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EDITORIAL

Relevance of long QT syndrome in clinical neurology

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Abstract

Long QT syndrome (LQTS) is a cardiac conduction disorder that predisposes patients at potentially fatal cardiac events. Inherited conditions and acquired factors contribute to LQTS. A number of frequently prescribed CNS-active drugs prolong the QT interval. The clinical neurologist may encounter LQTS when initiating a pharmacotherapy or when increasing the dosage of drugs. The clinical neurologist may also encounter LQTS during the diagnostic work-up of patients with unexplained loss of consciousness, because LQTS may present as convulsive syncope. Some studies report an association of LQTS and stroke. Awareness of LQTS may help to recognize and prevent potentially fatal cardiac events associated with LQTS. This concise article highlights the clinically most relevant aspects of LQTS in the field of neurology.

Key words: Cardiac conduction disorder; Adverse drug effects; Antipsychotics; Antidepressants; Torsades de pointes; Syncope; Seizure disorder; Stroke

Core tip: Long QT syndrome (LQTS) is a potentially fatal condition. Considering the fact that many CNS-active drugs prolong the QT interval and considering the fact that diagnosis of LQTS may be missed in neurological patients with unexplained loss of consciousness, this concise article highlights the most relevant aspects of LQTS for clinical neurologists.

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INTRODUCTION

The long QT syndrome (LQTS) is characterized by an abnormally delayed repolarization of the heart. The delayed repolarization results in a prolonged QT interval that is detectable by electrocardiography. Inherited conditions (channelopathies, gender) as well as acquired factors (drugs, electrolyte imbalances, age) affect cardiac repolarization and can prolong the QT interval[1]. Different types of channelopathies that cause congenital LQTS have been described. Each channelopathy follows a distinct inheritance pattern, presents with distinct clinical symptoms and is associated with a distinct outcome. Irrespective of the affected type of ion-channel, the net result in LQTS is an abnormal repolarization of the heart muscle that predisposes at so-called early after depolarization which in turn can result in ventricular arrhythmias. The ancient discrimination between congenital LQTS and acquired LQTS seems to reflect insufficiently the underlying pathophysiology: so-called acquired LQTS may as well be unmasking of a clinically and electrocardiographically silent congenital LQTS, *i.e.,* exogenic factors (*e.g.,* hypokalemia) may be the trigger that a pre-existing (but so far clinically silent) channelopathy results in electrocardiographical changes and clinical symptoms.

SYMPTOMS OF LONG QT SYNDROME

Many patients with LQTS may not have any symptoms at

all. These patients may only be aware of their condition due to an incidental finding on the electrocardiogram or due to a family history of sudden cardiac death. If clinical symptoms are present in patients with LQTS, the spectrum of symptoms includes unspecific dizziness, fainting spells, paroxysmal tachycardia (torsades de pointes), ventricular fibrillation and sudden cardiac death. It has been reported that LQTS can also present with focal neurological signs (subsequent to a focal vascular lesion potentially caused by LQTS associated arrhythmia)[2]. Yet, a causal relationship between LQTS and a focal brain lesion remains disputable.

ANALYSING AND INTERPRETING THE QT INTERVAL

The QT interval is influenced by different factors, including gender, age and heart rate. Especially the heart rate has a major impact on the QT interval: the slower the heart rate, the longer the QT interval. It is therefore mandatory to use the frequency-corrected QT time (QT_c) when interpreting an electrocardiogram. Different formulas and standards tables are used to determine QT_c. All these formulas take into account that the (non-corrected) QT interval shortens with increasing heart rates and correct for this fact. There is a lack of unanimously accepted recommendations and guidelines concerning determination of corrected QT_c. The most often used formulas for the determination of QT_c are Bazett's formula (measured QT_c divided by the *square root* of the measured RR interval) and Fridericia's formula (measured QT_c divided by the *cube root* of the measured RR interval). The United States Food and Drug Administration (FDA) considers a QT_c < 430 ms for men and QT_c < 450 ms for women to be normal and QT_c > 450 ms for men and QT_c > 470 ms for women to be prolonged (source: http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_01_ruskin/sld023.htm).

QT INTERVAL AND CNS-ACTIVE DRUGS

A number of frequently prescribed CNS-active drugs confer the potential of prolonging the QT interval. The main mechanism by which drugs affect the QT interval is the blocking of the potassium outward current by interaction of these drugs with cardiac potassium channels. At present, more than 100 drugs have been shown to prolong the QT interval. The list of drugs discussed below does therefore not claim to be exhaustive but rather presents examples of drugs frequently used in neurological patients. More comprehensive and regularly updated lists of drugs that affect the QT interval are available one different websites (*e.g.* http://www.qtdrugs.org).

Many dopamine receptor antagonists affect the QT interval. The effect accounts for typical high-potency neuroleptic drugs (*e.g.* haloperidol, especially when injected intravenously)[3,4], low-potency neuroleptic drugs that are frequently used in the elderly due to their sedative effects, but also for atypical neuroleptic drugs[5]. Domperidone (a dopamine receptor antagonist with predominant antiemetic properties) is frequently used in patients under levodopa treatment to prevent levodopa-associated nausea. Also this antiemetic drug confers a substantial risk for LQTS with potential fatal outcome[6,7].

Another group of drugs that prolong the QT interval are antidepressants, especially some selective serotonin reuptake inhibitors (SSRI). Although there has been a number of reports concerning LQTS and SSRI, *e.g.,* citalopram[8], it is important to note that other groups of antidepressants, *e.g.,* tricyclics like amitriptyline may prolong the QT interval in a dose dependant manner as well[9].

Amantadine, a NMDA-receptor antagonist, is another potentially QT prolonging drug[10] that is frequently used in neurological patients. Amantadine is used in Parkinson's disease (due to its anti-glutamatergic properties) and sometimes also administered (off-label) for its vigilance-enhancing effects.

Besides the dugs mentioned above, polypharmacotherapy (and the resulting additive effects on the QT interval) as well as co-morbidities (*e.g.,* hypokalemia due to diuretics administered to treat hypertension or chronic heart failure) predispose the elderly neurological patient clientele to LQTS.

RECOMMENDATIONS, MANAGEMENT OF COMPLICATIONS

The clinical neurologist may prevent imminent harm to the patient by checking the patient's medication for drugs known to affect QT interval. In case a QT prolonging drug needs to be introduced or increased after careful risk-benefit assessment, the treating physician should obtain a baseline electrocardiogram in order to exclude a pre-existing prolonged QT interval. A control electrocardiogram should be obtained after introduction of the new drug and also after each dose adjustment (as QT prolonging effects are dose-dependent). In case of a significant increase in the QT interval, withdrawal of QT prolonging drugs needs to be considered. In addition, special attention should be given to prevent circumstances that may have additive effects on the QT interval (*e.g.,* hypokalemia, combination of different drugs with QT-prolonging potential). For patients with LQTS who develop torsades de pointes, the withdrawal of drugs that affect the QT interval and a cardiovascular monitoring are obligatory. Besides withdrawal of drugs that affect the QT interval, therapeutic options include the reduction of other pro-arrhythmogenic factors (*e.g.,* hypokalemia) and infusion of magnesium. Some patients with ventricular tachycardia may also require electrical cardioversion or electrical cardiac pacing. It is of importance to note that the anti-arrhythmic drug amiodarone is absolutely contraindicated in these patients due to its own QT-prolonging potential which will deteriorate the situation.

LONG QT SYNDROME PRESENTING AS "SEIZURE"

Besides the risk of inducing LQTS by pharmacotherapy, the clinical neurologist may encounter LQTS when patients with transient unexplained loss of consciousness are referred to the hospital: LQTS may present as (convulsive) syncopes that are misdiagnosed as epileptic seizures. There is a number of case reports about LQTS misdiagnosed as epileptic seizures (reviewed by Burghaus *et al*[11]). MacCormick *et al*[12] report a consecutive case series of 31 patients with genetically and electrocardiographically confirmed LQTS. Seizure disorder was the most common initial misdiagnosis in this cohort (5 of 31 patients). In some of these cases, the diagnosis of LQTS was missed despite prolonged QT intervals in the electrocardiogram. According to MacCormick's study, the misdiagnosis of LQTS as seizure disorder may be particularly fatal as the misdiagnosis "seizure disorder" resulted in a significantly longer diagnostic delay compared with other misdiagnoses (median delay 11.8 years compared to a median delay of 1 year for other misdiagnoses). Obtaining an electrocardiogram and evaluating the QT interval is therefore recommended in every patient with transient loss of consciousness, even in cases when an epileptic seizure is suspected. Gospe and Gabor stress the need to routinely and carefully assess the simultaneously recorded electrocardiogram for QT abnormalities in patients who undergo an electroencephalography[13].

Interestingly, there are also data that indicate that patients with some types of inherited LQTS-associated channelopathies have an increased risk of epilepsy[14,15]. The increased risk of epilepsy in these patients might be explained by the presence of the mutated channel proteins (and a consecutively altered channel activity) in brain tissue[14]. In conclusion, seizure disorder and inherited LQTS are not mutually exclusive conditions. In some cases, a detailed history taking and thorough diagnostic work-up (including implantable event recorders) may be necessary to distinguish between LQTS-associated syncope and seizure as the cause for a specific event.

LONG QT SYNDROME AND STROKE

There are reports that LQTS might be associated with an increased risk for stroke, even after correction for other cardiovascular risk factors[16]. The mechanisms that confer an increased risk for stroke in patients with LQTS remain speculative and may include arrhythmia-associated embolization and hypoperfusion[2]. Irrespective of the underlying causal relationship between LQTS and stroke, cardiac monitoring is obligatory in stroke patients given the increased mortality rates in these patients[17]. Stead *et al*[18] investigated the association between a prolonged QT_c and early mortality in acute ischemic stroke. The authors found a significantly increased early mortality rate in stroke patients who had a prolonged QT_c at the time of admission. In Stead's study this association was independent of other cardiovascular risk factors. The exact reasons for the increased mortality remain to be investigated. One explanation for the association of neurological disorders and LQTS (and other cardiac arrhythmias) might be cerebral arrhytmogenesis[19-21].

In summary, awareness for circumstances that can trigger LQTS and awareness that LQTS may present as seizure are important to prevent a potential fatal outcome in this condition. The studies on LQTS and stroke suggest that a prolonged QT_c is associated with a poor outcome in this patient population.

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