The idiopathic long QT syndrome (LQTS) is a congenital disease with frequent familial transmission, characterized primarily by prolongation of the QT interval and by the occurrence of life-threatening tachyarrhythmias, particularly in association with emotional or physical stress. Among untreated symptomatic patients, lethality is high, with 20% mortality in the first year after the initial syncope and approximately 50% within 10 years; however, the risk of death varies among different families. This poor prognosis has been significantly improved by the use of pharmacological or surgical antiadrenergic therapy or both, which has reduced long-term mortality to <5%. The availability of effective therapy for this often lethal disease emphasizes the importance of early and accurate diagnosis. Unfortunately, there is frequently a delay in the diagnosis of LQTS, and patients with syncope are often misdiagnosed, most commonly as affected by a seizure disorder.

In its most characteristic presentation, with obvious QT prolongation and stress-induced syncope, the diagnosis of LQTS is quite straightforward for physicians aware of the disease. In cases of borderline QT prolongation and/or absence of symptoms, however, a correct diagnosis may be more difficult. It was for this reason that a first set of diagnostic criteria (Table 1) was proposed in 1985. The major merit of that proposal was that it provided a logical and quantitative approach to the clinical diagnosis of LQTS by giving a different weight to major and minor criteria. Its major limitation was that it used the traditional, but untested for diagnostic purposes, cutoff value of QTc >440 msec. This also resulted in a rather black-and-white situation in which patients were judged to have an entirely normal or abnormal duration of ventricular repolarization on the basis of a difference of a few milliseconds in a measurement fraught with difficulties, such as interobserver variability.

Three events have contributed to a reassessment of those diagnostic criteria. The first has been the quantification of the traditionally known but previously poorly documented sex-related differences in the duration of ventricular repolarization. Merri et al analyzed a large series of normal individuals and found that the average QTc values were significantly longer among women than men (421±18 versus 409±14 msec, P<.0001). These data suggest that different QTc criteria are necessary for men versus women and that approximately <2.5% of normal men and women have QTc values >440 and >460 msec, respectively.

The second event has been the progressive realization that the spectrum of clinical abnormalities observed in LQTS is larger than previously realized and that it includes several features that might contribute to a more accurate diagnosis. These abnormalities have been documented, almost always in case-control studies, to occur frequently in LQTS patients and quite rarely among healthy control subjects. They include the following: (1) a larger than normal area of negative potentials in the anterior chest leads and a complex multipolar distribution as assessed by body surface mapping. These findings suggest the presence of delayed repolarization of the anterior ventricular wall, of regional electrical disparities in the recovery process, and of a high degree of dispersion of ventricular recovery times. (2) Several other quantifiable components of ventricular repolarization in addition to the QT interval are prolonged among LQTS patients. (3) Two peculiar mechanical abnormalities have been demonstrated by echocardiography, namely, a more rapid early contraction and a much longer time spent at a very low thickening rate just before the fast relaxation. (4) Peculiar changes in the T wave and an abnormal relation of QT interval to cycle length changes during and after exercise. (5) Biphasic or notched T waves are frequently present in several ECG leads.

Since some of these recently described abnormalities have not yet been confirmed by other investigators or, as in the case of body surface maps, are not readily observed, they have not been entered into the new diagnostic criteria. However, they may become valuable diagnostic tools and may be included in subsequent versions of diagnostic criteria. At this time, these additional clinical features may already be of practical value when dealing with borderline patients, those identified by the new diagnostic criteria as having an "intermediate probability of LQTS."
The third event has been the contribution of molecular biology to the genetic understanding of LQTS. Keating et al found linkage in three LQTS families with a DNA marker at the Harvey ras-1 locus, located on the short arm of chromosome 11. This linkage has been confirmed in some additional families but not in others. This supports the concept of genetic heterogeneity in LQTS, a notion that reflects the differences in clinical manifestations and particularly in the degree of malignancy known to be present in LQTS families. After Harvey ras-1 linkage had been identified, Vincent et al described the range of QTc of 83 LQTS gene carriers and 199 noncarriers. Several findings emerged. First, a large overlap of QTc values existed between carriers and noncarriers; the overlap range was 410 to 465 msec and included about 60% of all 242 study subjects. Second, approximately 5% of LQTS gene carriers (all males) had QTc values <440 msec, confirming previous suspicions of "normal QTc" LQTS patients. Third, the sex difference in QTc values was confirmed for LQTS patients, since a QTc of ≥480 msec in females and of ≥470 msec in males was 100% predictive of positive linkage. These findings emphasized the limitations of QTc measurement for LQTS diagnosis; indicated that any single QTc cutoff point might lead to misclassifications and, therefore, that a variable weighting of QTc was necessary; and further supported the need for non-ECG criteria for LQTS diagnosis.

It was on the basis of these developments and of the attendant implications that we felt it necessary to upgrade the criteria for diagnosing LQTS. The new diagnostic criteria are listed in Table 2, with relative points assigned to various ECG, clinical, and familial findings. The score ranges from a minimum value of 0 to a maximum value of 9 points. On the basis of our experience, we have arbitrarily divided the point score into three probability categories: (1) ≤1 point, low probability of LQTS; (2) 2 or 3 points, intermediate probability of LQTS; and (3) ≥4 points, high probability of LQTS. Since QTc overcorrects at fast heart rates, additional diagnostic caution is necessary when scaling with a tachycardia patient.

Note, QTc >480 msec is assigned the highest value (3 points), but QTc prolongation (QTc >450 msec) is not an absolute prerequisite for the diagnosis of LQTS. Note also that torsade de pointes and syncpe with stress are each assigned a value of 2 points, but they are mutually exclusive. Torsade de pointes receives no points if the patient is taking drugs known to favor QT prolongation. We felt it important to include some aspect of family history in the diagnostic criteria, but we assigned low point values for the presence of family members with overt manifestations of the disease to avoid a potentially excessive hereditary bias. The diagnostic weight of "lower-than-normal" heart rate also has now been reduced and is restricted to children; we suggest using the lower second percentile from the large study by Davignon et al. T-wave alternans is defined as the regular alternation, in amplitude or in polarity, of two different configurations of T wave while the RR interval remains unmodified. This type of T-wave alternans is rather gross and does not need, for its detection, sophisticated computerized analyses.

When a patient receives a score of 2 or 3 points on the basis of the QT interval measurement, we suggest obtaining serial ECG records, because the QTc value in LQTS patients may vary from time to time. In this group, with an intermediate probability of LQTS, the presence of the more recently described abnormalities listed earlier may be of help to the physician in his or her diagnostic and therapeutic decisions.

### Table 2. 1993 LQTS Diagnostic Criteria

<table>
<thead>
<tr>
<th>Points</th>
<th>ECG findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A. QTc†</td>
</tr>
<tr>
<td></td>
<td>≥480 msec 0.5</td>
</tr>
<tr>
<td></td>
<td>460-470 msec 0.5</td>
</tr>
<tr>
<td></td>
<td>450 msec (males)</td>
</tr>
<tr>
<td>B. Torsade de pointes§</td>
<td>2</td>
</tr>
<tr>
<td>C. T-Wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>D. Notched T wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>E. Low heart rate for age§</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Syncope§</td>
</tr>
<tr>
<td>With stress</td>
</tr>
<tr>
<td>Without stress</td>
</tr>
<tr>
<td>B. Congenital deafness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history#</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Family members with definite LQTS#</td>
</tr>
<tr>
<td>B. Unexplained sudden cardiac death below age 30 among immediate family members</td>
</tr>
</tbody>
</table>

LQTS, long QT syndrome.

*In the absence of medications or disorders known to affect these electrocardiographic features.
†QTc calculated by Bazett’s formula, where QTc = QT/√RR.
§Mutually exclusive.
§Resting heart rate below the second percentile for age.
#The same family member cannot be counted in A and B.
#Definite LQTS is defined by an LQTS score ≥4.

Scoring: ≤1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.
certainly deserve to be followed carefully over time for the possible appearance of a more definitive diagnostic clue.

Any set of diagnostic criteria involving a quantitative score has an unavoidable arbitrary component, and we believe that, as time progresses, further updates will be possible. On the other hand, this scoring system incorporates and reflects >20 years of direct personal experience with LQTS shared by the authors. We also believe that, based on present knowledge, these diagnostic criteria represent a valid tool to facilitate the correct diagnosis of LQTS and to increase the number of affected patients who are recognized as such and who accordingly can benefit from promptly receiving the proper therapy.

Acknowledgment

This study was supported in part by National Institutes of Health grant HL-33843.

References


KEY WORDS • long QT syndrome • Current Perspectives
Diagnostic criteria for the long QT syndrome. An update.
P J Schwartz, A J Moss, G M Vincent and R S Crampton

Circulation. 1993;88:782-784
doi: 10.1161/01.CIR.88.2.782
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/2/782.citation