CLINICAL QUIZ (p130) ANSWER

Our patient's electrocardiogram showed sinus rhythm with normal axis and no evidence of heart block. Corrected QT interval measured 526 ms which was markedly prolonged. Echocardiogram confirmed normal cardiac structure. Family screening showed prolonged QTc in his mother and elder sister. Genetic testing was performed after pre-test counselling, and a missense mutation in the KCNQ1 gene, described as a heterozygous substitution of a cytosine to a thymine at nucleotide 965 in exon 8 (c.965 C>T) was detected. This substitution creates an amino acid change of a threonine to a methionine at codon 322 (p.Thr322Met). The mutation has previously been reported in a Chinese family with LQT and is not present in a cohort of normals or in a Single-Nucleotide Polymorphism (SNP) database, together with assessment of conservation and amino acid properties, it is considered a pathogenic mutation. The family was interviewed again and cascade testing offered.

Long QT syndrome (LQTS) is an example of Sudden Arrhythmia Death syndromes (SADS) which also include short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. Acquired long QT syndrome can occur as a result of electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypocalcaemia), drug use (antiarrhythmic, macrolide group antibiotics), intra-cranial bleeding and anorexia but the following discussion will focus on congenital long QT syndrome.

There is increasing recognition of patients with LQTS and a prevalence of up to 1 in 2500. Diagnosis depends on a high index of suspicion in otherwise healthy patients presenting with syncope, convulsion, ventricular arrhythmia and cardiac arrest. These should prompt a thorough cardiac evaluation including a resting 12-lead ECG. Accurate measurement of the QT interval, which corresponds to the time of ventricular depolarization and repolarization, is crucial to the definition of LQTS. Lead II or V5 are the preferred leads for study and the tangent method is used. In this method, a tangent line is drawn against the maximum downslope of the T wave, the intersection between the tangent and isoelectric lines determine the end of a QT interval (Figure 2). U waves are disregarded unless they measure more than half the T-wave amplitude. Correction for heart rate can then be made using the Bazett's formula (QTc), bearing in mind its tendency to overcorrect at high heart rate and undercorrect at low heart rate. In case of remarkable beat to beat variation, as in the case of sinus arrhythmia or atrial fibrillation, an average of several consecutively measured QTc should be used. Clinical criteria, commonly the Schwartz score, utilise ECG findings, together with clinical and family history to stratify patients into high, intermediate and low probability of LQTS (Table 1), they are highly specific (99%) in the detection of mutation carriers with nevertheless low sensitivity (19%-39%). Genetic tests for LQTS have emerged to become an indispensable tool in the diagnostic algorithm.

LQTS is classically inherited in an autosomal dominant (AD) manner with the exception of the autosomal recessive (AR) Jervell and Lange-Nielson syndrome. Twelve LQTS-susceptibility genes (Table 2) have been identified, each with its specific effect on various ion channels leading to prolonged repolarization. This predisposes to the occurrence of early after depolarizations (EADs), which underlies the development of polymorphic ventricular tachycardia and SCD. Currently, known mutations encompass 80% of patients with LQTS with those in LQT1-3 being responsible for 75% of all patients. The majority of these mutations belong to coding region single-nucleotide substitutions or small insertions and deletions. Phenotype-genotype correlations allow symptom-driven targeted testing in patients with obvious trigger, for example, exertion and swimming in LQT1, auditory stimulation and post-partum state in LQT2. They also allow prognostication and therapy guidance. Whilst trigger avoidance (exercise, drugs) is important for all patients with LQTS, therapeutic effect of medications differ. Beta-blocker, which is widely used in the prevention of cardiac event, is in fact most protective in patients with LQT1 but less so in those with LQT2 or 3. Mexiletine – a sodium channel blocker, on the other hand, effectively targets patients with LQT3 where gain-of-function mutations in the SCN5A gene prolong repolarization by causing abnormally sustained inward sodium current during the plateau phase of the action potential. The use of implantable cardioverter-defibrillator should also be considered in patients with LQT3 where fatal arrhythmia may present while these patients are at rest. Cascade testing, which refers to screening of the probands' relatives when a pathogenic mutation is identified, is useful to define pre-symptomatic carriers and reassure those who are not affected.

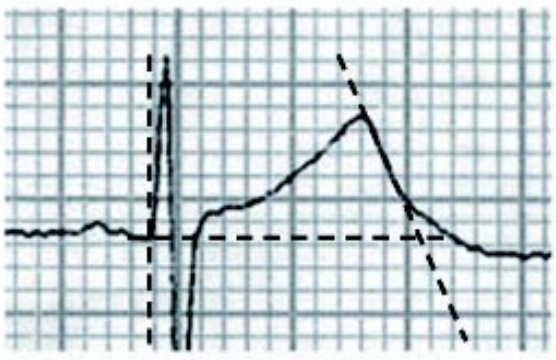

Figure 2

Table 1

Schwartz score		
Diagnostic criteria		**Points**
ECG findings	QTc calculated by Bazett's formula	
	>/= 480 ms	3
	460-470 ms	2
	450 ms (male)	1
	Torsades de pointes	2
	T wave alternans	1
	Notched T wave in three leads	1
	Resting heart rate below second centile for age	0.5
Clinical history	Syncope	
	With stress	2
	Without stress	1
	Congenital deafness	0.5
Family history	Family members with definite LQTS by Schwartz score	1
	Immediate family members with sudden cardiac death <30 years old	0.5

Score </= 1, low probability of LQTS; 2-3, intermediate probability of LQTS; >/= 4, high probability of LQTS

Table 2

LQTS subtype	Gene	Protein	Ion channel	Frequency
LQT1	KCNQ1	$K_v7.1\alpha$	I_{Ks}	30-35%
LQT2	KCNH2	$K_v11.1\alpha$	I_{Kr}	25-30%
LQT3	SCN5A	$Na_v1.5\alpha$	I_{Na}	5-10%
LQT4	ANK2	Ankyrin-B	I_{NCX}	1-2%
LQT5	KCNE1	minKβ	I_{Ks}	1%
LQT6	KCNE2	MiRP1β	I_{Kr}	Rare
LQT7	KCNJ2	Kir2.1α	I_{K1}	Rare
LQT8	CACNA1C	$Ca_v1.2\alpha1c$	$I_{Ca,L}$	Rare
LQT9	CAV3	Caveolin-3	I_{Na}	Rare
LQT10	SCN4B	$Na_v1.5\beta4$	I_{Na}	Rare
LQT11	AKAP9	Yotiao	I_{Ks}	Rare
LQT12	SNTA1	A1-syntrophin	I_{Na}	Rare

Modified from Bastiaenen R, Behr ER. Sudden death and ion channel disease: pathophysiology and implications for management. Heart 2011;97: 1365-72.

The application and impact of genetic testing for patients with LQTS and other SADS is expected to rapidly expand in the coming era. Potential problems from these tests will include extra cost, patient anxiety, vocational or insurance issue, false negative results and genetic variants of uncertain pathogenicity. Such testing will therefore be beneficial only with appropriate pre- and post-test counseling, support from accredited genetic laboratory, and joint input by cardiologists and geneticists.

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Further Reading

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