Long QT syndrome

Key facts

- Long QT syndrome (LQTS) is an inherited heart rhythm problem, characterised by QT prolongation and T wave abnormalities on an ECG that are associated with tachyarrhythmias, most typically the ventricular tachycardia torsade de pointes (TdP).
- TdP is usually self-terminating, thus causing a syncopal event (fainting): the most common symptom in individuals with LQTS.
- Such cardiac events typically occur during exercise or emotional stress, less frequently during sleep, and often without warning.
- Cardiac events may occur from infancy through to middle age, but are most common from preteen years into the 20s.
- The prevalence of LQTS is estimated to be 1 in 2,500, and occurs across all ethnic groups.
- Approximately 75% of LQTS cases are caused by pathogenic variants in one of 15 known genes, most frequently with autosomal dominant inheritance, though there are also recessive forms.

Clinical features

- Syncope is the most common symptom in individuals with LQTS, often occurring precipitously and without warning.
- In some instances, TdP degenerates to ventricular fibrillation and aborted cardiac arrest, or sudden death.
- Approximately 50% of untreated individuals with a pathogenic variant in one of the 15 known genes are symptomatic.
- Whilst the majority of those affected by LQTS have only cardiac features, some types of LQTS are associated with phenotypes extending beyond the cardiac arrhythmia (Table 1)

Table 1: Syndromic forms of LQTS with additional clinical features

Syndrome	Principal features	Causative genes
Andersen-Tawil syndrome (LQTS7)	Prolonged QT interval, muscle weakness and facial dysmorphism	Autosomal dominant: *KCNJ2*
Timothy syndrome (LQTS8)	Prolonged QT interval and hand/ foot, facial and neurodevelopmental features	Autosomal dominant: *CACNA1C*
Jervell and Lange-Nielson syndrome (JLNS)	Profound sensorineural hearing loss	Autosomal recessive: *KCNQ1* or *KCNE1*

Diagnosis

- Consider a diagnosis in a patient presenting with:
  - » ECG characteristics;
  - » clinical history of syncope; or
  - » family history of syncope, aborted cardiac arrest, or sudden death in a child or young adult.
- The Schwartz scoring system (Table 2) can be used to estimate probability of diagnosis.

Table 2: The clinical diagnosis of LQTS (Schwartz et al. (1993), Schwartz and Crotti (2011))

Findings		Points
QTc	≥480 ms	3
	= 460-479 ms	2
	= 450-459 ms (in males)	1
	≥480 ms during 4th minute of recovery from exercise stress test	1
ECG	Torsade de pointes	2
	T wave alternans	1
	Notched T wave in 3 leads	1
	Low heart rate for age	0.5
Clinical history	Syncope with stress	2
	Syncope without stress	1
Family history	Family member(s) with definite LQTS	1
	Unexplained sudden cardiac death at age <30 years in immediate family member	0.5
Scoring	**Outcome**	
	≤1.0 point	Low probability of LQTS
	1.5-3.0 points	Intermediate probability of LQTS
	≥3.5 points	High probability of LQTS

The diagnosis of LQTS is established in a proband with one or more of the following (Priori et al. 2013):

- A risk score of ≥3.5 in the absence of a secondary cause of QT prolongation.
- The presence of a corrected QT interval ≥500 ms in repeated ECGs in the absence of a secondary cause of QT prolongation.
- The identification of a pathogenic variant in one of the genes known to be associated with LQTS.

Genetic basis and genetic testing

- LQTS is typically inherited in an autosomal dominant manner, except for JLNS (Table 1). Pathogenic variants in *KCNQ1* (LQT1, 30-35% of cases), *KCNH2* (LQT2, 25-30% of cases) and *SCN5A* (LQT3, 5-10% of cases) are the most common causes of LQTS. There are 12 further forms caused by other pathogenic variants (LQTS4-15).

- Molecular genetic diagnostic testing is usually performed by sequencing a panel of genes – a panel test. Approximately 20-25% of families meeting clinical diagnostic criteria for LQTS do not have detectable pathogenic variants in a known gene, however relatives should still be considered at risk of sudden death in these families, and referred to an Inherited Cardiac Conditions (ICC) clinic for clinical evaluation.

Clinical management

The focus in the management of individuals with LQTS is to identify the subset of individuals at high risk of cardiac events. Risk stratification would include:

- ECG evaluation.
- Medical history – individuals with syncope or cardiac arrest in the first year of life, or those younger than seven years, are at higher risk.
- Family history – consultation with a clinical geneticist and/or genetic counsellor or ICC specialist nurse. Pre-symptomatic diagnosis of at-risk relatives via clinical screening and targeted variant analysis, followed by treatment, is necessary to prevent syncope and sudden death in those individuals who have inherited a pathogenic variant and/or have ECG findings consistent with LQTS. At-risk family members should be alerted to their risk.

Management is focused on the prevention of syncope, cardiac arrest and sudden death using:

- ß-blockers;
- implantable cardioverter-defibrillators;
- left cardiac sympathetic denervation; and
- sodium channel blockers.

The postpartum period is associated with increased risk for a cardiac event, especially in individuals with a LQTS2 phenotype. ß-blocker treatment and close clinical surveillance has been associated with a reduction of events during the nine month postpartum period.

Direction to further reading, guidelines and patient groups

- GeneReview: Long QT syndrome
- Romano-Ward syndrome
- Priori SG, Wilde AA, Horie M et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES and AEPC in June 2013. Heart Rhythm 2013 10:1932-1963.
- Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):868-77.
- Schwartz PJ and Crotti L. QTc behaviour during exercise and genetic testing for long-QT syndrome. Circulation 2011, 124: 2181-2184.

This information is intended for educational use and was current in September 2019. For clinical management, it is recommended that local guidelines and protocols are used.

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