational and postnatal, case one) was found to carry a mutation in \textit{KCNQ1}. Neonate in case-1 was treated effectively with propranolol, which was shown an effective way of treating these patients (Lupoglazoff et al. 2004).

The second patient mentioned in case report-2, had LQTS combined with 2:1 AV block. Mutations in \textit{KCNH2} have been reported in neonates with similar disorders, homozygous mutations in \textit{SCN5A} also has been reported in patients with LQTS with AV block. We have also previously reported homozygous mutations in \textit{KCNH2} gene in LQTS neonates with AV block. We have not found a mutation in either of these three genes in the patient mentioned in second case report. Mutation in \textit{SCN4B} gene was reported to cause intermittent 2:1 atrioventricular block and a QTc of 712 ms in a 21 months old Mexican female child. Our analysis did not yield a mutation in \textit{SCN4B} in the second patient who had LQT phenotype admixed with heart block. Additionally, we have not found a mutation in rest of the presently known LQTS causal genes. In rare instances, LQTS was reported to occur due to genomic rearrangements of the LQTS causing genes, in patient-2 no such deletion or duplication in any of the main LQTS causing genes were found.

It is a known fact that 30% of the LQTS patients go undetected without a mutation. Further, neonates with atrioventricular block were not always found to have a mutation in the presently known LQTS causing genes. Mutation in a presently unidentified gene or a mutation in the regulatory region in one of the known LQTS causing genes could not be excluded in our second patient. At present, the second child is awaiting a pacemaker insertion at a tertiary heart institute in Kuala Lumpur.

Finally, as gene specific clinical management is available, LQTS patients and their family members should be routinely screened for a pathogenic mutation in the causal gene/s. In case of LQT1, as in our first patient, presymptomatic β-blockers were shown to reduce mortality in 81% of the LQT1 patients. In conclusion; we report clinical and genetic findings in two Malay children with LQTS. To our knowledge, this is the first molecular report about the identification of a pathogenic LQTS causing mutation in a LQTS patient from Malaysia and also from Singapore.
References: