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Editor's Note

Inherited Long QT Syndrome: Phenotype and Therapy to Use and Avoid

Key words: long QT

Introduction

Most cardiologists (non-electrophysiologists) know about the hazards of long QT syndrome but cannot remember many of the details. I consider myself one of those cardiologists.

What follows is an effort to educate myself and perhaps some of the readers of *Clinical Cardiology*. I thought it might be useful to outline some of the features of the long QT syndrome that will be easy to recall.

Diagnosis

QTC > 440 ms makes the electrocardiographic phenotype diagnosis of long QT.

QTC > 600 ms is associated with a high incidence of ventricular arrhythmias.

It has been my experience that computers don't often measure the QT interval accurately. Thus, it is important for anyone concerned about QT prolongation that it be measured by hand and the corrected QT interval calculated by the methods that are available.

Genetic and Clinical Characteristics of Long QT

There are now eight known long QT genetic types; three of these are major genetic types: QT 1, QT 2, and QT 3. This editorial will focus only on long QT 1, 2, and 3.

We worry about patients with a long QT interval because of the risk of ventricular arrhythmias and death. Arrhythmias associated with long QT 1 are usually precipitated by exercise or stress. In contrast, arrhythmias associated with long QT 2 can occur at rest or exercise or with auditory stimulation. Arrhythmias associated with long QT 3 generally occur at rest. Obviously there is overlap in all the QT prolongation syndromes, but those are the generalities that can be remembered.

Both long QT 1 and long QT 2 are related to channelopathies involving inward potassium currents. Long QT 3 in-

volves the late sodium channel. All three channelopathies result in prolongation of cardiac repolarization and an increased risk of arrhythmia. The most common forms of QT prolongation are QT 1 and QT 2, comprising about 90% of those with the clinical syndrome. Long QT 3 occurs in about 10% of those with the clinical syndrome. The inheritance of long QT is both autosomal dominant and recessive. The recessive form combines the cardiac phenotype with deafness.

Electrocardiographic Phenotypes

Patients with long QT 1 have broad T waves; a normal electrocardiogram (ECG) is seen in 12% of those with the clinical syndrome. Patients with long QT 2 have notched T waves; a normal ECG is seen in 17%. Patients with long QT 3 have the longest QT segment; a normal ECG is found in only 5% of patients with the clinical syndrome.

Drug Therapy for Patients with Long QT Syndrome

Although it may be helpful in the long term to know the genetic patterns of these different QT prolongation syndromes, clinically they are not very useful since it takes quite a long time to get results, and it is expensive. The physician treating these patients must make some decisions promptly. In general, beta blockers seem to be reasonable starting therapy for all patients with long QT, particularly those whose symptoms are exercise or emotion related, that is, patients with long QT 1 and long QT 2. Mexilitene may be useful in patients with long QT 3, since it is a sodium channel blocker. Ranolazine, a slow sodium current blocker recently approved by the Food and Drug Administration for angina, may also be useful but no data are available at this time.

Implantable Cardiac Defibrillator Therapy for Patients with Long QT Syndrome

Individuals who have prolongation of the QT interval > 600 ms should probably receive an implantable cardiac defibrillator (ICD), although arguments can be made for using an ICD only after failure (syncope, cardiac arrest) of beta blockers, left cardiac sympathetic denervation, and pacemaker therapy. In patients with long QT whose first presentation is resuscitated

TABLE I Key features of the different long QT syndromes

Cardiac phenotype	Clinical syndrome usually precipitated by...	Channelopathy (% of patients)	Inheritance ^a	T-wave characteristics	Normal ECG (%)	Therapy	Use of ICD in asymptomatic patients
LQT 1	Exercise or stress	I _{Ks} (45%)	Autosomal dominant	Broad	12	Beta blockade	QTC > 600 ms, T wave alternans positive
LQT 2	Stress/rest, auditory stimuli	I _{Kr} (45%)	Autosomal dominant	Notched	17	Beta blockade, cardiac sympathetic denervation, pacemaker	QTC > 600 ms, T wave alternans positive
LQT 3	Rest	Late Na (10%)	Autosomal dominant	Longest QT prolongation	5	Beta blockade, mexilitene, pacemaker, ? ranolazine	Consider in all

^a The recessive form combines the cardiac phenotype with deafness.

Abbreviations: ECG = electrocardiogram, ICD = implantable cardiac defibrillator, I_{Ks} = slowly activating component of delayed rectifier potassium current, I_{Kr} = rapidly activating component of delayed rectifier potassium current, LQT = long QT syndrome.

cardiac arrest, ICDs should be used. A positive T wave alternans may be a poor prognostic sign in patients with long QT since this is a sign of enhanced electrical instability, although the data are limited in this entity.

Drugs to Be Avoided in Patients with Long QT Syndrome

Among the drugs that should be avoided in patients with long QT syndrome are the following:

1. Antiarrhythmics: those that prolong the QT interval, for example, quinidine and sotalol
2. Antihistamines: for example, terfenadine
3. Antimicrobials and antifungal agents: the most common agents are bactrim, erythromycin, ketoconazole, clindamycin, and clarithromycin
4. Psychotropic drugs: if a patient with long QT syndrome needs a psychotropic drug, warning labels of these drugs should be checked to determine whether they prolong the QT interval.

Summary

Patients with long QT syndrome are most commonly of three types. It is important to understand several points about this potentially lethal syndrome:

1. What precipitates the syndrome?
2. What channelopathies are involved?
3. What are the characteristic T-wave abnormalities seen in patients with long QT syndrome?
4. What therapy should be initiated?
5. Who needs an ICD?

Table I summarizes several key features of the different long QT syndromes.

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Suggested Reading

Chiang CE, Roden DM: The long QT syndrome: Genetic bases and clinical implications. *J Am Coll Cardiol* 2000;36:1–12