Case Report

Malignant familial long QT syndrome

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ABSTRACT

We report a family with congenital long QT syndrome, an inherited disorder of myocardial repolarization in which affected individuals have prolongation of corrected QT interval on the electrocardiogram and a tendency to develop ventricular arrhythmia, leading to syncope, convulsion or sudden death. Our family is characterized by several affected members (11/16), early onset of symptoms, malignant course prior to diagnosis and good response to beta-blocker therapy. The genetic basis of long QT syndrome has been traced to defective proteins encoding cardiac ion channels. Diagnosis is based on an unexplained prolongation of QT interval >0.45 second in the presence of suggestive symptoms or evidence, or both of a familial pattern. Beta-adrenergic blocker therapy gives symptomatic relief in 80%-85% of patients. Precipitating factors like vigorous exercise especially swimming and exposure to significant emotional or auditory stimuli should be avoided. Occasional patients require in addition, a demand cardiac pacemaker, left cardiac sympathectomy or an implantable cardioverter-defibrillator, or both. Regular follow up is mandatory even after subsidence of symptoms.

Keywords: Long QT syndrome, ventricular fibrillation, sudden death, convulsions, beta-blocker, pacemaker.

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Congenital long QT syndrome (LQTS) is a serious group of disorders of myocardial repolarization associated with lethal ventricular arrhythmias, and is often underdiagnozed in children.[1] We report a family with a malignant form of the disease.

Case Report. The patient was first seen at the age of 2 months with an episode of fever and convulsion. He was readmitted a month later with several episodes of tonic-clonic fits without fever over a period of 24 hours. Examination showed a normally growing infant with no neurological or cardiovascular abnormality. An electrocardiogram (ECG) taken during this admission showed a markedly prolonged corrected QT interval (QTc) ranging from 0.53 to 0.62 seconds. The T waves exhibited marked variation in shape, size and duration and were at times alternating in direction (T wave alternans) as shown in (**Figure 1).** A 24-hour ambulatory ECG did not yield any additional information, the heart rate varied from 62 to 118/ minute and no significant arrhythmia was detected. Echocardiogram showed normal cardiac anatomy and function. The left ventricular posterior wall movement was abnormal with prolonged thickening and a double-peak anterior movement in systole. Hematological and biochemical tests were normal. Audiometry did not show any evidence of neural deafness. The patient was diagnosed to have LQTS, and family screening was carried out. His parents were consanguineous and had a total of 14 children, 4 of whom had died earlier between one year and 4 years of age from either convulsions or syncope that

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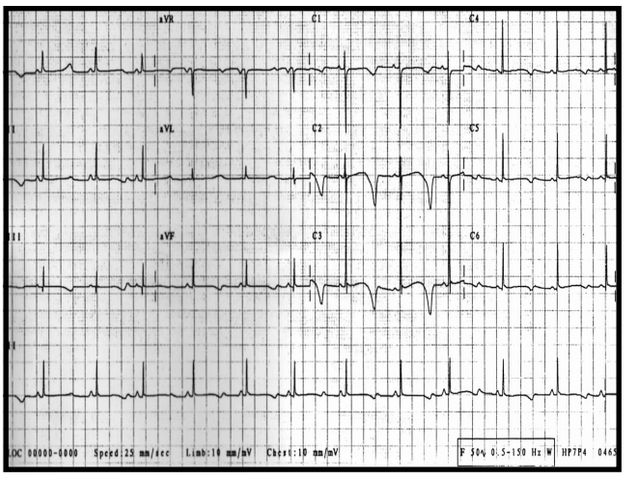

Figure 1 - Electrocardiogram showing marked variation in shape, size and duration of T waves and T wave alternans in a child with familial syndrome. LOC - loss of consciousness.

had been treated as epilepsy. The parents and 9 surviving siblings were evaluated and 6 of the siblings had evidence of LQTS **(Table 1).** His mother's ECG showed mildly prolonged QT interval, but she was asymptomatic. The patient was commenced on propranolol but returned a month later with recurrence of fits while on therapy. A permanent ventricular epicardial demand pacemaker (VVI) was then implanted, and propranolol was continued. The pacemaker was changed to an endocardial VVI system at 6 years of age. He has remained well and asymptomatic during the last 8 years of follow-up. Six of his siblings were commenced on propranolol and one of them also required a pacemaker. There has been no death, convulsion or syncope in any family member after initiation of therapy.

Discussion. Long QT syndrome (LQTS) is characterized by a prolonged QTc and episodes of presyncope, syncope, convulsions, sudden death, or palpitations, or both.[2,3] Symptoms, mostly secondary to ventricular tachycardia (VT) and fibrillation (VF), usually manifest in the preteen to teenage years and are induced by exercise (especially swimming), auditory stimuli (ringing of alarm clock, or telephone, or sound of thunder) or intense emotional upset (anger or fright).[4] About one 3rd of patients are asymptomatic. The syndrome is usually associated with a structurally normal heart.[1] Physical findings are generally unremarkable, as in our patient.

Diagnosis. Diagnosis requires a high index of suspicion. Long QT syndrome should be considered in patients with syncope or seizures who give a history of sudden death in other family members. Abrupt onset-abrupt offset syncope is more suggestive of LQTS than gradual onset-gradual offset episodes (as with hypoglycemia and vasovagal reaction) or abrupt onset-gradual offset syncope (primary seizures).[4] Atypical seizures or poor response to anticonvulsant therapy may indicate anoxic seizures related to a primary cardiac arrhythmia.[5] Often the arrhythmia is never documented due to its transient nature and the diagnosis is made by inference. The criteria put forth by the Pediatric Electrophysiology Society[2] for the diagnosis of LQTS include an otherwise unexplained prolongation of QTc interval >0.44 seconds or a positive family history of LQTS plus unexplained syncope, seizures or cardiac arrest associated with

Table 1 - Details of the family with long QT syndrome.

Age*	Sex	Symptoms	QTc (sec)	Treatment**	Outcome
1 year	Male	Convulsions	NK	None	Dead
1.5 years	Male	Convulsions	NK	None	Dead
20 years	Female	None	0.42	None	Alive and well
3 years	Male	Convulsions	NK	Anticonvulsants	Dead
16 years	Female	None	0.44	None	Alive and well
4 years	Male	Convulsions	0.52	Anticonvulsants	Dead
13 years	Male	Convulsions Syncope	0.54	Propranolol	Alive and well
11 years	Male	None	0.48	Propranolol	Alive and well
10 years	Female	Dizzy spells	0.52	Propranolol Pacemaker	Alive and well
8 years	Male†	Convulsions	0.58	Propranolol Pacemaker	Alive and well
6 years	Female	None	0.44	None	Alive and well
4 years	Female	None	0.48	Propranolol	Alive and well
2 years	Male	None	0.56	Propranolol	Alive and well
0.5 years	Male	None	0.50	Propranolol	Alive and well
41 years	Female (mother)	None	0.44	None	Alive and well
42 years	Male (father)	None	0.43	None	Alive and well

* - in years at diagnosis or death, ** - current or at time of death, † - index case
NK - not known

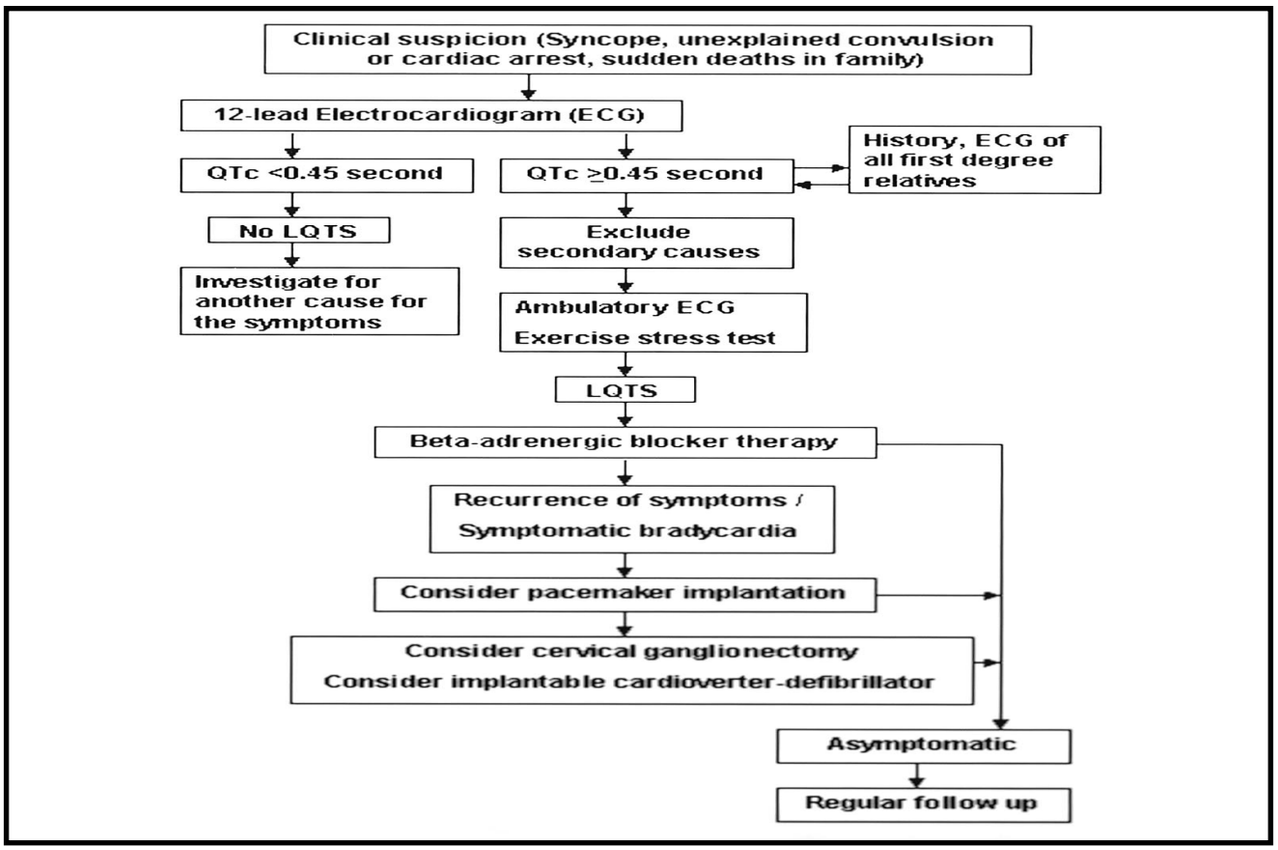

Figure 2 - An approach to patients presenting with symptoms suggestive of long QT syndrome (LQTS). QTc - QT interval

exercise or emotion, even if QTc interval is normal. An alternate recommendation[6] makes use of a scoring system based on ECG findings, clinical features and family history to assess the probability (low, intermediate or high) of LQTS. **Figure 2** outlines an approach to patients presenting with symptoms suggestive of LQTS.

QT interval prolongation on ECG at times may be subtle and difficult to identify with certainty.[7] It is essential to measure manually the QT interval and then derive the QTc (corrected to a heart rate of 60/ minute) using the Bazett's formula (QTc=Measured QT interval/ square root of the RR interval). Since up to 4% of normal children could have a QTc >0.45 seconds, in borderline cases it is necessary to perform further evaluation before making the diagnosis.[8] T wave abnormalities like wide-based slowly generated T waves, biphasic or bifid T waves, notched T waves, low amplitude humps on the descending limb of the T wave, indistinct termination of T waves due to U waves (TU complex), alternate positive and negative T waves (T alternans) also support the diagnosis.[9,10] Echocardiography generally shows normal cardiac chambers and valves, and excludes other cardiac causes of syncope. The posterior left ventricular wall in LQTS may show an increased rate of thickening in the early phase and a double-peak anterior movement in systole (plateau morphology).[11] Twenty-four hour ambulatory ECG helps to measure QT intervals and identify T-wave morphologies at different points while the patient is awake as well as during sleep.[12,13] Treadmill exercise test may show a significant prolongation of QTc (especially 1-2 minutes post exercise), and maximal heart rates are not achieved.[14] Ventricular arrhythmia may be induced during the test in 12%-30% of patients.

The diagnosis of LQTS could be made with confidence in our patient from the strong family history and definite prolongation of QTc along with T wave changes, although an arrhythmia was never actually documented. Eleven out of the 16 family members studied were affected indicating a high penetrance of the disorder in the family. Affected patients had an early onset of symptoms (mean 5.4 years), and there were several sudden deaths before the diagnosis was established. Our patients presented mostly with anoxic convulsions indicating a longer lasting cardiac arrhythmia.[15] Labile T wave changes pointed to the malignant potential of LQTS in this family. Carriers of the disease especially females are

more likely to exhibit borderline prolongation of QTc,[16] as was the case with the mother in our family. However she did not have any symptoms of LQTS until this age and hence therapy was not indicated.

Pathophysiology. QT lengthening reflects a prolongation of the ventricular action potential brought out by altered ion channel function.[17] The myocardial repolarization is inhomogeneous and the consequent dispersed refractoriness gives rise to triggered activity or reentry, responsible for the VT.[18-21] More than 100 mutations have been identified in 5 separate cardiac ion channel genes, LQT1, LQT2, LQT3, LQT5 and LQT6.[22] LQT1 and LQT2 together account for 90% of all genotyped cases. Typical ST-T-wave patterns can be used to identify LQT1, LQT2, and possibly LQT3.[10] Twenty-four hour ambulatory ECG has been of greater value, with notched T waves being more often associated with LQT2.[23] LQT1 has an earlier onset of symptoms compared to LQT3, and experience majority of their events during exercise.[24] An alternate hypothesis for LQTS suggests enhanced myocardial sensitivity to catecholamines secondary to either reduced cervico-thoracic sympathetic activity on the right side or increased activity on the left.[25] Two syndromes, Jervell and Lange-Nielsen syndrome with deafness[26] and Romano-Ward syndrome with normal hearing[27] described in relation to LQTS have lost their earlier significance with the advent of genetic analyses. Early onset of symptoms, absence of symptoms during sleep, malignant course before initiation of therapy and good response to beta-blockers points towards LQT1 genotype in our family. However we could not perform genetic studies due to lack of facility. Genetic studies can help to identify patients with normal or borderline QTc and carriers in affected families.[16]

Management. Beta adrenoceptor blockers form the cornerstone of therapy and reduce or even eliminate symptoms in 80%-85% of patients.[28] The QT interval generally remains prolonged, although recent reports suggest a significant reduction in QTc on therapy in patients who respond well.[28] Propranolol is the most widely used beta-blocker, but others like atenolol, metoprolol and nadolol requiring less frequent dosing are also effective.[28,29] Moderate doses are preferred, as higher doses do not give additional benefit, and may even lead to dangerous bradycardia. Genotypes LQT1 and LQT2 respond better to beta-blockers.[30] Efficacy of therapy can be assessed clinically by freedom from symptoms and by 24-hour ambulatory ECG and Treadmill exercise test. Beta-blocker therapy is also indicated in asymptomatic patients from high-risk families, especially if the QTc is markedly prolonged (0.48 seconds or more). Life style modifications suggested include avoidance of vigorous exercise (especially swimming), competitive athletics, and exposure to significant emotional or auditory stimuli. Eliminating alarm clocks, doorbells, rock concerts, hunting and gun range shooting are important for adolescents. Management of LQTS also includes treatment of acute symptoms, screening of all first degree relatives, family counseling, and regular follow-up. Recurrence of life threatening events or development of severe bradycardia with beta-blocker therapy indicates the need for additional implantation of a demand pacemaker.[31] The pacemaker helps to prevent bradycardia that often precedes symptomatic arrhythmia and patients with documented pause-dependent syncope derive maximum benefit.[32] Resistant patients may require either left stellectomy or left cervicothoracic sympathectomy,[33] or an implantable cardioverter-defibrillator.[34] Four of the affected children in our study had died from cardiac events before the diagnosis was made. Propranolol therapy alone eliminated symptoms in one of the living children, however 2 others required insertion of demand cardiac pacemakers. We also believe that prophylactic beta-blocker therapy in 4 other asymptomatic siblings with markedly prolonged QTc helped to prevent arrhythmic events.

Prognosis. With the introduction of beta-blocker therapy, mortality has been reduced from 60%-70% to 3%-5%.[28] Longer duration of QTc (>0.54 second) and a higher basal heart rate have been identified as indicators of poor prognosis.[3] Other suggested poor prognostic indicators include young age at onset of symptoms, strong family history of life threatening events, documented repetitive ventricular arrhythmia, labile T waves especially T wave alternans and notched T waves, slow base line heart rate, sudden increases in heart rate and atrioventricular block in the neonatal period.[35,36] Deaths can occur even while on beta-blocker therapy[2] and caution should be exercised in the presence of bradycardia or atrioventricular block.[3,35] Asymptomatic patients with markedly prolonged QTc from families with frequent lethal cardiac events are at high risk. LQT1 patients respond better to betablockers and hence survive longer.[30] As age advances the severity of symptoms[4] and even the degree of QT prolongation tends to decrease.[37] Thus elderly patients who are asymptomatic with borderline QTc do not require therapy.

In conclusion, we have presented a family with LQTS, showing several unique features of the syndrome, and outlined the diagnosis, pathophysiology, and management. Early diagnosis requires a high index of suspicion and is fundamental to successful treatment and improved survival. The majority of patients respond to beta-blocker therapy alone, while others may require a demand pacemaker implantation.

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