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Long QT syndrome - causes and risk factors

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Abstract

Sudden cardiac death is a major public health challenge, which can be caused by genetic or acquired structural or electrophysiological abnormalities. These abnormalities include channelopathies such as long QT, short QT and Brugada syndromes. Long QT syndrome is a cardiac repolarization disorder and is associated with an increased risk of torsades de pointes (TdP). Main causes of acquired syndrome are specific medications and/or electrolytes imbalance. On the other hand common congenital causes are Jervell and Lange-Nielsen or Romano- Ward syndromes.
Patients with risk factors, treated with specified QT prolongating drugs always require slow dose titration and electrocardiography monitoring.
Aim of this study is to comprehensively and critically review the pathomechanisms of QT prolongation, risk factors and prevention methods.

Key words: Long QT syndrome, sudden cardiac death, QT prolongating drugs, channelopathies.

Introduction

Long QT syndrome (LQTS) is a cardiac repolarization disorder, and is associated with an increased risk of torsades de pointes (TdP), a life-threatening type of

polymorphic ventricular tachycardia, and sudden cardiac death [1]. Acquired forms of long QT syndrome are usually provoked by the presence of extrinsic triggers such as QT-prolonging drugs, hypokalemia, hypocalcemia or hypomagnesemia, and bradycardia. However, the most common cause of acquired LQTS are prolonging drugs which are still regularly being used in clinical practice, namely antihistamines, antiarrhythmic, antibiotics, antidepressants, proton-pump inhibitors and prokinetics. Polypharmacy often occurs in patients suffering from chronic pain. Antidepressants, opioids and neuroleptics are often combined for neuropathic pain treatment, causing significant LQTS prolongation. The association of antidepressants and antipsychotic medications with the consequent prolongation of the QT interval is well known [2]. Despite those prolongation reasons also general factors are being mentioned. Female sex category and age above 65 yr. are proven factors of LQTS. [3]. Main chronical diseases proven in QT prolongation are pheochromocytoma [4], Takotsubo cardiomyopathy [4] or Celiac disease [5]. Congenital channelopathies of potasium or sodium channels cause QT prolongation and torsade de pointes risk. Main congenital syndroms are Romano- Ward, Jervell and Lange-Nielsen. Awareness of those factors becomes crucial in clinical practice, which is why knowledge about QT prolongating drugs is strongly required.

Main Body

The QT interval is defined as the duration from the beginning of the QRS complex to the end of the T wave. It is a visual presentation of ventricular depolarization and repolarization in ECG. QT interval changes due to heart rate. It is calculated form following Bazett's formula [Figure 1.].

$$QTc = \frac{\text{QT interval in seconds}}{\sqrt{\text{cardiac cycle in seconds}}} = \frac{QT}{\sqrt{RR}}$$

Figure 1. Bazett’s formula for corrected QT interval.

Prolongation of QTc above 450ms in men and 460ms in women should be regarded as abnormal [6].

Some risk factors may also interact causing QT abnormalities such as female sex, advanced age, polytherapy, genetic predisposition, hypokalemia, hypocalcemia, hypomagnesemia, cardiomyopathy, heart failure or bradycardia [7,8]. Cardiac muscle repolarization strongly depends on voltage related potassium channels related to (hERG) human gene, which can be blocked by many medications causing LQTs [9]. There are several main groups of drugs that cause QT prolongation [Figure 2.], most of which are metabolized by hepatic cytochrome P450 (CYP450) enzymes [10]. Some of the antiarrhythmics act through direct blocking of potassium channels. Full list of updated drugs implicated in QT prolongation can be found at www.crediblemeds.org.

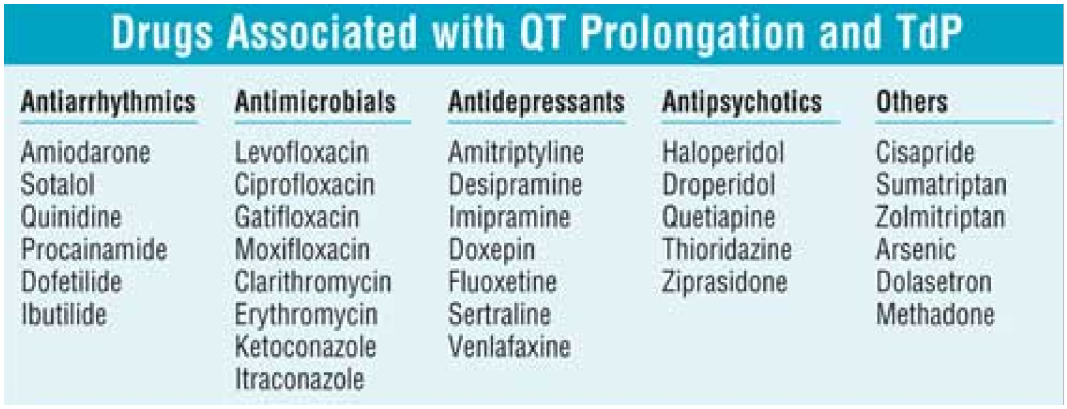

Figure 2. Main drug groups causing QT prolongation.

Antiarrhythmic drugs
Medicaments used in cardiac arrhythmia tend to be the most harmful because of their direct pathomechanism. Among all the groups especially Williams class III drugs (e.g. amiodarone, sotalol, dofetilide, ibutilide), class Ia (e.g. procainamide) and class Ic (e.g. propafenone). Apart from the well-known QTc prolongation effect, amiodarone tends to not cause TdP, when used alone [11].

Antimicrobial drugs
Macrolide antibiotics are the most common reason of QT prolongation in this group. Erythromycin and Clarithromycin metabolize through cytochromes P450 in liver, increasing risk of TdP [12]. Quinolones such as levofloxacin were also proved to cause serious arrhythmias in many studies. TdP has also been reported with antifungal drugs, mainly fluconazole [12].

Antidepressant and Antipsychotic drugs
Commonly used tricyclic antidepressants (TCA) such as amitriptyline and nortriptyline, especially overdosed, were associated with a significant risk of QT prolongation. Selective serotonin reuptake inhibitors such as fluoxetine or sertraline are also included. Venlafaxine is associated with the highest risk of LQTs [13]. Both of these groups act by blocking rapid sodium currents, causing repolarization disturbance.
Similarly, phenothiazine antipsychotics (including perphenazine and thioridazine) are well known reasons of drug induced Brugada syndrome [14]. Medicaments of these groups are also used for treatment of neuropathic pain, especially combined with opioids. Polytherapy and overdose are main reasons of hospitalisation of such patients on Toxicology Departments [15].

Antihistaminic drugs
Among antihistaminic drugs especially first and second- generation are causing QT prolongation [16]. Torsadogenic activity of loratadine, desloratadine, cetirizine and fexofenadine, was recently proven [17]. Drugs are already signed to AZCERT list. These medicaments are metabolised by cytochrome P450.

Other drugs

Opioids (e.g. methadone), antiemetics (e.g. dolasetron), proton pump inhibitors (e.g. lansoprazole) or even diuretics (e.g. furosemide) may also cause QT prolongation affecting a variety of receptor/electrolyte mechanisms [18-21].

Congenitive causes

Main congenital syndroms are Romano- Ward, Jervell and Lange-Nielsen. Both are diagnosed in childhood, mainly causing sudden cardiac death, chest pain, faint or loss of consciousness often coexisting with deafness (Romano- Ward) [22]. Several gene mutations had been found past years [Figure 3.]. Some of those are currently used for diagnose in child risk groups, presenting symptoms with ECG changes difficult to capture during examination.

LQTS Type	Chromosomal Locus	Mutated Gene	Ion Current Affected
LQT1	11p15.5	*KVLQT1* (*KCNQ1*) (heterozygotes)	Potassium current (I_{Ks})
LQT2	7q35-36	*HERG*	Potassium current (I_{Kr})
LQT3	3p21-24	*SCN5A*	Sodium current (I_{Na})
LQT4	4q25-27	Ankyrin B	
LQT5	21q22.1-22.2	*KCNE1* (heterozygotes)	Potassium current (I_{Ks})
LQT6	21q22.1-22.2	*MiRP1*	Potassium current (I_{Kr})
LQT7	17q23.1-q24.2	*Kir2.1* *KCNJ2*	Potassium current

Figure 3. Several main genes mutations involved in QT prolongation.

Studies have proven that main risk factors such as female sex, advanced age, heart failure, bradycardia or hypertension are also involved in LQTS patogenesis [23].

Conclusions

Extending heart repolarization is a serious complication caused by many substances. Increasing knowledge of clinicians causes decrease of jatrogenic QT prolongation in everyday therapy. However, the awareness of problem, knowledge of risk and possible outcomes is crucial.

There are a few strategies for reducing the risk of QT prolongation. First of all, identification of patients from risk groups such as females, advanced age, hypokalemia, hypocalcemia, hypomagnesemia, heart failure, and heart rhythm disorders. Secondly, awareness of drugs used for chronical treatment of such patients, maintaining low effective doses and avoiding polytherapy.

Thirdly, patients with identified risk factors should always be ECG monitored, treated with alternative medicaments or even some beta blockers should be given as prevention.

Physicians should always weigh the risks of potentially fatal outcomes against therapeutic benefits when making decisions about drug prescriptions. Treatment of allergy, chronic pain, depression or even infection should always make us consider QT prolongation. Future studies might prove that genetical aspect may play a key role in diagnosis and early prevention of TdP.

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