Modulating effects of age and gender on the clinical course of long QT syndrome by genotype

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Adaptation of the original article "Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. J Am Coll Cardiol 2003; 42:103-109".
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Objectives: To determine whether in long QT syndrome (LQTS), the genotype causes a different effects on the clinical course in male and female children and adults taking QTc duration into consideration.

Background: We know that genotype influences clinical course; however, data on this influence on age and gender are very few.

Methods: Patients with the three best-known variants of congenital LQTS were studied: LQT1 KCNQ1 mutation (243 cases), LQT2 HERG mutation (209) and LQT3 SCN5A mutation (81). In these three groups, the probability was analyzed, of developing cardiac events (syncopes, aborted cardiac arrest or sudden cardiac death (SCD)), taking into account genotype, gender, and age (children with an age = or < than 15 years and adults 16 to 40 years). In addition, the risk of SCD was evaluated in 1,075 relatives of carriers of the LQT1 variant of the genotype, 976 with the LQT2 variant, and 324 with the LQT3 variant.

Results: During the = or < than 15 years period, the risk was significantly higher in the LQT1 variant in males than in females (hazard ratio = 1.72). No significant gender-related difference was found for the risk of cardiac events among carriers of the LQT2 and LQT3 variants. In the adult phase, females with

the LQT1 and LQT2 variants had a higher risk of cardiac events than males. In the LQT3 variant, the lethality of cardiac events was highest in both sexes. In the LQT2 and LQT3 variants, it was higher in males than in females.

Conclusions: Age and gender have different, genotype-specific modulating effects on the probability of developing cardiac events and in the electrocardiographic presentation of the LQT1 and LQT2 variants.

The hereditary long QT syndrome (LQTS) is a familial entity characterized by prolonged ventricular repolarization and a tendency to the appearance of post-polymorphic ventricular tachycardia (PVT) syncopes of the torsades de pointes (TdP) type, that may lead to SCD**1–3**. The cause of this syndrome is due to genetic modifications in the potassium and sodium channels**4–6**. The clinical course is influenced by genotype (6-7). The LQT1 variant, carrying the KCNQ1 mutation, affects the delayed rectifier potassium channel (IKs); the LQT2 variant is responsible for the HERG mutation that affects the fast rectifier potassium channel (IKr). Both variants, 1 and 2, present a higher rate of risk of cardiac events than variant 3 (LQT3), which affects the SCN5A sodium channel**6**. However, the LQT3 variant has a higher lethality in each event when compared to the LQT1 and LQT2 variants (6). Observations made by Zareba et al and Locati et al (**8-9**) indicate that cardiac events occur more frequently in male children, who present a higher risk and earlier onset than female children.

In adults between the ages 16 to 40 years, the risk of events is lower; however, there is a gender-related difference:

-Females carriers of this entity present a higher number of events than males (**8-9**).

-QTc duration also shows differences related to age and gender, both in healthy and in LQTS patients (**11**);

-LQTS genotype influences the characteristics and morphology of ventricular repolarization in ECG (**11–13**).

The facts described above indicate that a complex relationship between genotype, age, gender, and QTc duration influences the clinical course in patients carriers of congenital LQTS, with a possible modulating effect of age and gender on the specific clinical presentation. The small number of cases constituted a limitation to study the complex relationship between age, gender and genotype (6-9). Currently, the sample has been greatly expanded, which allows investigating this relationship through cohort studies of the different genotypes of LQTS, as well as studying the influence of sex and age after determining the QTc interval.

Methods

Study population

The patients were collected from the International Long QT Syndrome Registry (**1**).

The LQTS genotype was determined in 533 patients distributed as follows:

243 patients with the LQT1 variant, carriers of the KCNQ1 mutation from 53 families;

209 patients with the LQT2 variant, carriers of the HERG mutation from 61 families and;

81 LQT3 patients carriers of the SCN5A mutation from 9 families.

Table 1 shows the three groups divided by gender, and age.

Table 1

	LQT1		LQT2		LQT3	
Age = or < 15y	Males	Females	Males	Females	Males	Females
Number of carriers	108	135	88	121	42	39
Mean follow-up in years	12+- 5	14 + - 4	13 + - 5	14 + - 4	13 + - 5	13 + - 5
Age from 16 to 40y						
Number of carriers	34	68	43	76	27	26
Mean follow-up in years	20 + - 8	18 + - 8	19 + - 8	15 + - 9	17 + - 9	17 + - 8

The initiation of beta-blocker therapy was used as an indicator for the modification of natural course of LQTS. The effectiveness and limitations of beta-blockers were recently evaluated by Moss et al (**14**).

The choice of age categories (children from 0 to 15 years and adults from 16 to 40 years) was based on the fact that risk of cardiac events occurrence changes after the age of 15 years (**8-9**).

When analyzing the risk of cardiac events in children, all gene carriers with QTc measurements < 15 years were included.

When assessing the risk of occurrence of cardiac events in adults, gene carriers with ECGs, older than 16 without cardiac events and without beta-blocker treatment were included.

The group of children included all carriers.

In the adult group, carriers with events or beta-blocker treatment were excluded. In addition to gene carriers, cardiac events in all family members carriers of the gene were analyzed, without requiring ECG or genotyping, to determine the risk of SCD and lethality of cardiac events, unbiased by QTc duration or access to genetic testing.

In first-degree family members LQTS was confirmed, for example: in the case of disease inherited from the mother, only the maternal part of a family was analyzed.

Furthermore, 1,075 such family members, including 243 carriers of LQT1, 976 family members, including 209 carriers of LQT2, and 324 family members including 81 carriers of LQT3.

ECG parameters.

The first recorded ECG was used to determine heart rate (HR) and the QTc interval by applying the Bazett formula. Because in 2/3 of carriers, the first ECG was recorded after age 15, QTc duration was analyzed by genotype and gender, using ECGs from ages 0 to 15 and from 16 to 40 years separately. This analysis was also performed excluding probands, to diminish potential bias introduced by the definition of probands (requiring QTc higher than 440 ms).

Cardiac events.

Cardiac events were defined as syncope, aborted cardiac arrest that required defibrillation, or SCD, whichever occurred first.

The cardiac events that occurred before the initiation of beta-blocker therapy were considered as the primary end point.

The analysis of the first cardiac event as a primary end point, regardless of beta-blocker use, was also performed.

The age limit with potential of confusion with coronary artery disease was 40 years. The risk of recurrent cardiac events (at least two events) and cardiac event rates per patient per year was analyzed in mutation carriers.

In family members, the occurrence of death in males versus females was compared, and gender in specific subgroups.

The lethality of cardiac events was defined as the number of deaths divided by the total number of cardiac events (**6**) and was compared between males and females by gender in genotype groups. These analyses were performed before beta-blocker treatment.

Statistical analysis.

Welsh and Wilcoxon Rank-Sum tests were used for continuous variables to compare the characteristics between men and women within a genotype. Chi-square tests were used for binary variables.

The Kaplan-Meier method was applied to study the distributions of time to first cardiac event, stratified by genotype, gender, and age.

In children, birth was used as the time origin, whereas for adults, age 16 was considered as the time origin. The Cox stratification model was used to stratify proportional hazards models

To separate baseline risk for each genotype, the conditional relationships of gender model was used, with the time of the first cardiac event within each genotype and age group, adjusted for the QTc interval at first ECG.

To group standard errors, P values and confidence intervals were used within-family dependence not directly modeled by the stratified Cox models (**15**).

Results:

ECG characteristics of LQTS carriers.

In children, the LQT3 males had a higher QTc duration and lower HR than females. There were no differences in this regard found in LQT1 and LQT2 carriers between males and females.

In LQT1 adults, there was no gender difference in QTc and HR, whereas in LQT2, females had significantly longer QTc and faster HR than males. LQT3 adult males had a longer QTc interval and slower HR than females.

When comparing by age within gender-genotype sub-groups, QTc interval was longer in LQT1 children than in LQT1 adults.

In LQT2, QTc did not present differences between male children and adults; however, between females QTc was longer in adulthood than in childhood.

Cardiac events in LQTS carriers age = or < 15 years.

In carriers with 15 years or less, there were 165 patients with cardiac events before beta-blocker treatment among 533.

There was a significantly lower risk of cardiac events in LQT1 females than in LQT1 males. In LQT2 and LQT3 children, there was no significant difference found between both sexes in carriers younger or up to 15 years.

When comparing by genotype, the cumulative probability of a first cardiac event by age 15 years was 56% in LQT1 males, 42% in females with the same variant, 33% in LQT2 males, 27% in females, and 6% to 8% in LQT3 males or females. The result was similar when using first cardiac event between patients using beta-blocker.

Cardiac events in LQTS carriers with ages ranging from 16 to 40 years.

From 274 patients, there were 68 with first cardiac event before beta-blocker treatment.

Females had a significantly higher risk than males among LQT1 and LQT2 carriers, but not in LQT3 carriers.

When comparing by genotype, and confined to patients without cardiac events before age 16, the cumulative probability of first cardiac event between ages 16 and 40 years was 48% in LQT2 females, 31% in LQT1 females, and 10% to 20% in LQT1 males, LQT2 males, and LQT3 males and females. The result was similar when using first cardiac event between patients using beta-blockers.

Recurrent events in LQTS carriers.

In carriers who had survived their first cardiac event, there was no significant difference found between males and females in the three genetic types, in the risk of recurrent events before treatment with beta-blockers.

Cardiac event rates per patient and per year were not significantly different between males and females in LQT1 and LQT2 carriers and were higher in LQT3 females than males. In this analysis there was no separation in two age groups because of the limited number patients.

Sudden death and lethality of cardiac events in members of families LQTS genotype.

Both affected and unaffected family members were included, but only from the side of a family affected, whether the mother or the father side.

In LQT1 family members, the occurrence of at least a first cardiac event and recurrent events was higher in males and females and in females among LQT2 family members than in LQT2 males and in both sexes in the LQT3 variant.

The total number of events was much higher in female LQT1 and LQT2 family members than in all other groups, indicating a higher risk of recurrent events in these.

There were 84 SCD before age 40 years in family members with LQTS genotype. In children, the occurrence of SCD was higher in males than in females between LQT1 family members; it was similarly low in males and females from LQT2 and LQT3 families. In adults, the occurrence of death was higher in females than in males among family members. However, the lethality of cardiac events in males was higher in LQT1 and LQT2 families. The lethality between LQT3 relatives was similar in both sexes; however, it was significantly higher than in LQT1 and LQT2 families.

Discussion:

In this study, it was observed that there are differences in the probability of cardiac events between male and female children and adults who are patients with congenital LQTS, indicating a genotype-specific modulating effect of age and gender primarily in the LQT1 and LQT2 variants, but not in LQT3 patients.

In the age group of children, the risk of cardiac events was significantly higher in LQT1 males than in the females with the same variant. In LQT2 and LQT3 children, there was no significant difference found between males and females for the risk of cardiac events.

Among adults who remained event-free until age 16, LQT2 and LQT1 females had a significantly increased risk of cardiac events compared with males of the same genotype, independently of QTc

interval duration. LQT1 and LQT2 males and LQT3 females and males, who remained event-free until age 16, presented a lower rate of events, unless their QTc interval would be very prolonged.

This analysis demonstrates that the rate of risk of cardiac events diminishes substantially with age in LQT1 and LQT2 males, and also decreases somewhat in LQT1 females.

In women carriers of the LQT2 variant, an increased risk of cardiac events both in children and in adults was verified.

Although the risk of cardiac events in the LQT3 variant patients was lower, the their lethality was higher and no age- and gender-dependency was observed.

The vulnerability to cardiac events changes primarily with age in LQTS males with potassium channel gene abnormalities. The risk of cardiac events in LQTS females and potassium channel alterations remain increased both in children and in adults. This effect remains this way after introducing beta-blocker therapy.

In LQT1 and LQT2 females, the recurrence of cardiac events is most prevalent, however, the rate of lethality is lower, indicating that bursts of torsades de pointes are self-terminating.

The rate of lethality is the highest in both sexes in the LQT3 variant (19% in males and 18% in females), and higher in LQT1 males than females (5% against 2%) and in LQT2 (6% against 2%).

The effectiveness of beta-blocker therapy was already studied in carriers of congenital LQTS by Moss et al. (**14**), demonstrating that the efficacy of these drugs was about 70% and that events continued to occur in the remaining 30%. Likewise, in LQT1 and LQT2 patients, these drugs were very efficient.

In this paper the authors did not perform an analysis on the effectiveness of beta-blockers in connection to gender, age and genotype, since at the time (year 2000) they did not have a sufficient number of patients that would enable the analysis of different subsets.

There is no clear explanation of why there is an age-dependent decrease in the risk of cardiac events in LQT1 and LQT2 patients. Possibly, the increased levels of serum androgens and decreased HR after puberty contribute to this phenomenon (**16**). Because there is no evidence for gender-related differences in the rate of cardiac events in LQT3 adults, it is likely that androgens modulate the function of potassium, but not that of sodium.

In experimentation animals, a decreased density of potassium currents in the myocardium of females was observed (**17**), what would yield a plausible explanation for gender-related differences in patients carrying IKr or IKs channel mutations.

Higher lethality of cardiac events in LQT3 observed in both sexes could be attributed to increased transmural heterogeneity of repolarization observed in pharmacological models of sodium channel dysfunction (**18**).

It is possible that a higher lethality of events in LQT1 and LQT2 males than females could be explained by a slower HR verified in adult males compared to females, eventually presenting non self-terminating TdP.

These differences found between genders and ages in the clinical course of the disease are accompanied by sex- and age-related differences in QTc interval duration and HR. Although previous studies showed a significantly longer QTc interval in adult LQTS females than males (**7–11**), this fact could only be confirmed in LQT2 carriers, but not in LQT1 and LQT3 carriers. LQT1 children showed longer QTc interval than adults regardless of gender.

Congenital LQTS patients who were event free until age 16 years may display a more benign course of the disease in adulthood. However, these data demonstrate that the clinical course is not homogenous in the various variants of LQTS, and that the risk of new events could be stratified by age and gender.

The cumulative risk of events in LQT2 females is 48% between ages 16 and 40 years, a comparable figure to the cumulative risk in male children, except those with the LQT1 variant (56%).

These data point out the need of follow-up and treatment in adult patients, particularly females, who remain at high risk of cardiac events despite being asymptomatic during their life in childhood and adolescence. Priori et al. (**19**) demonstrated that the differences in the clinical course are determined by the genetic background and by the degree of penetrance, even inside the same family carrying the same mutation.

There would be factors independent from genetics, such as a higher or lower sensitivity to sympathetic activation and the different degrees of heterogeneity in the myocardium repolarization, which could influence on the carriers, preventing appearance of events.

The risk of cardiac events and their rate of lethality depend on age and gender in different genetic types of LQTS, and observations on this dependence on age and gender in the QTc interval duration, indicate different modulating effects of this variables on the clinical manifestation of LQTS.

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