Prevalence and risk factors for acquired long QT syndrome in the emergency department: a retrospective observational st

Diogo Filipe Fernandes[1], Guilherme Camões[1], Diana Ferreira[1], Carolina Queijo[2], Carlos Fontes-Ribeiro[2], Lino Gonçalves[1], Rui Pina[1], and Natália António[1]

[1]Centro Hospitalar e Universitário de Coimbra EPE
[2]University of Coimbra Faculty of Medicine

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Abstract

Purpose: Long QT syndrome (LQTS) is a rare heterogeneous syndrome that may be congenital or, more frequently, acquired (aLQTS). The real-world prevalence of acquired LQTS in the emergency department is unknown.

Methods: The aim of this study was to determine the prevalence of this syndrome in the emergency room and to identify risk factors. Electrocardiograms (ECG) of 5056 consecutively patients admitted in the ER of a tertiary hospital between January 28th and March 17th of 2020 were reviewed. All patients with aLQTS were included. Clinical data with a focus on QT prolonging drugs and clinical factors were recorded. Statistical comparison was made between the groups with and without corrected QT interval greater than 500ms (value that is considered severely increased).

Results: A total of 383 ECGs with prolonged QTc were recognized, corresponding to a prevalence of aLQTS at admission of 7.81%. Patients with aLQTS were more commonly men (53.3%) with an age of 73.49±14.79 years old and QTc interval of 505.3±32.4ms. Only 20,4% of these patients with aLQTS were symptomatic. No ventricular arrhythmias were recorded. Patients with QT interval greater than 500ms were more frequently female (59,5%; p<0.001) and were more frequently on QT prolonging drugs (77,3%; p=0.025). Main contributing factor was intake of antibiotics (OR 4.680) followed by female gender (OR 2.473) and antipsychotics (OR 1.925).

Conclusions: aLQTS is particularly prevalent in the ER. Female patients on antibiotics and antipsychotics are at particularly high risk. Efforts must be made to avoid, detect and treat aLQTS as early as possible.

INTRODUCTION

Long QT syndrome (LQTS) is a rare heterogeneous syndrome that may be congenital or acquired [1], the latter being more common [2]. It is defined as a prolonged QT interval in the electrocardiogram with values greater than 470ms in men and 480ms in women [3]. Values higher than 500ms are considered severe for both genders and indicate a particularly high risk for *Torsades de Pointes* (TdP) or polymorphic ventricular tachycardia (pVT) [3,4]. An increase >60ms from QTc baseline is also considered an alarming sign [5]. pVT and TdP may present with syncope, cardiac arrest or sudden cardiac death (SCD). Timely diagnosis and treatment is crucial in order to prevent them [4,6].

Risk factors for aLQTS (aLQTS) include female gender, advanced age, metabolic disorders and cardiac diseases (acute coronary syndromes and myocarditis) [7–9].

The most common cause of prolongation of the QT interval is drug-related. A wide range of different drug classes influence repolarization, including class IA antiarrhythmics [8], class III antiarrhythmics [7], fluoroqui-

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nolones, macrolides, antifungals, antipsychotics, antidepressants, H1 antihistamine and anticholinergics [8,10–16]. Other contributors include electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesemia), hypothyroidism, hypothermia, severe bradycardia or autoimmune diseases [17]. Anorexia nervosa [18] and head trauma with subsequent subarachnoid haemorrhage or thalamic haematoma also lead to LQTS [19].

The foundation of treating aLQTS includes two pillars: identifying and stopping drugs contributing to prolongation of the QT interval; and correction of any reversible risk factors (with a main emphasis in ionic disturbances) [6,7].

The real-world prevalence of aLQTS remains to be determined and specific data regarding its prevalence in the emergency department is largely unknown. Additionally, this syndrome includes a heterogeneous group of patients that lacks better analysis.

Previous studies reported a prevalence between 28.5-35% in emergency department (ER) for QT prolongation, both acquired and hereditary [20–23]. Also of note about 25% of the patients admitted to cardiac intensive-care units (ICU) had prolonged QTc interval at admission [3] and 20-24% had a severely prolonged QTc interval when admitted to any ICU [24,25]. The prevalence of QTc interval greater than 500ms in other hospital wards was 0.7 to 0.9% [26,27]. To the best of our knowledge, there are no studies addressing specifically the prevalence of aLQTS in the ER.

Our aim was to determine the prevalence of aLQTS syndrome in patients admitted to the ER and to characterize the subset of patients at particularly high risk of TdP.

METHODS

Study design and Patient selection

We performed a retrospective study of consecutive patients admitted to the emergency department of a tertiary hospital between the 28th of January and 17th of March 2020.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee (OBS.SF.23/2021). Due to the observational aspect of this study, informed consent was waived.

Patient eligibility criteria

Patients were eligible for inclusion if they had an electrocardiogram (ECG) with a prolonged corrected QT interval (cQT) using Bazett's formula (greater than 470ms in men and 480ms in women as defined by the American Heart Association and American College of Cardiology Foundation) [3].

Exclusion criteria were the following: 1) congenital LQTS or known relative with LQTS; 2) repeated ER admissions; 3) bad ECG quality; 4) atrial fibrillation (AF)/arrhythmias; 5) pacemaker rhythm.

Data Collection

Variables retrieved were duration of the cQT (calculated using the Bazzett formula), age, gender, clinical presentation (palpitations, pre-syncope, syncope, seizure or cardiac arrest) and QT prolonging drugs or with known risk of TdP and risk factors contributing to prolonged QT interval as determined by CredibleMeds® [8].

Drugs were grouped according to drug class: antiarrhythmics, antibiotics, antihistamines, antiemetics, antifungal, immunomodulators, opioids, antipsychotics, antidepressants, diuretics, anti-migraine, bronchodilators, hormones, proton-pump inhibitors (PPIs) and others.

Study endpoints

The primary endpoint was to determine prevalence and clinical impact of aLQTS.

The secondary endpoints focused on determining risk factors for severely prolonged QT interval defined as values greater than 500ms. [3]

Data analysis

Statistical analysis was performed using IBM®SPSS® Statistics version 26. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations if normally distributed, or medians and interquartile ranges for variables with skewed distributions. Normal distribution was verified through the Kolmogorov-Smirnov test or skewness and kurtosis (maximum tolerated interval of -1 to 1).

Bivariate analysis was performed by using χ2 test (or Fisher exact test as appropriate) for categorical variables and independent t test for continuous variables. Using logistic regression, odds-ratio (OR) were determined. All reported p values are two-tailed with values inferior to 0.05 indicating statistical significance.

Results

A total of 6280 ECGs were identified. These ECGs belonged to 5056 patients. A total of 1337 ECGs were subsequently excluded. No patients with prior diagnosis of LQTS were identified. A total of 383 ECGs with prolonged QTc were recognized (figure 1). The total prevalence of aLQTS was 7.81%.

Patients with aLQTS were more commonly detected in men (n= 204; 53.3%) with an average age of 73.49 ± 14.79 years old (range 19 to 95) and average QTc interval of 505.3 ± 32.4ms (470-680ms). The majority of patients were asymptomatic (n= 305; 79.6%) and the most common symptom was syncope (39; 50%) followed by pre-syncope (n= 22; 28.2%). No TdP or pVF were documented. Baseline characteristics are shown in table 1

Sub-group analysis of patients with severely prolonged QTc interval (>500ms)

There were 163 patients with severely prolonged QTc interval (> 500 ms), corresponding to a prevalence of 3.5% (and to 42.6% of the overall aLQTS group).

Female patients (59,5%; p<0.001) and patients on QT prolonging drugs (77,3%; p=0.025) were more likely to have a severely prolonged QTc interval (table 2). Additionally, use of a greater number of drugs and particularly, intake of antibiotics (p=0.004), antipsychotics (p=0.014) or antidepressants (p=0.028) were associated with severely prolonged QTc interval (table 2). There was also a trend for prolonged QTc intervals in patients on diuretics (p=0.051) (table 2). Of note, despite the fact that clinical factors *per se* did not lead to severely prolonged intervals, there was a tendency for a severely prolonged QTc interval in patients with a greater number of risk factors (p=0.55) (table 2). No statistically significant differences were found regarding age, clinical presentation and type of risk factors present.

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Using logistic regression, patients on antibiotics had the greatest odd of severely prolonged QTc interval (OR 4.860; 95% confidence interval(CI95%) 1.497-14.631; p =0.008). Female patients had an odd almost 2.5 times greater of severely prolonged QTc (OR 2.473; CI 95% 1.663-3.747; p < 0.001). Remaining OR are shown on figure 2.

Discussion

Acquired LQTS is an often-overlooked entity that lacks better understanding and study. Despite previous studies estimating the prevalence of LQTS in the emergency department as 30 to 40% [20–23]. to the best of our knowledge, this is the first study that attempted to analyse exclusively patients with aLQTS. Furthermore, this was the only study that used the most recent cut-off recommendations for cQT as defined by the American Heart Association and the American College of Cardiology Foundation [3]. Our results show that this syndrome is particularly common in this setting, even when accounting only for patients with a severely prolonged QTc. Similarly to other studies, we detected a that these were mainly older patients (73.7 years) [2,28]. Of note, the great majority of patients in this study had no symptoms that could draw attention to LQTS. As such, careful evaluation of the QT interval is key, even in asymptomatic patients, as it may be the only sign detected before a dysrhythmic event and death.

Regarding drugs contributing to this syndrome, most interact with the hERG gene and the I_{Kr} channel [17]. In this study, and in contrast to previous studies where antiarrhythmics had the spotlight [2,28], diuretics (and in particular, furosemide) were the drugs most commonly associated with LQTS in our emergency population. In addition to contributing to ionic imbalance, furosemide may lead to QT prolongation even when corrected for low serum levels of calcium and potassium [29], We hypothesize that the high prevalence of these drugs in our population reflects the advanced age and the fact that heart failure and hypertension are particularly frequent in the ER setting.

The second most prescribed drug class in this population was proton pump inhibitors, mainly pantoprazole. Its impact is mainly due to decreased absorption of magnesium and consequent hypomagnesaemia and not by directly prolonging QT [30,31]. This effect is particularly magnified in the presence of diuretics [30].

Psychotropic medication also plays a crucial role in a large subset of patients [32]. Antidepressants (SSRI but also tricyclic) are increasingly prescribed and used chronically [33]. The main mechanism for QT prolongation appears to be Na channel blockage in tricyclic agents and inhibition of the IKr channel in SSRIs [14]. Their impact on the QT interval demands a careful risk-benefit analysis prior to their initiation and in every hospital appointment [34,35], as excessive dosage or co-administration with other drugs such as potassium channel blockers may lead to a devastating effect [14,36]. Regarding antipsychotics, their impact has been long studied and is mainly mediated by hERG channel blockade [37]. Nearly all antipsychotics cause QT prolongation [34] but particular attention needs to be given to patients on haloperidol, thioridazine, pimozide, ziprasidone, risperidone, melperone, quetiapine as they are known to prolong QT the most [36].

Also of note are antibiotics. Macrolides and fluoroquinolones are increasingly utilized in clinical practice as beta-lactams resistance surges. Similarly to SSRIs, blockade of the IKr channel is the main contributor to QT prolongation [14,32,38]. In addition, CYP3A4 inhibition by macrolides can also increase half-life and concentration of other QT prolonging drugs and dramatically increase of QTc [14].

Classically regarded as the main culprits of prolonged QT, antiarrhythmics were found in only a small proportion of our sample. Nonetheless, the same channel blocking capabilities responsible for their antiarrhythmic effect contribute to QT prolongation and TdP [14,32,39]. As such, careful ECG monitoring, especially in class IA (quinidine, procainamide and disopyramide) and class III agents (such as amiodarone and sotalol), is needed in order to maintain a tight control of the clinical status [14].

Pertaining clinical risk factors, our study showed that patients with elevated CRP had more frequently LQTS in the ER. Recent studies showed that the inflammatory pathway affects the electrophysiological properties of cardiomyocytes, contributing to changes in repolarization and consequent QT prolongation

[40]. Heart failure was also particularly prevalent in our study population. Multiple mechanisms have also been hypothesized as contributing to QT prolongation in heart failure, including structural changes and heterogeneous depolarization, in addition to the effect of drug iatrogenesis [41,42]. Hypokalemia is also a determinant factor in prolonging QT. Its impact on the functioning of the potassium channels leads to synergy with the inhibiting properties of QT prolonging drugs and a marked increase of the risk of VF and TdP [43].

A QT interval greater than 500ms has been linked to an increased risk of ventricular arrhythmias and complications [3,27]. Our study demonstrated that female patients on antibiotics were at an increased risk of severely prolonged QT interval. Other particularly relevant contributors for this severely prolonged QTc were number of QT prolonging drugs and of clinical risk factors, and use of antipsychotics and antidepressants. Studies have shown that antipsychotics and antidepressants are being prescribed at a particularly high and increasing rate in the last years, particularly in elderly patients [44–46]. In fact, most recent national studies found an increasing trend for overall polypharmacy in the elderly, reaching in some cases a general prevalence of 8-29% [47–50]. This fact leads not only to increased direct costs in health care systems, but also greater risk of drug and clinical factors interaction. Accordingly, careful monitoring of baseline and follow-up ECG in this therapeutic setting is crucial to avoid severe QT prolongation.

Despite the increased risk of TdP, direct correlation between QT prolongation and clinical presentation remains to be fully determined [7,27]. Our study showed no link between a severely prolonged QT interval and symptoms.

Limitations

Our study was retrospective and unicentric which may have led to bias in the selection of our sample and increase the probability of the presence of confounders. Other factors contributing QT prolongation such as race and socioeconomic status were not evaluated due to the lack of reporting on the clinical data used. Additionally, it was impossible to ascertain the prognostic influence of aLQTS during follow-up and correction using Bazett's formula may overcorrect the QT interval at higher heart rate.

Conclusion

In conclusion, aLQTS is particularly prevalent in the ER setting. The complex interaction of clinical factors and drug iatrogenesis and the unpredictability of its manifestations render its management and recognition difficult but essential. Efforts must be made in order to raise clinicians' awareness in order to avoid, detect and treat aLQTS, as early possible.

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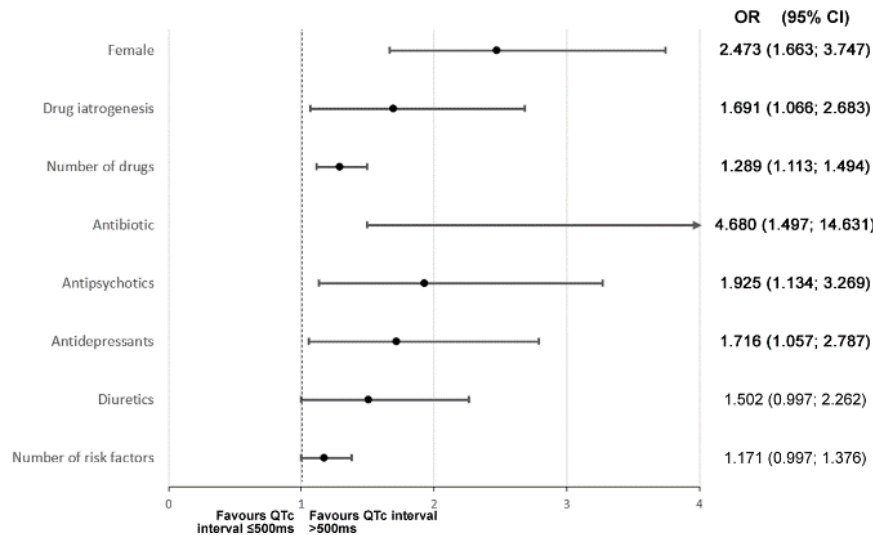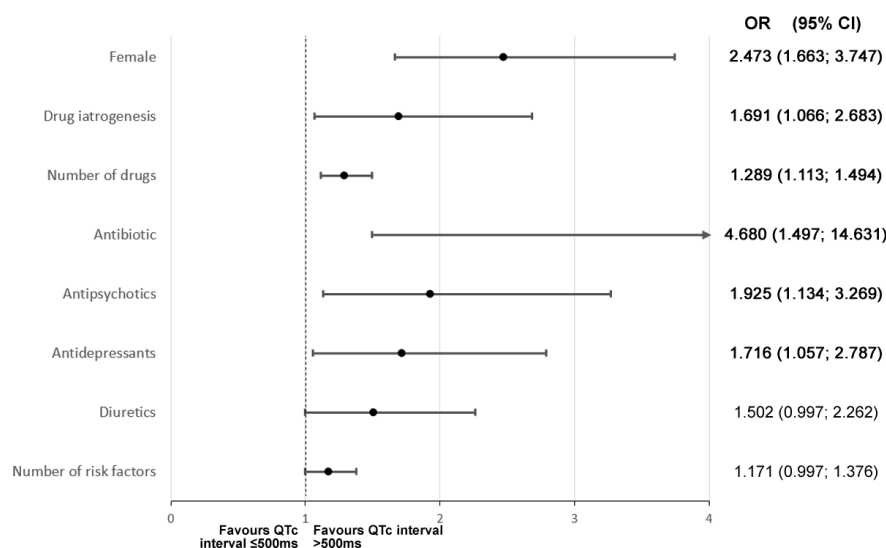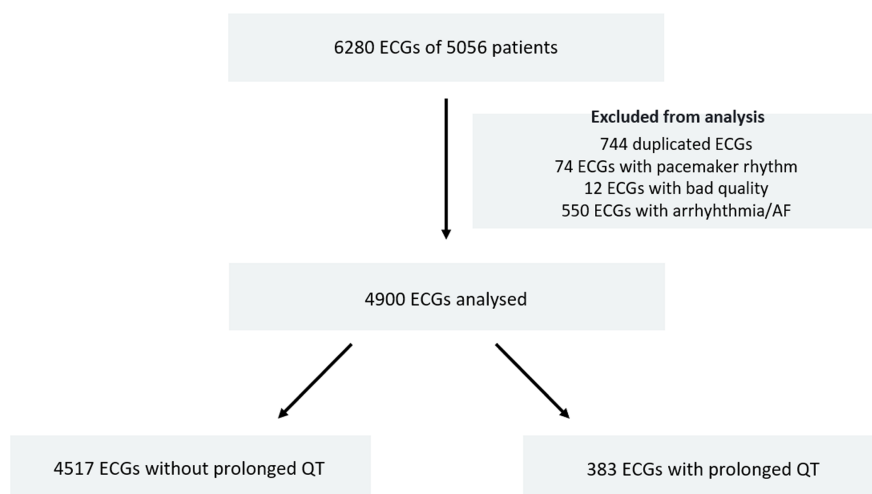
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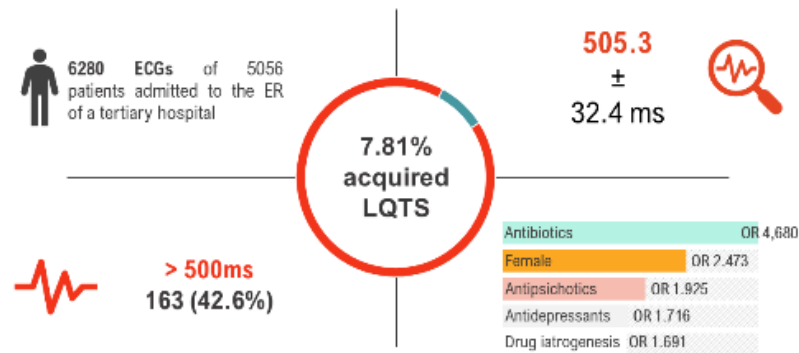
Legend: ECG – electrocardiogram; ER – emergency room; LQTS – Long QT Syndrome

Figure 1 - Flowchart of ECG selection

Figure 2 - Forest plot of contributors to severely prolonged QT interval

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