Clinical and genetic analysis of long QT syndrome in two Malay children

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SUMMARY

Long QT syndrome (LQTS) is predominantly a genetic cardiac arrhythmia disorder. We report here our study on long QT syndrome from two children from Kelantan, Malaysia. Clinical and genetic findings of these two unrelated Malay children with LQTS is discussed. We 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.

INTRODUCTION

Congenital Long QT syndrome (LQTS) is an inherited cardiac arrhythmia caused by mutations in the ion channels in the ventricular cell membrane. It is characterized by prolongation of the QT interval, hence its name. Its importance lies in that patients are predisposed to ventricular tachyarrhythmias and fibrillation leading to recurrent syncope or sudden cardiac death. LQTS affects an estimated 1 in 2,500 people world-wide.[1] Whereas 70% of the LQTS patients were reported to have a mutation in one of the presently known 12 LQTS causing genes, with mutations in *SCN5A, KCNH2* and *KCNQ1* accounting for 90% of the genotyped LQTS patients.[1]

Here, we report the clinical and genetic findings of two children with LQTS from non-consanguineous families in Kelantan, a state in Malaysia.

CASE 1

The first case, a boy was detected perinatally presenting with a low heart, ranging between 100-110 beats per minute (bpm) *in utero*, and because of that, the case was delivered via Caesarean section at 38-week of gestation due to "foetal distress" because of a cardiotocograph performed at the time. The child remained asymptomatic at birth with a heart rate ranging from 66bpm during sleep to 110bpm 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 530ms, and bifid T waves in more than 3-leads (Figure 1). Investigations were carried out to rule out acquired causes of the LQTS, and calcium and magnesium levels were normal as were glucose.

The child is currently on the β-blocker propranolol (0.3mg/kg/day) with recovery of his heart rate to above 80bpm, and since then, he had become more active. Basal ECG of his mother is normal, and she had no complaints pertaining to arrhythmias although there was a male sibling who passed away at a young age without an obvious cause. We had performed an exercise ECG of the mother, and at a heart rate of 128bpm, her QTc was 510ms (Figure 1), which returned to normal after the exercise. On the paternal side there is history of hypertension and coronary heart disease, but no early deaths.

In this case, we had screened the main three LQTS (LQT1, LQT2 and LQT3) causing genes, *KCNQ1* (NCBI ref: NM_000218), *KCNH2* (NCBI ref: NM_000238) and *SCN5A* (NCBI ref: NM_000335), respectively, as mutation in these three genes accounts for 90% of the mutation in positive LQTS patients.[2] We have identified a pathogenic missense mutation p.Ile567Thr (c.1700T>C) (NCBI Ref. NM_000218) in exon 14 of the *KCNQ1* gene in the neonate (Figure 1). No other mutation was detected in the *KCNH2* and SCN5A genes. Proband (neonate) inherited the p.Ile567Thr (*KCNQ1*) mutation from his apparently asymptomatic mother.

CASE 2

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

His ECG showed bradycardia with varying degrees of intermittent heart block and QTc of 560ms (Figure 2). In addition, there was also inverted T wave. He was given intravenous Lignocaine (infusion of 50mg/kg/min) and

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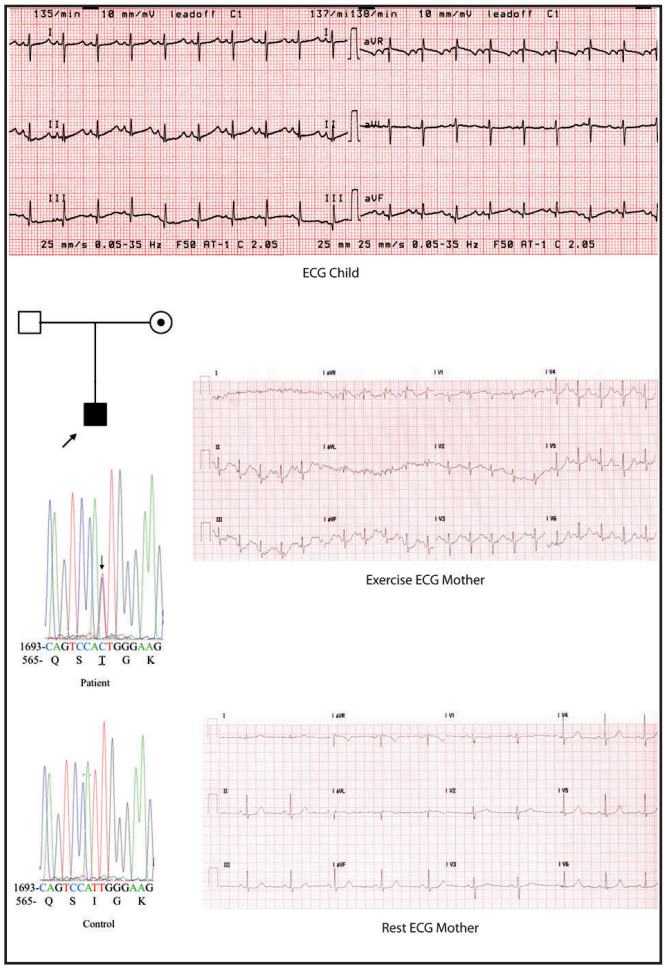

Fig. 1: Screening of the KCNQ1 gene shows substitution of nucleotide "T" for a "C" at exon-14 arrow marked) (NCBI ref: NM_000218) in the proband (patient). This nucleotide substitution causes a non-synonymous change of a conserved amino-acid (p.Ile567Thr) in KvLQT1 protein (encoded by KCNQ1 gene), which has been underlined. DNA sequence of a non-diseased control individual is also shown. Proband is arrow marked in the pedigree. ECG of the neonate shows a QTc of 530ms with bifid T waves. Resting ECG from proband's mother shows QTc of 440ms, during exercise QTc prolonged to 510ms.

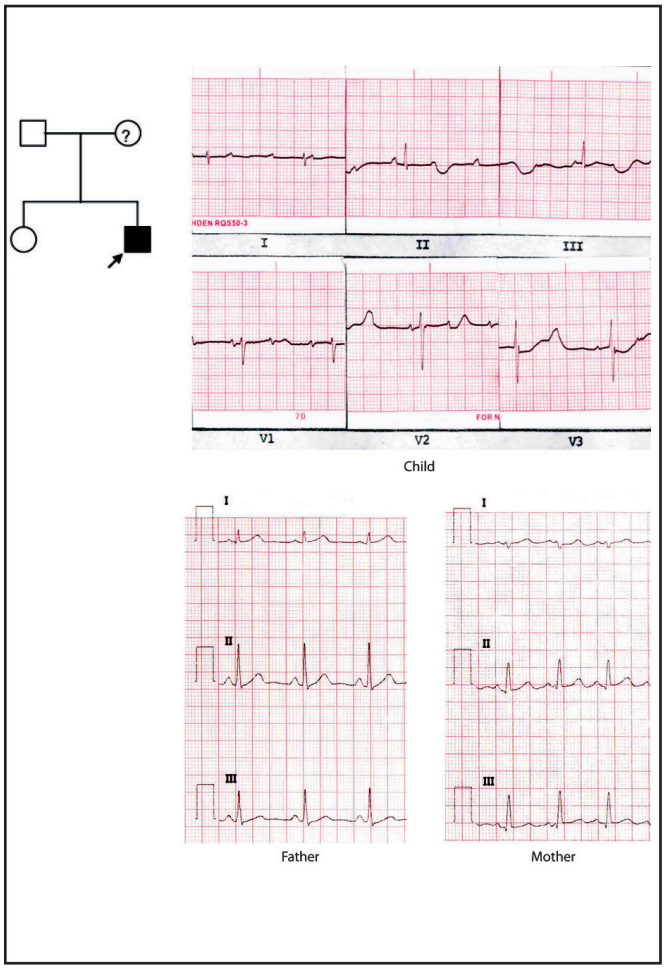

Fig. 2: ECG of the second child, his father and mother are shown. ECG of the child shows a prolonged QTc of 560ms and 2:1 AV block. ECG from the mother shows borderline prolonged QTc of 480ms. ECG from the father is normal. Proband is arrow marked in the pedigree.

subsequently prescribed propranolol 0.2mg/kg/dose twice daily. However, there was no improvement of heart rate. He was discharged on low dose propranolol and had surgical insertion of a pacemaker at the National Heart Institute, Kuala Lumpur.

We also had performed ECG on both parents and his sibling. Father and sibling's ECG were normal, but the mother's ECG showed sinus rhythm with QTc of 480ms (Figure 2). Both parents and his sibling were well. There was no history of sudden death in the family, but his father has had many episodes of syncope (without any known cause) and had been referred to a Heart Institute in 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 *SNTA1* (LQT12; NM_003098). A pathogenic mutation could not be detected in any of these LQTS causing genes. As conventional PCR cannot identify a large genomic deletion/duplication, which in some instances were shown to cause LQTS,[3] we 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 genetic disorder, mutations in one of the presently known 12 genes constitute 70% of the LQTS patients.[1] We found a LQTS causing pathogenic mutation p.Ile567Thr in KCNQ1 gene in case one, which was inherited from the child's mother. His mother is devoid of any LQTS related symptoms, but, on exercise, her ECG showed a prolonged QTc (510ms) (Figure 1),[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 did 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 was no apparent history of SCD or syncope in her family members except for her younger sibling, who had passed away in childhood. LQTS causing mutation, p.Ile567Thr in *KCNQ1* gene detected in case-1 has been reported previously also in an Italian LQTS patient.[4] 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 the report of this mutation from the known reported Italian case, and in our case, we ought to consider that the p.Ile567Thr mutation in *KCNQ1* a recurrent mutation in LQT1 pathology.[4]

Patient reported in case report-1 harboured a mutation in *KCNQ1*, who had bradycardia during intrauterine stages and also postnatally. Lupoglazoff et al.,[5] reported 23 LQTS afflicted neonates for a causal genetic mutation, divided clinically in two different groups: LQTS with 2:1 atrioventricular block and LQTS with bradycardia. In the report by Lupoglazoff et al.,[5] neonates with LQTS and sinus bradycardia preferentially harboured a mutation in the *KCNQ1* gene; LQTS with 2:1 AV block were preferentially associated with a mutation in *KCNH2* gene. Concordant with the findings by Lupoglazoff et al., neonate with sinus bradycardia in our report (both gestational and postnatal, case one) was found to carry a mutation in *KCNQ1*. Neonate in case-1 was treated effectively with propanolol which had been shown to be effective in treating these patients.[5]

The second patient mentioned in case report-2, had LQTS combined with an intermittent 2:1 AV block. Mutations in *KCNH2* have been reported in neonates with similar disorders, homozygous mutations in *SCN5A* also has been reported in patients with LQTS with AV block.[5] We did not find a mutation in any of these three genes in the second case. Our analysis also did not yield a mutation in *SCN4B* in the second patient who had LQT phenotype admixed with heart block. Additionally, we were unable to find mutations in the rest of the presently known LQTS causal genes for this second case. In rare instances, LQTS was reported to occur due to genomic rearrangements of the LQTS causing genes,[3] in case 2 no such deletion or duplication in any of the main LQTS causing genes were found.

It is known that 30% of the LQTS patients present without any detectable mutation.[1] Further, neonates with atrioventricular block were not always found to have a mutation in the presently known LQTS causing genes.[5] 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.

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.[1] In conclusion, we report clinical and genetic findings in two Malay children with LQTS. To our knowledge, one of them provided the first positive identification of a molecular report about a pathogenic LQTS causing mutation in a LQTS patient from Malaysia.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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