

Genetic testing for the long QT syndrome: who and why?

Insights for clinical management

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The long QT syndrome (LQTS), a major cause of sudden death in the young, is a well-known genetic disorder with prevalence among Caucasians of approximately 1 in 2 000 live births.⁽¹⁾ It is characterised by QT interval prolongation on the ECG and by syncopal episodes caused by a ventricular tachycardia called Torsades-de-Pointes which often deteriorates into ventricular fibrillation.^(2,3) Most of these arrhythmic episodes occur during physical or emotional stress, but they may also occur at rest.⁽⁴⁾ Thirteen LQTS genes have been identified so far⁽³⁾ but more than 90% of cases are due to mutations on 3 genes encoding the I_{Ks} (LQT1) and I_{Kr} (LQT2) currents and the cardiac sodium current (LQT3). Symptomatic patients who are not treated properly⁽³⁾ have a very high risk of dying suddenly whereas for those treated with anti-adrenergic interventions, either β -blockers or left cardiac sympathetic denervation (LCSD),^(5,6) mortality has been dramatically reduced from almost 60% within 10 years from the first cardiac event to 1%.⁽³⁾ The identification in 1995-1996 of the first 3 major genes for

ABSTRACT

This article deals with a specific issue of growing importance for cardiologists or internists who happen to have to take care of a patient affected by the congenital long QT syndrome (LQTS), namely when to consider to request a genetic test. The focus is on who are the patients for whom genetic screening should be requested and why. One often ignored issue is also discussed, the potentially very serious consequences – for the patient and also for the doctor – of omitting genetic screening. The bottom line is that genetic screening for LQTS can no longer be regarded as a research tool but is an integral part of current medical management of this life-threatening but highly treatable disorder.

SAHeart 2012; 9:100-104

LQTS⁽⁷⁻⁹⁾ has represented a major revolution not only from a conceptual point of view but also from a practical one. Initially, the general attitude was that "genetics" were a lab curiosity that could interest researchers but not the clinical cardiologist who had to take the day-by-day decisions on how to best manage his/her patients. It is no longer so. Molecular screening for the diagnosis of LQTS has become an essential tool for clinical management and can no longer be ignored by clinical cardiologists. Indeed, during 2011 two different documents were produced aimed at providing guidelines for genetic screening for a variety of diseases associated with sudden death.^(10,11)

I will not discuss these documents and I will, instead, present my personal views – based on over 40 years of clinical and research experience with LQTS – on the role of genetic testing for this disease. I will discuss why genetic testing should be performed, who should undergo genetic testing, and the consequences for not performing it.

WHY IS GENETIC SCREENING REQUIRED?

For diagnostic purposes

Genetic testing should be performed whenever there is a strong or reasonable suspicion that the patient is affected by LQTS. As a

matter of fact, this is not always so obvious. It is for this reason that in 1993⁽¹²⁾ we proposed a set of diagnostic criteria which became subsequently known as the “Schwartz criteria”. These criteria were subsequently updated in 2006⁽¹³⁾ and 2011⁽¹⁴⁾ (see Table 1). They provide a quantitative score so that, for example, from 3.5 points upward the likelihood of the patient to be affected by LQTS is high. Besides its immediate use in the office for a first clinical diagnostic assessment, the Schwartz score should be used to select patients for genetic screening and its results will then be used to identify, by cascade screening, the “silent” mutation carriers (see below). It is important to keep in mind that in patients with a firm diagnosis of LQTS the success of genotyping in identifying the disease-causing mutation exceeds 80%.

For gene-specific clinical management

Gene-specific triggers for life-threatening cardiac events have been identified.⁽⁴⁾ For LQT1 patients over 90% of these events occur during conditions of sympathetic activation, physical or emotional stress. Swimming is especially dangerous for these patients and 99% of the LQTS patients with syncope while swimming are LQT1. LQT2 patients are exquisitely sensitive to sudden noises, such as an alarm clock going off or a telephone ring and 80% of the LQTS patients with noise-related syncope are LQT2. LQT3 patients most commonly die while at rest or during sleep. On the other hand, because of their normal I_{Ks} current which allows proper QT shortening during heart rate increases,⁽³⁾ LQT2 and LQT3 patients are at very low risk during exercise. After successful genotyping it becomes possible to make gene-specific recommendations to avoid risk. As an example, we discourage the use of alarm clocks and telephones in the bedrooms of LQT2 patients.⁽³⁾ Also, if a LQTS patient is found to be an LQT3 patient then we test the sodium channel blocker mexiletine which, in many of these patients, can markedly shorten the QT interval and become a useful addition to beta-blocker therapy.⁽¹⁵⁾

Genetic testing and ICD implants

The misconception that LQT3 patients are not well protected by β -blockers has led to a sort of knee-jerk reaction by which the simple notification that genetic testing has identified the patient as a LQT3 case prompts an almost immediate ICD implant.⁽¹⁶⁾ This has resulted in a large number of LQT3 patients being implanted with an ICD despite the fact that they are completely asymptomatic.⁽¹⁷⁾ The reality is quite different. It is true that LQT3 patients with syncope and cardiac arrest in the first year of life represent a special subset at very high risk and poorly responding to therapy, but most LQT3 patients without cardiac events during the first year of life, do very well on β -blockers or with LCSD without any need for an ICD.⁽¹⁸⁾ Our initial observation⁽¹⁸⁾ is fully supported by an upcoming study on over 400 LQT3 points.⁽¹⁹⁾

The genetic results also help to stratify risk, which differs according to genotype, gender, and QT length.⁽²⁰⁾ Furthermore, the intra-genic location of the mutations, their different types and functional effect are important contributors to outcome.^(21,22) The situation is

TABLE 1: 1993-2011 LQTS diagnostic criteria

			Points
Electrocardiographic findings[#]			
A	QTc*	≥480ms	3
		460 - 479ms	2
		450 - 459 (male) ms	1
B	QTc* 4th minute of recovery from exercise stress test ≥480ms	1	
C	Torsades-de-Pointes**	2	
D	T-wave alternans	1	
E	Notched T-wave in 3 leads	1	
F	Low heart rate for age [†]	0.5	
Clinical history			
A	Syncope**	With stress	2
		Without stress	1
B	Congenital deafness	0.5	
Family history			
A	Family members with definite LQTS [‡]		1
B	Unexplained sudden cardiac death below age 30 among immediate family members [‡]		0.5

[#] In the absence of medications or disorders known to affect these electrocardiographic features

* QTc calculated by Bazett's formula where $QTc = QT/\sqrt{RR}$

** Mutually exclusive

[†] Resting heart rate below the 2nd percentile for age

[‡] The same family member cannot be counted in A and B

Score	
≤1 point	low probability of LQTS
1.5 to 3 points	intermediate probability of LQTS
≥5 points	high probability
From reference 3	

becoming intriguingly more complex as we have shown that we are moving toward mutation-specific risk stratification.⁽²³⁾ Indeed, in the South African founder population that we have been extensively investigating with our partner Professor Paul Brink,⁽²³⁻²⁷⁾ we have provided the unexpected evidence that the clinical severity of this mutation (KCNQ1-A341V) which causes LQTI is strikingly greater than that of other LQTI mutations. Furthermore, in the same South African population we have found that the presence of relatively common polymorphisms on the NOS1AP gene can actually double the already high risk for sudden death in the patients carriers of the A341V mutation.⁽²⁸⁾ The practical implication is that whenever genetic testing identifies particularly malignant mutations we can modify our management in the sense of a more aggressive strategy in order to better protect our patients.

Genetic testing and identification of “silent” mutation carriers

In 1980, against current wisdom, I made the highly controversial suggestion that the spectrum of LQTS might have been larger than previously suspected and might have included individuals with a normal QT interval on the surface ECG.⁽²⁹⁾ Within 20 years this concept was vindicated,^(30,31) and the evidence of low penetrance in LQTS was provided.⁽³¹⁾ The quantification of the phenomenon was provided in 2003⁽²⁰⁾ when we showed that 37% of LQTI patients, 19% of LQT2, and 10% of LQT3 patients actually had a normal QT interval. Thus, these large numbers of individuals who apparently are not affected by LQTS actually are the “silent” mutation-carriers.

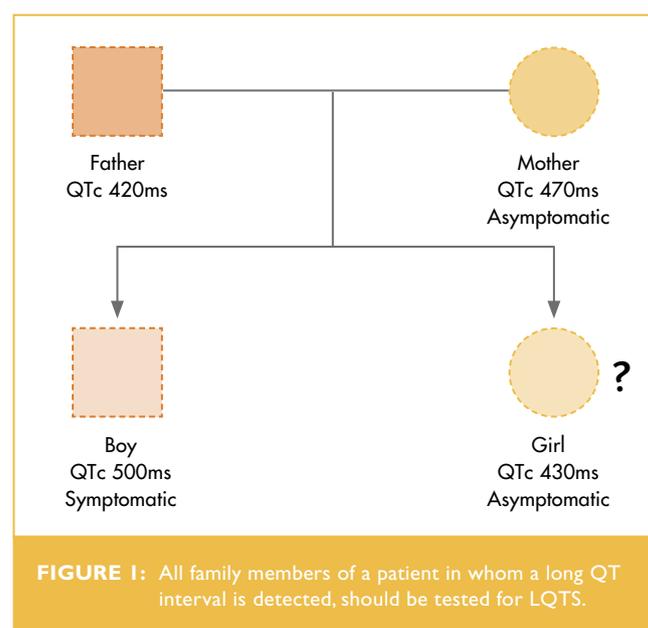
The huge clinical implication is that these individuals, who are at relatively low risk spontaneously, may become at very high risk for Torsades-de-Pointes ventricular tachycardia and sudden death if they are treated with one of the zillions drugs which have an I_{Kr} blocking activity and which are commonly used for a variety of benign conditions. Once we learn about the mutation of our patient, then it becomes easy, inexpensive, and quite rapid, to screen his/her entire family for that specific mutation. This operation, referred to as “cascade screening”,^(32,33) is one of the major benefits of genetic testing because it allows to identify mutation-carriers and to protect them from life-threatening arrhythmias by insuring that they are never treated with dangerous drugs. Also, and equally important, cascade screening allows the identification in the enlarged families of other still asymptomatic but fully affected

patients who can be rapidly placed under proper therapy. A final very important point is that cascade screening, by demonstrating the absence of the culprit mutation, allows us to reassure the non-carriers who, by living in families with recurrent sudden deaths, often and understandably have major fears and are under significant psychological stress.

WHO SHOULD DO GENETIC SCREENING?

Clearly everyone with a definite clinical diagnosis of LQTS should undergo genetic screening. The same is true for individuals with a Schwartz score >3 points, independently from presence or absence of cardiac symptoms.

- Selected survivors of out-of-hospital cardiac arrest, specifically those who in the days following the aborted cardiac arrest have a QT interval prolongation and those who had their episode in conjunction with specific triggers,⁽⁴⁾ as discussed above.
- One month old infants with a QTc >470ms and at least 2 abnormal measurements. The rationale for this statement comes from the larger prospective study of neonatal electrocardiography ever performed and is based on over 44 000 newborns.⁽¹⁾ That study, besides providing the first data-based prevalence of LQTS, showed that 43% of infants with a QTc >470ms in the first month of life were carriers of LQTS-



causing mutations. Importantly, it also demonstrated that 90% of infants with a QTc >460ms in the first month of life and who had the same QTc values at one year of life were carriers of LQTS-causing mutations. Given the clearly established relationship between LQTS and the risk of Sudden Infant Death Syndrome (SIDS),⁽³⁴⁻³⁸⁾ the possibility of an early identification and early treatment of those apparently healthy infants who nonetheless may be at risk for early death represents an important step to prevent avoidable tragedies.⁽³⁹⁾

- By the same token all victims of sudden death below age 30 and all SIDS victims should undergo genetic testing. The Mayo Clinic group has shown a percentage close to 30% of disease-causing mutations among young victims of sudden death.⁽⁴⁰⁾ Thus, genetic testing on post-mortem tissue samples can not only lead to find the cause of the lethal event but also to the diagnosis of affected family members.⁽⁴¹⁾

CONSEQUENCES OF OMITTING GENETIC SCREENING

Before the identification of the LQTS genes, a normal QT interval in the family members was sufficient to allow the physicians to exclude the presence of LQTS. This is no longer possible. Figure 1 is a cartoon depicting a fairly common situation that may present itself in our medical rooms. Imagine a family coming for diagnosis and advice after their young boy has fainted at school. You perform an ECG and observe a clear cut QT prolongation (QTc 500ms): The father has normal QTc while the always asymptomatic mother has a modest QT interval prolongation. You turn to the parents and say that the boy is affected by LQTS, almost certainly inherited by the mother, and that you will immediately start him with β -blockers at full dose. And this is all good. Then, the parents ask you: "What about our girl"? Her QTc is 430ms, within normal range. Twenty years ago you would have said: "Nothing to worry, she does not have it". Not now.

Nowadays, with the evidence that 20-30% of LQTS patients may be silent mutation carriers and have a normal QT interval we cannot say that anymore. Imagine again that the little girl is indeed a silent mutation carrier and that you have discounted her possibility of being affected just based on the normal ECG; few months later she may have an acute tonsillitis and her good pediatrician

treats her with erythromycin, which is a potent I_{Kr} blocker, and 5 days later she dies suddenly because of drug-induced QT prolongation and Torsades-de-Pointes. Cruel fate? Destiny? No, it is your fault. You, or anyone of us, have no right in assuming that a normal QT interval in a family member of a LQTS patient excludes the disease. And everything depends on genotyping the proband, the first affected member of the family who comes to medical attention. If genotyping is negative, nothing else can be done; but if it is positive then cascade screening can take place immediately.

The growing knowledge about LQTS is also complicating the lives of medical doctors and previously unsuspected reasons for medico-legal considerations are now on the table.⁽⁴²⁾ Please, remember: The physician who decided not to genotype his/her patient has also willfully chosen to ignore the possibility that some family members are silent mutation carriers. This is no longer justifiable. If genetic testing is not available, then the responsible physician should at least alert the family to the existence of this potential danger and it will be up to the family to decide the next move.

CONCLUSION

The genetic era has catapulted all of us practicing cardiologists into a new dimension. We can no longer ignore the implications of the fact that it is now possible to identify the specific mutations responsible for LQTS. Molecular screening and genetic testing do no more represent research tools, they have become a fully fledged part of what has to be routine clinical management of patients affected by the long QT syndrome.

Conflict of interest: none declared.

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