

Long QT syndrome type 2 – can alarm clock really kill? (RCD code: V-1A.2)

Marek Czajkowski*

Students' Scientific Association, Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wrocław Medical University, Wrocław, Poland

Abstract

This paper's aim was to critically analyze existing research supporting statement found in many review articles that auditory stimuli may specifically and exclusively trigger cardiac events in patients with type 2 of congenital long QT syndrome (LQTS2). By the use of thorough systematic literature search relevant papers were gathered and analyzed. As a result, 8 publications were included in this analysis: 5 case-series studies, 2 single case reports and 1 expert opinion. 5 of the studies proved that auditory stimuli often precede cardiac events in patients with many types of congenital long QT syndrome (LQTS). None of the included studies concerned auditory stimulus as an exclusive trigger of cardiac events in LQTS2 patients (it was most often combined with exercise and/or sleep, or performed on groups with small part of LQTS2 patients). There is lack of strong evidence that auditory stimuli specifically and exclusively trigger cardiac events in patients with LQTS2. However, high occurrence of cardiac events shortly after being awoken from sleep by auditory stimuli and nocturnal deaths in families of patients with LQTS2 may provide indirect support. Due to high risk associated with auditory stimuli for patients with all types of LQTS it is still advisable for them to remove loud and noisy equipment from their close environment. JRCD 2014; 1 (7): 4–6

Key words: LQTS2, auditory stimuli, cardiac events

Introduction

Type 2 of congenital long QT syndrome (LQTS2) is a rare arrhythmogenic disorder caused by a hereditary mutation in KCNH2 gene, lying in the q35–36 region of chromosome 7 (locus LQT2) and encoding HERG protein, which is α -subunit of potassium (K^+) channel (I_{Kr}) [1]. This mutation causes abnormally prolonged repolarization of ventricular heart cells and subsequently lengthens the QT interval on electrocardiogram (ECG) [2] (corrected QT, QTc >450 ms in males and QTc >470 ms in females [3]) (Figure 1). In addition, LQTS2 is characterized by low T-wave amplitude in the extremity leads on ECG.

Many review articles on topic of long QT Syndrome (LQTS) suggest that particularly in patients with LQTS2 cardiac events are triggered specifically and exclusively by auditory stimuli but in most cases this suggestion is not supported with relevant evidence in references.

Aim

The aim of this review is to evaluate whether there is sufficient data to imply that auditory stimuli can be the trigger of cardiac events in patients with LQTS2.

Methods

A literature search in PubMed database (1972–2014) and Google search engine as well as manual cross-referencing were performed to identify papers qualifying the terms “long QT syndrome”, “LQT2”, “auditory stimuli” and “cardiac events”. All gathered available English language papers in full versions were analyzed. Additionally, PubMed database (2005–2014) was searched for review articles regarding “Long QT Syndrome” and their references supporting the claim that auditory stimuli trigger cardiac events in patients with any type of LQTS were analyzed. Relevant papers were categorized according to their level of evidence as well as analyzed for the number of patients with LQTS2 and the evi-

Conflict of interest: none declared.

* Corresponding author: Students' Scientific Association, Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wrocław Medical University, Wrocław, Poland, Oświęcimska street 147B, 45-641 Opole, tel.: +48602709655; e-mail: maroczajkowski@gmail.com

Copyright © 2014 Journal of Rare Cardiovascular Diseases; Fundacja Dla Serca w Krakowie

dence that auditory stimuli trigger cardiac events in patients with LQTS2.

In our analysis we recognized patients with LQTS2 by documented prolongation of QT interval with low T-wave amplitude in the extremity leads on ECG, by genetically confirmed mutation in KCNH2 gene or by being described as such. As an auditory stimulus we classified ringing of alarm clock, telephone or door bell, thunder, gun shot, ambulance, siren or any other sudden, unexpected loud noise. As a cardiac event we counted syncope, documented cardiac ventricular arrhythmia or sudden cardiac death.

Results

Of 8 relevant publications (Table 1), 7 studies constituting level-IV evidence were analyzed.

They consisted of 5 case-series studies and 2 single case reports. The remaining study was a level-V evidence expert opinion on neurophysiological connection between auditory stimuli and cardiac events [4]. All 5 case-series studies provided evidence that auditory stimuli often precede cardiac events in patients with LQTS. None of the studies concerned auditory stimulus as an exclusive trigger for cardiac event in patients with LQTS2. One of case-series studies proved that auditory stimulus may trigger cardiac events when combined with exercise [5], another proved the same when combined with exercise or sleep [6] and the remaining 3 studies were conducted on groups with only few patients with LQTS2 [7–9]. Also, three case-series studies proved that auditory stimuli trigger cardiac events more often in patients with LQTS2 than with type 1 of congenital long QT syndrome (LQTS1) [6–8]. In review papers on topic of LQTS, the analyzed references were always a combination of aforementioned articles.

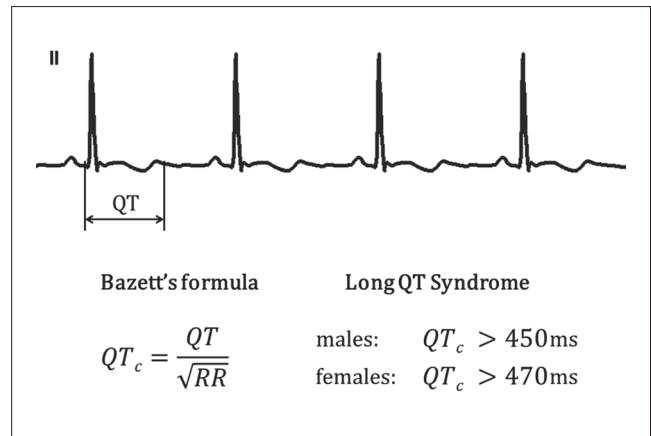


Figure 1. Prolonged QT interval on ECG in Long QT Syndrome

Discussion

There is very little research on triggering of cardiac events by auditory stimuli in patients with LQTS2. Additionally, none of the research available provide strong evidence that auditory stimulus alone can trigger cardiac event in patient with LQTS2.

There is a lack of physiologically confirmed mechanism of this connection between auditory stimuli and the triggering of cardiac events in patients with LQTS. Only one paper attempts to explain the possible neurophysiological connection between auditory stimuli and triggering of cardiac events in patients with LQTS2 [4].

First patient, presumably with LQTS2, with cardiac events triggered by auditory stimuli, was described by Wellens in 1972 [10]. Since then, very little similar cases were published [11]. From their analysis it can be inferred that the arrhythmia causing life-threatening cardiac events is most likely to begin within the first 10 seconds after auditory stimulus (Figure 2). In some cases, during this time ECG registered an increase of heart rate, T-wave inversion or ventricular extrasystoles.

Table 1. List of analyzed publications

Number	Authors	Year	Title	Level of evidence	Type of study
1	Topaz O et al.	1988	The role of arrhythmogenic auditory stimuli in sudden cardiac death	V	Expert opinion
2	Wellens HJ et al.	1972	Ventricular fibrillation occurring on arousal from sleep by auditory stimuli	IV	Case study
3	Nakajima T et al.	1995	Auditory stimuli as a major cause of syncope in a patient with idiopathic long QT syndrome	IV	Case study
4	Garson A Jr et al.	1993	The long QT syndrome in children. An international study of 287 patients	IV	Case-series study
5	Wilde AA et al.	1999	Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1)	IV	Case-series study
6	Moss AJ et al.	1999	Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome	IV	Case-series study
7	Jongbloed RJ et al.	1999	Novel KCNQ1 and HERG missense mutations in Dutch long-QT families	IV	Case-series study
8	Schwartz PJ et al.	2001	Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias	IV	Case-series study

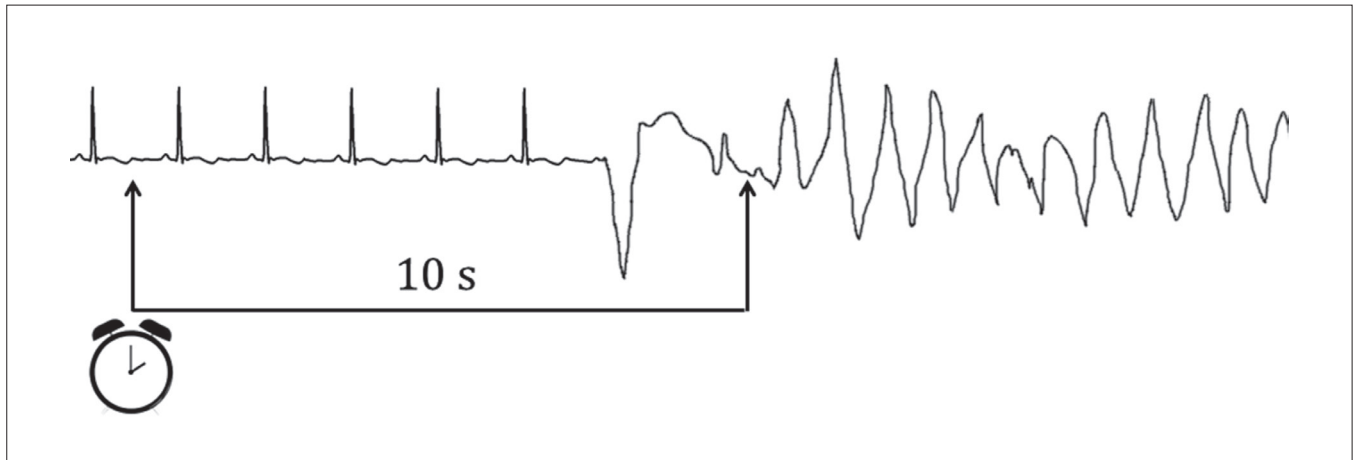


Figure 2. Cardiac arrhythmia triggered by auditory stimulus

The majority of recent review articles, claiming that specific and exclusive connection between auditory stimuli and cardiac events in patients with LQTS2 exists, lack strong evidence supporting this suggestion in references. Most frequently the references consist of 3 researches, which provide only indirect support for this claim. First of those studies identified auditory stimuli as a trigger for cardiac event in 26% of a 234 patients with LQTS2, but in this study auditory stimulus wasn't measured as an exclusive trigger [6]. In the second study, a group of 77 patients with LQTS and cardiac events triggered by auditory stimuli was gathered. Only 6 of them underwent genetic analysis and only 5 had LQTS2 [7]. The third study gathered 15 symptomatic patients with LQTS2 and 23 symptomatic patients with LQTS1. 9 patients with LQTS2 experienced cardiac events triggered by auditory stimuli, which in comparison to absence of such events in patients with LQTS1 was recognized as statistically significant [8].

In analyzed studies, high occurrence of cardiac events shortly after being awoken from sleep by auditory stimuli and cases of nocturnal death in families of patients with LQTS2 seems to be important and may also provide indirect support for this claim. Therefore, screening for such patients and their families is advisable and molecular analysis for mutation in *KCNH2* as it is in LQTS2 should be considered.

To conclude, despite the absence of direct evidence, auditory stimuli may be a significant risk factor for cardiac events in patients with LQTS2. A new, case-control or cohort study is needed to precisely evaluate if cardiac events in patients with LQTS2 are specifically and exclusively triggered by auditory stimuli. Since there is obviously high risk associated with auditory stimuli for patients with LQTS, it is advisable for them to remove alarm clocks, telephones and loud, noisy equipment from their bedrooms.

References

1. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995; 80: 795–803.
2. Roden DM, Lazzara R, Rosen M, et al. Multiple mechanisms in the long-QT syndrome. Current knowledge, gaps, and future directions. The SADS Foundation Task Force on LQTS. *Circulation* 1996; 94: 1996–2012.
3. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *Journal of cardiovascular electrophysiology* 2006; 17: 333–336.
4. Topaz O, Castellanos A, Grobman LR, et al. The role of arrhythmogenic auditory stimuli in sudden cardiac death. *American heart journal* 1988; 116: 222–226.
5. Garson A, Jr, Dick M 2nd, Fournier A, et al. The long QT syndrome in children. An international study of 287 patients. *Circulation* 1993; 87: 1866–1872.
6. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; 103: 89–95.
7. Moss AJ, Robinson JL, Gessman L, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. *The American journal of cardiology* 1999; 84: 876–879.
8. Wilde AA, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *Journal of the American College of Cardiology* 1999; 33: 327–332.
9. Jongbloed RJ, Wilde AA, Geelen JL, et al. Novel *KCNQ1* and *HERG* missense mutations in Dutch long-QT families. *Human mutation* 1999; 13: 301–310.
10. Wellens HJ, Vermeulen A, Durrer D. Ventricular fibrillation occurring on arousal from sleep by auditory stimuli. *Circulation* 1972; 46: 661–665.
11. Nakajima T, Misu K, Iwasawa K, et al. Auditory stimuli as a major cause of syncope in a patient with idiopathic long QT syndrome. *Japanese circulation journal* 1995; 59: 241–246.