ORIGINAL ARTICLE

Spontaneous Variability of QTc Interval in Patients with Congenital Long QT Syndrome

Variaciones espontáneas en la duración de los intervalos QTc en pacientes con síndromes de intervalo QT largo hereditarios

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ABSTRACT

Background: QTc interval assessment is an essential tool to diagnose and stratify the risk of adverse cardiac events in patients with congenital long QT syndromes (LQTS). QTc intervals can markedly vary in shape and be intermittently prolonged only before, during and after an arrhythmic event.
Objectives: The aim of this study was to assess whether QTc intervals measured on different occasions vary significantly in patients with congenital LQTS.
Methods: QTc intervals were measured from three ECG recorded every 7 days, in 25 patients and 15 healthy controls.
Results: Both groups evidenced significant QTc interval variability. In patients with LQTS, minimum and maximum QTc were 492 ms (25-75 interquartile range (IQR) 463.5-501.5) and 522 ms (IQR 503.5-543), respectively ($p<0.0001$). In healthy individuals, these values were 409 ms (IQR 395-418) and 423 ms (IQR 413-431) ($p<0.001$). In 56% of patients, QTc intervals varied above and below 500 ms, in 24%, they were always below 500 ms and in 20% they were always above this value. QTc interval was always above 500 ms in 50% of symptomatic patients and in 10.5% of asymptomatic ones.
Conclusions: QTc intervals vary significantly in patients with LQTS. A single assessment is not enough to stratify risk.

Key words: QTc interval – Variations – Long QT syndrome

RESUMEN

Introducción: La medición del intervalo QTc es una herramienta indispensable para diagnosticar y estratificar el riesgo de eventos cardíacos adversos en los pacientes con los síndromes de QT largo (SQTL) hereditarios. Los intervalos QTc pueden variar en forma ostensible y prolongarse de manera intermitente sólo antes, durante o después de un evento arrítmico.
Objetivos: Determinar si, en los pacientes con SQTL, existen variaciones significativas de los intervalos QTc cuando se los mide en varias oportunidades.
Material y métodos: Se midieron la duración de los intervalos QTc en tres ECG registrados cada 7 días, en 25 pacientes con SQTL y 15 controles sanos.
Resultados: Los intervalos QTc variaron de manera significativa en ambos grupos. Los valores mínimos y máximos de QTc fueron de 492 mseg (rango intercuartil (RIC) 25-75: 463,5 - 501,5) y 522 mseg (RIC: 503,5 - 543) en pacientes con SQTL ($p <0,0001$), respectivamente. En los individuos sanos, dichos valores fueron de 409 mseg (RIC: 395 - 418) y 423 mseg (RIC: 413 - 431) ($p <0,001$). En 56% de los pacientes, las mediciones de los intervalos QTc oscilaron por encima y por debajo de 500 mseg. El 24% tuvo un intervalo QTc siempre por debajo de 500 mseg y el 20% siempre por encima. El intervalo QTc siempre fue mayor a 500 mseg en el 50% de los sintomáticos y en el 10,5% de los asintomáticos.
Conclusiones: En los pacientes con SQTL, los intervalos QTc varían significativamente. Una única determinación del mismo no es suficiente para estratificar el riesgo.

Palabras claves: Intervalo QTc – Variaciones – Síndrome de intervalo QT largo

Abbreviations

IQR	Interquartile range	**SD**	Standard deviation
LQTS	Long QT syndrome		

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INTRODUCTION

Congenital long QT syndrome (LQTS) is a group of disorders manifested in the electrocardiogram (ECG) as an abnormal prolongation of ventricular repolarization, predisposing to potentially malignant ventricular tachyarrhythmias which may lead to sudden death. (1)

Measurement of QTc interval on the surface ECG is an essential tool to diagnose individuals affected from this condition, and the risk of suffering adverse cardiac events (syncope or sudden death) keeps a close relationship with QTc interval duration, especially, when it is above 500 ms. (2, 3) Many factors influence QTc interval duration, such as heart rate, age, sex, circadian rhythm and different clinical situations, as hormone changes, abnormal electrolytes, the administration of certain drugs and/or the consumption of some foods and/or beverages (4-7)

Therefore, QTc intervals can undergo marked variability and may be intermittently prolonged only before, during and after an arrhythmic event. (8)

However, the diagnosis and stratification of risk in patients with this condition is based on the QTc interval measured from a single ECG recording during daytime. (9, 10)

The purpose of this study was to establish whether patients with LQTS evidence QTc interval variability when this is measured on various occasions in similar conditions. In case of QTc interval variability, could it have a different prognostic meaning in patients with congenital LQTS?

METHODS

The study included men and women from 10 to 40 years of age diagnosed with congenital LQTS according to Schwartz's and/or Keating's electrocardiographic and clinical criteria. (9, 10) Simultaneous 12-lead ECG recordings (ECGlab 2.0, USA) were obtained from each patient with an interval of 7 days between measurements. All tracings were recorded in similar conditions, during the morning, 2 hours after breakfast and after 10-minute rest, without food or drink intake that might alter them. (7) The different waves, intervals, segments and axes of QRS complexes were automatically measured, and manually verified and corrected by two independent observers. The QTc interval was defined as the time (ms) measured between the onset of the Q wave and the end of the T wave. (11) The return to the isoelectric line on the surface ECG was considered as the end of the T wave. In cases where the end of the T wave could not be established, the tangential method was applied. (8) The QTc interval was simultaneously measured from the 12-lead surface ECG in five consecutive beats. Values were averaged and corrected for heart rate according to Bazett's formula ($QTc=QT/\sqrt{RR}$, in seconds). (12)

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) or as median and 25-75 interquartile range (IQR), according to normal or non-parametric distribution, respectively. Student's t test and Wilcoxon signed rank test were used for statistical comparisons, as applicable. Qualitative variables were expressed as percentages and compared using the chi-square test. Statistical significance was established for $p<0.05$.

Ethical considerations

The protocol was accepted by the Ethics Committee of the Hospital General de Agudos Dr. J. M. Ramos Mejia and all the admitted patients or relatives, depending on the case, signed an informed consent.

RESULTS

The study included 25 patients (8 women) with LQTS and 15 healthy individuals (6 women), with mean age of 23±14 years and 22.5±14 years, respectively. Six patients with LQTS had recurrent syncopal episodes, all with family history of sudden death (Table 1). QTc intervals varied significantly in both groups. Median minimum and maximum QTc values were 492 ms (25-75 IQR: 463.5-501.5) and 522 ms (25-75 IQR: 503.5-543) in patients with LQTS ($p<0.0001$), respectively. In healthy individuals, these values were 409 ms (25-75 IQR: 395-418) and 423 ms (25-75 IQR: 413-431) ($p<0.001$) (Table 2). Heart rate did not show significant spontaneous differences [76±19 ms and 78±20 ms in patients with LQTS (p=ns) and 80±17 ms and 82±19 ms in healthy controls (p=ns)].

In 14 patients (56%), QTc interval assessments varied above and below 500 ms. In 6 patients (24%), the QTc interval was always below 500 ms and in 5 (20%) it was always above this value. An example of these variations is shown in Figure 1.

In the 6 patients with history of syncope, 3 (50%) always had QTc intervals above 500 ms, in 2 (33.3%) it fluctuated above and below 500 ms and in 1 (16.6%) it was always below 500 ms. Among the 19 asymptomatic patients, 2 (10.5%) always had QTc intervals above and 5 (26.3%) always below 500 ms, while 12 (63.1%) evidenced oscillations above and below 500 ms (Table 3).

Table 1. Clinical data

	LQTS (n=25)	Healthy (n=15)
Age (mean±SD)	23±14	22.5±14
Female gender	8	6
Family history of SD	25	0
Syncope	6	0

LQTS: Long QT syndrome. SD: Standard deviation. SD: Sudden death.

Table 2. Median minimum and maximum QTc intervals with their corresponding interquartile range (IQR) of patients with long QT syndrome and healthy controls

	QTc min. (IQR) ms	QTc max. (IQR) ms(n=15)	P
LQTS	492 (463.5-501.5)	522 (503.5-543)	<0.0001
Healthy	409 (395-418)	423 (413-431)	<0.001

QTc: Corrected QT interval. LQTS: Long QT syndrome. IQR: Interquartile range.

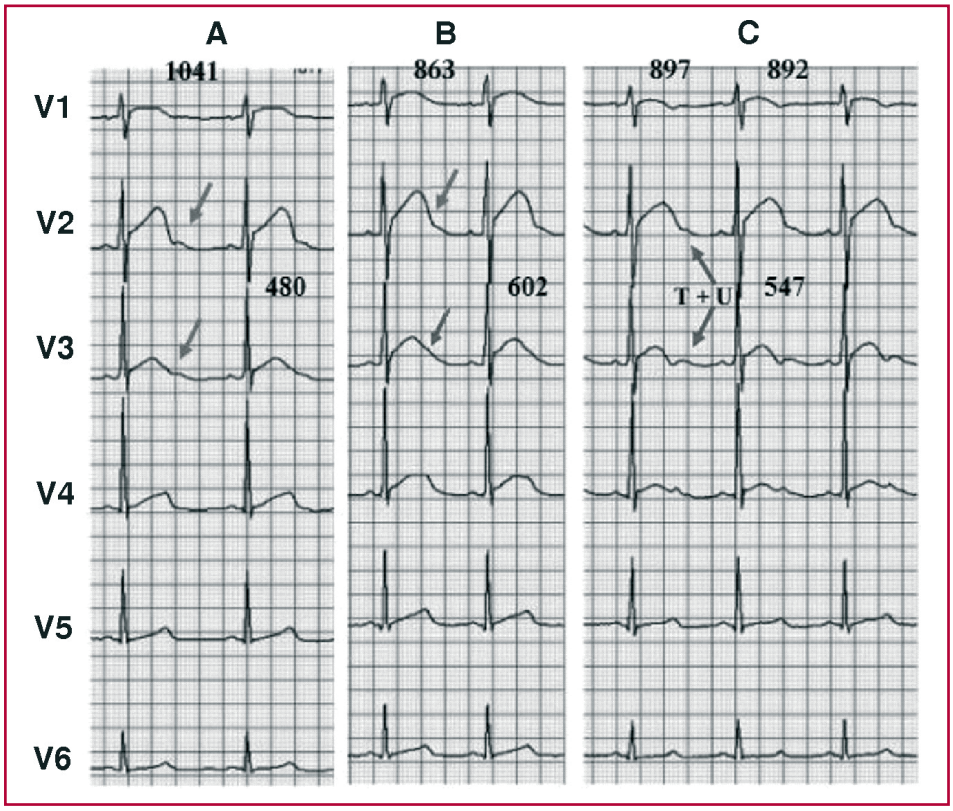

Fig. 1. Serial ECG, with a lapse of seven days between each recording, in a patient with congenital LQTS. The tracings show morphological changes in the T wave and QTc interval variability in the different recordings. A) In the first ECG, with RR interval of 1,041 ms, the QTc interval was 480 ms. The U wave appeared before the end of the T wave (*arrow*). B) In the ECG recorded one week later, with RR interval of 863 ms, the QTc interval was 602 ms, and the T and U waves were fused (*arrow*). C) In the last ECG, with RR interval of 897 ms, the QTc interval was 547 ms, and the U wave was separated from the T wave (*arrow*).

Table 3. Proportion of individuals with or without QTc interval variability in patients with symptomatic and asymptomatic long QT syndrome

	Symptomatic	Asymptomatic	p
QTc always ≥500 ms	3 (50%)	2 (10.5%)	0.03
QTc ≥ and <500 ms	2 (33.3%)	12 (63.1%)	NS
QTc always <500 ms	1 (16.6%)	5 (26.3%)	NS

DISCUSSION

Congenital LQTS described by Jervell and Lange-Nielsen in 1957 and Romano and Ward in 1964 is a familial cardiac syndrome characterized by altered ventricular repolarization. It is manifested as an abnormal prolongation of the QTc interval on the surface ECG, a situation which predisposes to potentially lethal ventricular arrhythmias (torsades de pointes and/or ventricular fibrillation). (13, 14)

To date, a total 15 congenital LQTS genotypes have been identified (LQTS-15) with mutations distributed in different specific genes (KCNQ1, HERG, SCN5A, KCNE1, KCNE2, ANKB, KCNJ2, CACNA1c, CAV3, SCN4B, AKAP9, SNTA1, GIRK4, CALM1 and CALM2, respectively) codifying proteins forming the potassium, sodium and calcium channels. (15) The specific genetic mutation is unknown in approximately 25% of patients, and the diagnosis is only based on the QTc intervals measured on the surface ECG. (16)

The duration of the QTc interval may vary dynamically and spontaneously according to sex, age, altered internal milieu, use of certain drugs and food/beverage intake, both in individuals with cardiac diseases as in healthy subjects. (4, 7, 17-20)

For more than two decades, it has been known that the QTc interval varies according to a circadian pattern, being longer at night (sleep) than during daytime (wakefulness), keeping an inverse relationship with heart rate changes and reflecting the influence of the sympathetic and parasympathetic nervous system (shortening and prolonging the QT and RR intervals, respectively). The continuous measurement of QT interval from the dynamic ECG of 24-hour Holter monitoring showed that the moment of longer QTc interval duration was the first hours after waking up. This phenomenon occurs because the abbreviation of the QT interval (which requires changes in action potential duration of ventricular myocardial cells) is delayed (QT hysteresis) with respect to the increase in heart rate. (21, 22)

Several studies performed in animals or humans (those dependent on permanent pacemaker, with autonomic denervation due heart transplantation or in diabetic neuropathy) confirm that the autonomic nervous system influences QTc interval duration acting directly (through alterations in the ionic currents originating

the action potential) or indirectly (by changing the RR intervals). (23-26)

In 2009, Hinterseer et al. showed beat-to-beat dynamic variability in the QTc intervals of patients with congenital LQTS. According to these authors, carriers of this disorder, especially those at high risk (with QTc interval ≥500 ms or with history of syncopal episodes), evidenced significant QTc interval variability measured during 30 consecutive beats. (27)

The results of our study showed that patients with congenital LQTS present marked changes in the QTc interval of ECG recorded in different days (lapse of 7 days between each ECG recording), similarly to the short-term variability observed by Hinterseer et al. (27) A prolonged QTc interval ≥500 ms in the three ECG recordings was a more common finding in symptomatic patients (with history of syncopal episodes) than in asymptomatic patients (50% vs. 10.5%, respectively; p=0.03). Wide variations in the duration of QTc intervals above and below 500 ms were also observed in both groups (33.3% vs. 63.1%; p=ns), and even occasionally, values below 460 ms were recorded.

Normally, congenital LQTS is diagnosed (QTc ≥480 ms in asymptomatic subjects or a QTc ≥460 ms in subjects with syncope) and the risk of adverse cardiac events is stratified measuring the duration of the QTc interval obtained from a single ECG recording (2, 3)

According to the results of our study, the assessment of the QTc intervals obtained from different ECG recordings with a lapse of several days in between is more appropriate both to diagnose and to stratify the risk of suffering adverse cardiac events in patients with LQTS, thus avoiding wrong therapeutic decisions.

Limitations

The present study evaluated the magnitude of the spontaneous and dynamic mid-term variability of QTc interval in patients with congenital LQTS. Because only a limited number of patients (n=25) aged between 10 and 40 years was included, the results cannot be extended to all syndrome carriers. The diagnosis of LQTS was based on clinical and electrocardiographic criteria according to current international guidelines. As no genetic mapping was done, the differences in the variability of QTc intervals between genotypes (LQT1-15) were not analyzed.

CONCLUSIONS

The QTc interval of patients with congenital LQTS may undergo significant variations in the ECG obtained on different weeks. Therefore, only one QTc interval assessment would not be sufficient to stratify the risk of suffering adverse cardiac events in patients with congenital LQTS.

Conflicts of interest

None declared
(See author´s conflicts of interest forms on the web / Supplementary Material)

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