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Post-acute management of the acquired long QT syndrome

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ABSTRACT

The mechanisms underlying drug induced QT prolongation and the immediate treatment of torsade de pointes have been extensively studied but the post-acute management of the Acquired Long QT Syndrome (ALQTS) remains to be addressed. We aimed to review the state of the art data regarding risk stratification, arrhythmic prevention and treatment of patients with ALQTS. A comprehensive review of the scientific data collectable from MEDLINE, EMBASE and COCHRANE (from inception to April 2013) was performed, and descriptive and qualitative information was extracted from the most relevant manuscripts. QT prolonging drugs are widely used in hospital clinical practice, and several studies have shown a high prevalence of QT interval prolongation in patients admitted to hospital and a high rate of prescription of QT interval prolonging drugs to patients presenting with QT interval prolongation. Therefore, the acute and post-acute management of ALQTS is of the utmost importance. Avoidance of offending triggers, electrocardiographic screening, pacing at a relatively fast lower rate limit and using pause prevention programming (preferably with concomitant β blocker treatment), implantable defibrillators in the highest risk patients, genetic testing and counselling in selected cases, and family screening are among the potentially applicable strategies. The latter is justifiable by the fact that some studies unveiled a surprisingly similar positive mutation rate in drug induced LQTS compared with congenital LQTS, supporting the hypothesis that the former can be regarded as a latent form of the latter. Drug challenge with D,L-sotalol in suspected LQTS and treatment with a carvedilol analogue, verapamil or an I_{kr} activating drug are still in need of further investigation. The post-acute management of patients with ALQTS has received scarce attention in the past, probably due to the fact that it is considered a reversible phenomenon in most cases. Considering the relatively high risk of arrhythmic recurrence in the highest risk ALQTS patients, effective preventive and treatment strategies are warranted, and further research is needed.

INTRODUCTION

The Long QT Syndrome (LQTS) is an electrophysiological disorder characterised by prolongation of the QT interval on an ECG and a propensity to ventricular tachyarrhythmias, especially polymorphic ventricular tachycardia (VT) or torsade de pointes (TdP). These arrhythmias may lead to syncope, cardiac arrest or sudden cardiac death. While the congenital form of LQTS is caused by mutations of the genes for cardiac potassium, sodium or calcium ion channels, acquired LQTS (ALQTS) is most often due to specific drugs, electrolyte disturbances, transient bradyarrhythmia or cardiac structural heart disease. An increasing number of cardiac and non-cardiac drugs prolong the ventricular action potential (AP) duration by inhibiting cardiac K^+ channels in general and selectively blocking the rapidly activating delayed rectifier channel I_{kr}. Drug induced QT prolongation and TdP may represent an iatrogenic equivalent to congenital LQTS, although an overlap between the two syndromes has already been proposed.

QT prolonging drugs are widely used in hospital clinical practice, including in patients with baseline QT interval prolongation. The current inability to accurately identify individuals at high risk for TdP is of major concern given that this is a potentially fatal condition. While the QT interval is the principal marker used while screening drugs and patients for proarrhythmia, it lacks sensitivity and specificity, reinforcing the need for better screening methods. To date, no article has thoroughly addressed the post-acute management of ALQTS beyond the usual recommendation of avoiding the offending drug(s).

We aim to review current knowledge relating to post-acute risk stratification, arrhythmic prevention and treatment of patients with ALQTS. It is beyond our scope to extensively address the mechanisms and genetic aspects of ALQTS.

APPROACH

We performed a comprehensive review of scientific data collectable from MEDLINE, EMBASE and COCHRANE using the following search string: 'acquired long QT syndrome' OR 'drug induced long QT syndrome' OR 'repolarisation reserve'. Manuscripts had to have a design allowing extraction of information concerning the post-acute management of ALQTS. The reference lists of the accessed full text articles were further evaluated for sources of potential information relevant to this review.

MECHANISMS OF DRUG INDUCED PROLONGED REPOLARISATION

The duration of the cardiac ventricular AP is mediated by a balance between inward and outward currents across cell membranes. Delay in repolarisation and increase in AP duration reflects either a decrease in outward repolarising currents, primarily through potassium channels, or an increase in inward currents through calcium or sodium channels. The delayed rectifier current, comprising rapid (I_{Kr}) and slow (I_{Ks}) components, is of particular importance to the AP plateau. Mutations in genes encoding potassium, sodium and calcium channels have been associated with the

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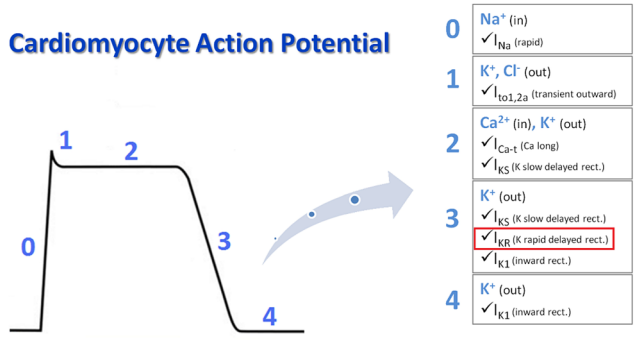

Figure 1 Multiple ionic currents ensuring maintenance of normal cardiac repolarisation. The site of action of QT prolonging drugs (the I_{kr} channel) is highlighted.

congenital form of LQTS. However, QT prolonging drugs almost exclusively target a specific potassium current, the rapid component of the delayed rectifier current I_{kr}, generated by expression of the human ether-à-go-go-related gene (HERG) (figure 1). Loss of function mutations in this channel are also associated with the congenital type 2 LQTS. Drug induced TdP often involves two other steps: (1) occurrence of early afterdepolarisations (EAD) during a prolonged repolarisation phase; and (2) generation of premature ventricular complexes when EAD reach threshold potentials, encroaching on the underlying substrate of heterogeneous repolarisation to initiate TdP or re-entrant polymorphic VT (figure 2).

EPIDEMIOLOGY OF ACQUIRED QT PROLONGATION

QT prolonging drugs are widely used in hospital clinical practice: 11.4–22.8% of patients admitted to hospital in observational studies, with 5–15% of these patients prescribed simultaneously with more than one drug with potential to prolong the QT interval.[1–3] Also, several studies have shown a high prevalence of QT interval prolongation (>500 ms) in patients admitted to hospital (24% of patients admitted to one of six critical care units over a 2 month period in a study by Pickham *et al*,[4] and 22.3% of those admitted to the internal medicine ward in a different study[5]) and a surprisingly high rate (up to 50%) of prescription of QT interval prolonging drugs to patients presenting with QT interval prolongation.[5 6] However, the exact incidences of LQTS and TdP remain largely unknown and are likely to be under reported by virtue of a failure to establish a clinical diagnosis of acquired or congenital LQTS based on baseline ECG measurements. Also, newly approved and marketed drugs often do not show evidence of significant QT prolongation until post-marketing surveillance in larger populations of advanced age and multiple comorbidities is performed. Despite these limitations, current estimates suggest that the incidence of drug induced TdP with non-antiarrhythmic drugs is 1 case in 10 000–100 000 drug exposures,[7] explaining how this potentially fatal drug effect is frequently undetected during typical pre-release trial screening enrolling 2000–3000 subjects.

QT INTERVAL MEASUREMENT

Measuring the QT interval is not always straightforward. It has been shown that only about 40% of internists and 70% of cardiologists are able to measure the QT interval properly compared with a group of experts.[8] Moreover, QT intervals vary according to ECG acquisition technique, electrolyte imbalance, intraobserver and interobserver variability, normal circadian variation, autonomic nervous system impulses and postprandial status.[9 10] Delineation of the end of the T wave when it is flat, bifid, biphasic or overlapping on a U wave is frequently difficult. The time measured from the earliest Q wave onset in any lead to the latest offset of T wave in any lead is the most reliable reflection of repolarisation duration. Nevertheless, there may be differences in the QT interval in separate leads (known as QT dispersion), and evaluation of the QT interval on serial ECGs requires using the same lead to be compared between different ECG tracings. Thus we recommend that the QT interval is measured from the beginning of the QRS complex to T wave termination and averaged over 3–5 beats in a single lead,

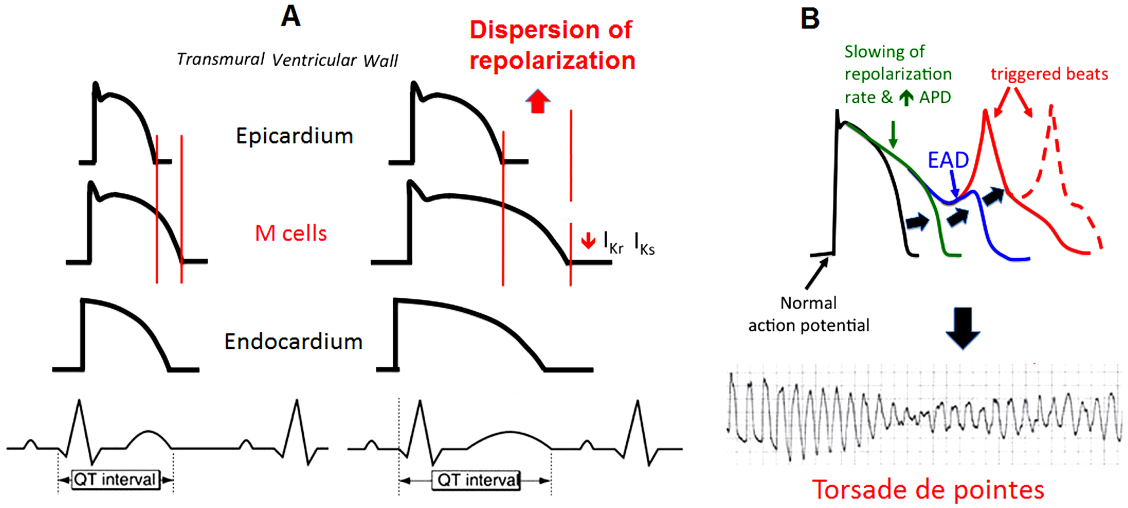

Figure 2 Diagram illustrating different features of the Long QT Syndrome. (A) Transmural dispersion of repolarisation, the action potential duration difference between different myocardial layers (epicardium, M cells, endocardium), is pronounced after the intake of QT prolonging drugs in genetically predisposed patients. (B) The occurrence of torsade de pointes usually involves different steps, including prolongation of the action potential duration (APD), occurrence of early afterdepolarisations (EAD) during a prolonged repolarisation phase and generation of premature ventricular complexes (triggered beats) when EAD reach threshold potentials, encroaching on the underlying substrate of dispersed repolarisation to initiate torsade de pointes.

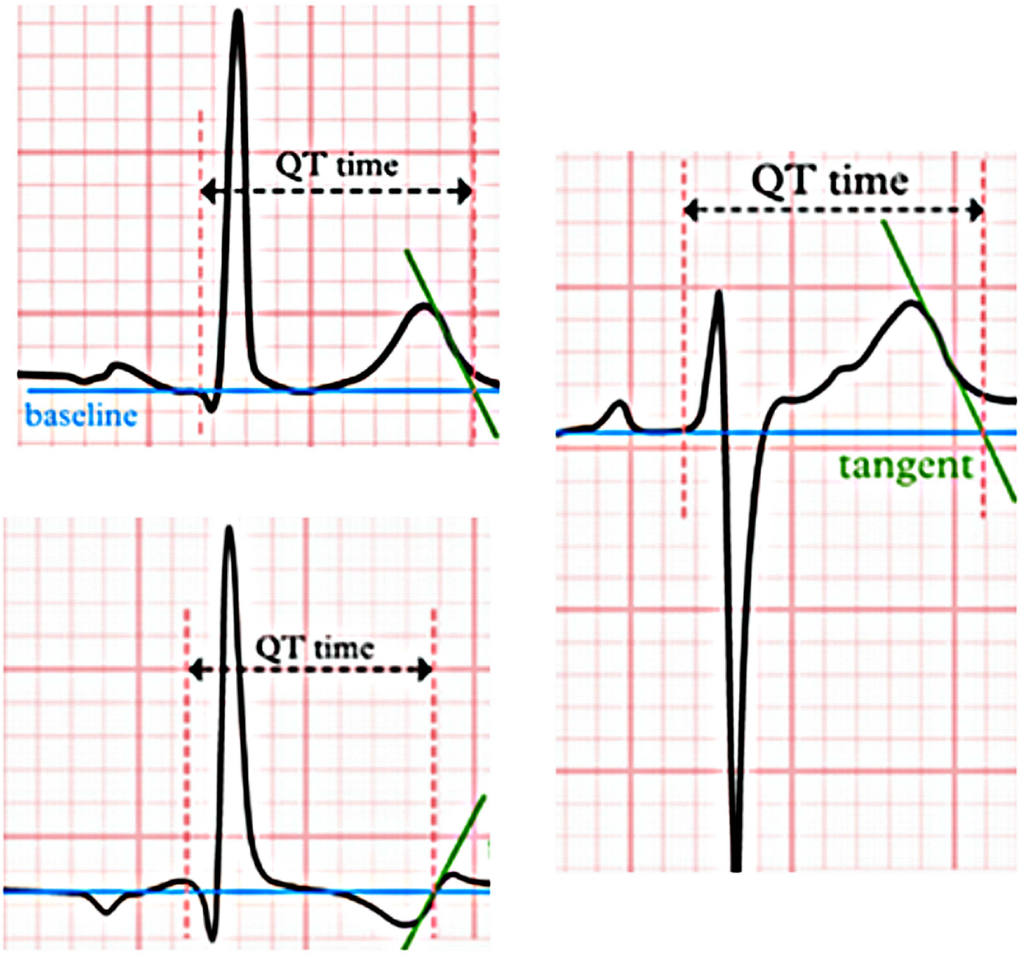

Figure 3 The maximum slope intercept method defines the end of the T wave as the intersection point between the tangent drawn at the maximum down slope of the T wave and the isoelectric line, and is a reliable method for determining the end of the T wave.

preferably V3 or V4.[11] The maximum slope intercept method defines the end of the T wave as the intersection point between the tangent drawn at the maximum down slope of the T wave and the isoelectric line, and is a reliable method for determining the end of the T wave (figure 3). Prominent U waves should be included when merging into the T wave. Also, the RR interval preceding the QT interval should be measured (3–5 consecutive beats may be averaged if the RR interval is not regular) for rate correction using either Bazett's square root formula ($QTc=QT/RR^{1/2}$),[12] Fridericia's cube root formula ($QTc=QT/RR^{1/3}$),[13] the Framingham algorithm ($QTc=QT+0.154\times[1000-RR]$)[14] or Hodges formula ($QTc=QT+1.75\times[HR-60]$).[15] Bazett's equation is the most widely used but it tends to overestimate the QT interval at fast heart rates and underestimate it at slow heart rates, and is thought to be gender biased. We reinforce the need for rate correction of the QT interval, as non-corrected values may differ substantially. Corrected QT (QTc) intervals ≥460 ms in men and ≥470 ms in women are considered prolonged,[16] although reported cases of drug induced TdP are most often seen with QTc intervals ≥500 ms, confirming similar observations from congenital LQTS.

REPOLARISATION RESERVE

Responses to QT prolonging drugs vary among individuals. A drug dose producing minimal QT prolongation in one patient may produce marked QT prolongation and TdP in a different subject, similar to the variability in the extent to which a particular mutation in congenital LQTS prolongs QT interval and leads to ventricular arrhythmias. To better understand the inter-individual variation in susceptibility to QT prolonging drugs, the concept of repolarisation reserve has been previously introduced.[17 18] It implies that normal cardiac repolarisation is achieved via multiple ion currents which provide a 'safety margin' or 'reserve'. As multiple ionic currents ensure maintenance of normal cardiac repolarisation, loss of one component will not usually lead to prolongation of the QT interval until a different component is concurrently affected (figure 4). For example, drug induced I_{kr} inhibition may lead to QT prolongation and TdP in patients with other repolarisation stressors, such as heart failure, left ventricular hypertrophy, bradycardia or hypokalaemia. Some investigators have also stressed the importance of genetic modulation of repolarisation reserve.[19] Transmural dispersion of repolarisation (figure 2), a known feature of congenital LQTS determined as the AP duration difference between different myocardial layers (epicardium, M cells, endocardium), has been shown to be more pronounced after intravenous quinidine administration in first degree relatives of patients with ALQTS compared with controls.[20] Also, genetic variations or polymorphisms in *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *SCN5A* and *ANKB* have been identified in some patients with drug induced TdP.[21] The forme fruste type of congenital LQTS results from a clinically unapparent

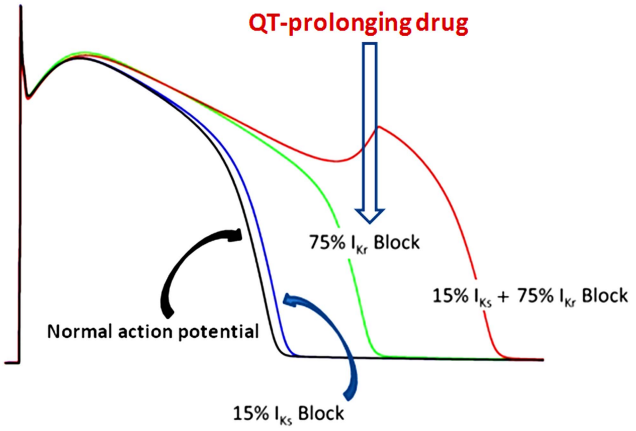

Figure 4 Concept of repolarisation reserve. Loss of one component (such as I_{ks}) will not usually lead to significant prolongation of the QT interval until a different component is concurrently affected, such as with superimposed pharmacological I_{kr} blockade.

mutation or polymorphism in one of the LQTS genes that becomes apparent when the patient is exposed to I_{kr} blocking drugs. Approximately 10–15% of the general population possess subclinical genetic polymorphisms or mutations in genes which encode for the ion channels regulating AP duration.[21] It might be that the variable expressivity and low penetrance of some of these genetic polymorphisms/mutations led to an overestimation of the true number of drug induced prolonged QT cases.[22 23]

CLINICAL MANAGEMENT

Treatment of ALQTS: where is the evidence?

Patients surviving an episode of TdP or sudden cardiac arrest due to acquired or drug induced LQTS pose a significant clinical dilemma. In general, these episodes are thought to represent a reversible phenomenon and, therefore, patients are not usually referred for more aggressive secondary prevention strategies, such as insertion of an implantable cardioverter defibrillator (ICD). In fact, in ALQTS, there is still little evidence for mandatory insertion of an ICD, provided that the precipitating cause can be safely removed and patients do not remain high risk for further events due to any baseline cardiac condition. Current guidelines only seem to support pacing to prevent pause dependent TdP in ALQTS patients (class IIa, level of evidence B).[24] Moreover, the optimal clinical management of asymptomatic patients with drug induced prolonged QT interval is also poorly understood. Avoidance of QT prolonging triggers is the mainstay treatment in most cases, but very few studies have investigated the post-acute risk of arrhythmic recurrence and the overall prognosis of these patients. Therefore, recommendations relating to the post-acute management of ALQTS are seldom evidence based and sometimes are extrapolated from the extensive research done on congenital LQTS, in particular type 2, given its mechanistic similarities to the acquired version.

Should we worry about the post-acute management of ALQTS?

Current evidence suggests there is a consistent association between prolonged QT interval and increased risk of total, cardiovascular and coronary mortality and sudden cardiac death in the general population.[25] Pickham *et al* have shown that acutely ill patients with QT prolongation may have nearly three times the odds of mortality than those without QT prolongation.[4] Their study was the first to use a continuous multi-lead QT/QTc monitoring system to examine QT prolongation in an acutely ill hospitalised population, and the authors suggested it could be prudent to provide QT monitoring to all acutely ill patients with multiple risk factors for QT prolongation. A study by Mönnig *et al* brought invaluable data to our current understanding of the real risk underlying ALQTS.[26] The authors evaluated the long term follow-up of patients with ALQTS who had received an ICD for secondary prevention of sudden cardiac arrest and reported that appropriate shocks occurred in 44% of patients during a mean follow-up of 84±55 months—128 shocks in 19 of 43 patients, secondary to polymorphic VT and ventricular fibrillation. There was no significant difference between patients with and without structural heart disease, and the results were particularly surprising given the relative normalisation of QTc interval once the proarrhythmic trigger was removed as well as the fact that none of the patients was re-exposed to the initial trigger. Although the frequency of appropriate ICD shocks was lower than that in high risk congenital LQTS,[27] it was nonetheless much higher than what would be expected after removal of the proarrhythmic trigger. As these patients had suffered an episode of cardiac arrest, we could speculate there might have been a bias towards higher risk of arrhythmic recurrence. This means that these data cannot be easily extrapolated to all ALQTS patients. Also, a proportion of the shocks reported in this study might have been unnecessary and due to suboptimal ICD programming, as inappropriately short detection times may have led to overtreatment of a significant proportion of patients. Nonetheless, their study was the first to suggest an ongoing risk of potentially life threatening arrhythmic events in ALQTS patients with a history of sudden cardiac arrest despite the apparent removal of QT prolonging triggers.

Genetic testing in ALQTS: why and when to consider it?

The risk of acquired LQTS is, in part, genetically determined. Common genetic variants associated with QT interval duration, some of which are located within genes related to congenital LQTS (such as KCNQ1, KCNH2, SCN5A and KCNE1), have been identified in the ALQTS population. This syndrome tends to occur in individuals who have a genetic predisposition but requires an additional stressor to become clinically manifest. Identification of congenital LQTS disease causing genes led to screening of large kindreds and recognition of the phenomenon of incomplete penetrance. Mutations not associated with prolonged QT interval duration may still confer a higher risk on exposure to a drug with 'QT liability'. Indeed, the subclinical congenital LQTS has been identified in up to 10–15% of probands with drug induced LQTS: mutations were reported in KCNQ1, HERG, the K+ channel subunit genes KCNE1 and KCNE2, and SCN5A, among others.[21 22] A study by Itoh *et al* unveiled a similar positive mutation rate in drug induced LQTS compared with congenital LQTS (40% vs 52%), supporting the hypothesis that the former can be regarded as a latent form of the latter.[28] In addition, Kannankeril *et al* administered intravenous quinidine to 14 relatives of patients who safely tolerated chronic therapy with a QT prolonging drug and 12 relatives of patients who developed ALQTS, and found out that the latter group had greater drug induced prolongation of terminal repolarisation (measured by the interval from the peak to the end of the T wave or the T wave peak to end interval divided by the QT interval) compared with control relatives.[20] With an anticipated yield of 10–15%,[22] LQTS genetic testing following drug induced TdP seems reasonable. The main mutations associated

with the most frequent congenital types of LQTS should be sought. Some analyses have also identified polymorphisms in LQTS ion channel genes that may be overrepresented in patients with drug induced ventricular arrhythmias and contribute to variability in an arrhythmia phenotype by altering normal channel function.[29 30] However, the very large number of candidate genes and polymorphisms, lack of consistent reproducibility and the problem of false positives limit its routine clinical applicability.

Survivors of drug induced TdP and first degree family members of drug induced case fatalities should be considered for genetic testing for the presence of an LQTS associated mutation. Unfortunately, as most ALQTS patients are not submitted to genetic testing, it is also rarely performed in their family members. When genetic testing of a patient with a severe form of ALQTS is not possible (either because the patient refuses it or has died), pharmacological challenge with intravenous quinidine[20] may be considered in asymptomatic first degree relatives with a borderline QT interval. Quinidine 300 mg should be administered intravenously over 30 min, with ECGs performed every 15 min during the infusion and 15 min after the infusion.[20] The test should be stopped if QRS duration increases by 50% from baseline, absolute QT interval exceeds 500 ms or TdP occurs. The fraction of the QT interval occupied by the descending limb of the T wave (TDR/QT) should be determined, as it is the strongest predictor for TdP in patients with ALQTS.[31] Kannankeril *et al* found that an increase in TDR/QT in lead V1 was seen in relatives of patients with ALQTS while such a finding was not seen in controls.[20]

An extensive analysis on the genetics of AQLTS is beyond the scope of this review and the interested reader should look elsewhere.[32–34]

How to identify high risk patients?

Identification of patients at highest risk for drug induced LQTS is crucial but it might be difficult to identify higher risk patients with genetic polymorphisms that manifest only after exposure to a drug. Arrhythmias are usually associated with QT intervals ≥500 ms, and the American Heart Association has considered QT intervals that have increased 60 ms from baseline to be potentially arrhythmogenic.[16] The major epidemiological risk factors for QT prolongation and TdP include older age, female gender (oestrogens are thought to increase susceptibility to TdP in women, although this is debated[35]), hypokalaemia, hypocalcaemia, severe hypomagnesaemia, baseline QT prolongation, exposure to drugs with QT liability or metabolic liability (leading to high serum drug concentrations), heart failure, left ventricular hypertrophy, history of thyroid disease or myocardial infarction, and polymorphisms or mutations in genes regulating cardiac ion channel expression and ventricular repolarisation.[36–38] Hypertension and coronary artery disease are known to cause downregulation of potassium channels. Bradycardia may especially lead to underestimation of QT interval duration, but is known to prolong the QT interval and predispose to TdP.

A study by Kannankeril *et al* suggested that overweight and obese patients had greater drug effects on QTc interval than subjects with normal or low body mass index.[39] Atrial fibrillation (AF) is historically considered a risk factor for QT prolongation, but Darbar *et al* suggested that, despite ongoing rate irregularity, persistent AF could reduce the likelihood of developing TdP after administration of drugs that prolong cardiac repolarisation.[40] In patients with paroxysmal AF, bradycardia dependent prolongation of the QT interval gradually attenuates as AF sustains.[41] The post-cardioversion period seems to be the most arrhythmogenic.

With the exception of class IA antiarrhythmics, the risk of further prolongation of the QT interval increases as the dose and plasma drug concentration increase. However, although most drugs that cause TdP do so via HERG channel blocking, TdP is not necessarily a potential consequence of all drugs blocking the HERG pathway. Milberg *et al* compared the TdP induction ability of two HERG blocking drugs—DL-sotalol and amiodarone.[42] While both can increase the QT interval, the former causes transmural dispersion of repolarisation and triangulation of the AP by prolonging phase 3 and triggers both EAD and TdP. On the other hand, amiodarone does not usually cause dispersion of repolarisation, EADs or TdP, and associates to squared shaped AP by prolonging phase 2.[42] Other studies have corroborated these findings, even in patients with heart failure.[43]

Although most antiarrhythmic drugs that are able to induce TdP prolong the QT interval by at least 50 ms, there is a dissociation between the risk of QT interval prolongation and the torsadogenic potential of a particular drug. An increase in QT interval does not necessarily lead to a higher risk of TdP. Therefore, other electrophysiological markers, such as transmural dispersion of repolarisation (figure 2) (translating differences in AP durations across the ventricular wall and measured by the difference between the T wave peaks and ends or the T wave peak to end interval divided by the QT interval),[43 44] configuration of the cardiac AP (triangulation, such as that caused by DL-sotalol, is usually proarrhythmic) and the beat to beat variability of repolarisation[45] might be better arrhythmic predictors. The descending limb of the T wave is considered to be the vulnerable period for torsadogenesis. Furthermore, several ECG early warning signs such as short-long-short RR sequences, frequent pauses, fragmented QRS,[46] long QT waves with abnormal T-U complex, giant T-U waves[47] and macroscopic T wave alternans may precede the onset of TdP. Giant T-U waves, in particular, have been shown to directly precede TdP in the majority of episodes of TdP in patients with the acquired and congenital forms of LQTS.[47] These abnormal T-U waves are larger than the largest T-U waves in LQTS patients without TdP.[47] In patients with bradyarrhythmia, such as due to complete heart block, the occurrence of TdP can be predicted by a longer corrected QT interval, longer T[peak] to T[end] interval and a notched T wave similar to that seen in patients with the type 2 LQTS.[44] In this study, LQT1-like and LQT3-like T wave morphologies were rare during bradyarrhythmias, and neither the ventricular rate nor the QRS width helped predict the risk of TdP. A two step model based on QT duration and the presence of LQT2-like T waves could identify patients at risk for TdP, with a positive predictive value of 84%.

Pharmacokinetic and pharmacodynamic interactions and a changing electrophysiological substrate are also important factors. As an example, some patients prone to drug induced QT interval prolongation may not show such abnormality until a second drug increases the concentration of the QT prolonging medication. Similarly, different electrophysiological substrates, such as de novo heart failure or bradycardia, may decrease the threshold for significant QT prolongation of a certain drug.

In conclusion, although accurate identification of patients at high risk for drug induced TdP is challenging, several clinical, electrocardiographic, electrophysiological and drug related parameters may help us perform reasonable risk stratification and implement preventive measures in those at highest risk. Some of these risk factors, such as bradycardia, electrolyte disturbances,

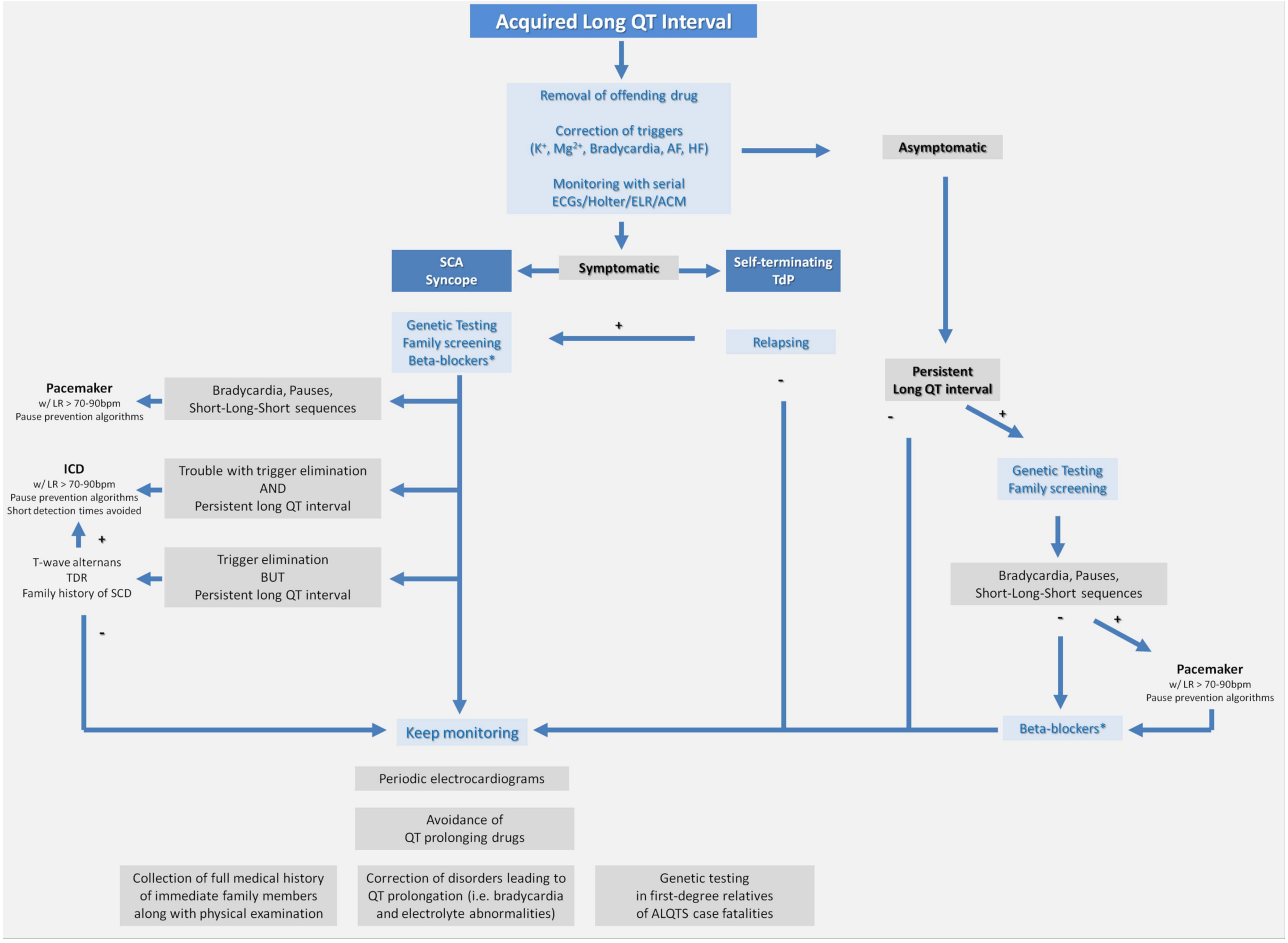

Figure 5 Algorithm for the management of the Acquired Long QT Syndrome (ALQTS). ACM, automatic continuous monitoring (for hospitalised patients); AF, atrial fibrillation; ECG, electrocardiogram; ELR, event loop recorder; HF, heart failure; ICD, implantable cardioverter defibrillator; LR, lower rate; TdP, torsade de pointes; TDR, transmural dispersion of repolarisation (traducing differences in action potential durations across the ventricular wall and measured by the difference between the T wave peaks and ends or the T wave peak to end interval divided by the QT interval); SCA, sudden cardiac arrest; SCD, sudden cardiac death. *In the absence of bradycardia, pauses or short-long-short sequences, unless added to pacing therapy.

heart failure, left ventricular hypertrophy and exposure to QT prolonging drugs, are modifiable and should be given particular attention.

Is there a role for pharmacogenetics in the prevention of drug induced LQTS?

Choosing the lowest effective dose of QT prolonging drugs when an effective alternative does not exist and identifying patients at higher proarrhythmic risk are important means of minimising the risk of TdP. Some investigators have also suggested the integration of pharmacogenetics into drug development programmes to decrease the risk of drug induced LQTS even further. Blockade of HERG channel has become an accepted surrogate marker for TdP, and the potential proarrhythmic risk associated with HERG inhibition should be considered in the context of drug potency of HERG block in relation to therapeutic plasma concentrations. Overt HERG blockers manifest as concentration dependent QT prolongation as drug concentrations approximate IC_{50} values for HERG block (the concentration of drug required to block 50% of HERG current). As most drugs associated with TdP have IC_{50} values close to free drug plasma concentrations found in clinical use, some investigators have suggested increasing the margin between the theoretical maximum plasma concentration and HERG IC_{50} values to ensure cardiac safety.[48] In the past decade, HERG channel mediated cardiac toxicity, manifested as QT interval prolongation, has become a major safety issue in drug development, superseding liver injury as the main cause of drug withdrawals. Given that in vitro electrophysiological testing of the drug's effects on the function of the HERG potassium channel may be cheaper, faster and potentially more sensitive than other surrogates for TdP risk, such as in vivo QT prolongation and AP potential prolongation in cardiomyocytes, it is reasonable to expect a progressively increasing role for pharmacogenetics in the near future.

General measures for post-acute management of ALQTS

The acute management of TdP has been extensively addressed before and includes: avoidance of trigger/drug; correction of electrolyte disturbances, including intravenous magnesium sulfate and potassium supplementation to achieve high–normal values; pharmacological or, preferably, transvenous overdrive pacing to a heart rate of 90–100 bpm; alkalisation of plasma with intravenous sodium bicarbonate in quinidine induced TdP; and immediate synchronised cardioversion or defibrillation if appropriate.

However, the post-acute management is a controversial subject. Some general measures in ALQTS patients to prevent post-discharge arrhythmic recurrence include the future avoidance of any QT prolonging drugs, correction of any disorders causing electrolyte abnormalities, permanent pacemaker implantation in those with chronic bradyarrhythmias (setting a pacing rate >70 bpm if possible),[49] collection of full medical history of immediate family members along with physical examination, ECG and genetic testing in first degree relatives of ALQTS case fatalities.

All patients with previous drug induced prolongation of QT interval should be regularly instructed about the importance of subsequent avoidance of QT prolonging drugs and should receive an updated list of QT prolonging medications (list of drugs to avoid are currently available for consultation by physicians and patients—http://www.qtdrugs.org or http://www.torsades.org). The use of a drug with 'QT liability' should be considered only on the conditions that no safer alternative exists and its benefits largely outweigh the potentially fatal, albeit very low, risk of TdP and sudden cardiac arrest. Potential pharmacokinetic and pharmacodynamic interactions must not be forgotten. For example, a drug with known 'QT liability' may pose significant risk when a second drug increases its serum concentration.

Patients with a prolonged QT interval or multiple risk factors should be monitored for the presence of further drug induced prolonged QT. A baseline QTc should be obtained and, if practicable, a new ECG should be performed before and after every dose of a suspected QT prolonging medication. In case of a QTc >500 ms, an increase in 60 ms from baseline, symptoms, documentation of T wave alternans, AV block or QRS widening, the patient should be admitted to hospital for telemetry.

If ALQTS is a potentially reversible condition, why and when should we consider ICD implantation?

Currently, there are no recommendations involving the potential applicability of ICD implantation in patients with ALQTS. Data from the European Long QT Syndrome Implantable Cardioverter Defibrillator (LQTS ICD) registry[50] suggested the following groups of (congenital) LQTS patients seemed logical candidates for ICD implantation:

- All of those who have survived an aborted cardiac arrest on therapy.
- Many of those who have survived an aborted cardiac arrest off therapy, except those with a reversible/preventable cause, but noting that, for most LQT1 grown up patients, full dose β blockers could be sufficient.
- Patients with recurrent syncopes despite full dose β blockade whenever the option of left cardiac sympathetic denervation was not available or was not considered.
- All patients with high risk mutations who continued to have syncope despite β blockade, irrespective of left cardiac sympathetic denervation.
- Exceptionally, the rare asymptomatic patients with a QTc >550 ms who also manifested signs of high electric instability (T wave alternans) or other evidence of being at very high risk (eg, very long sinus pauses that might favour EAD).

We could be tempted to conclude that high risk ALQTS patients could somehow be integrated in some of the aforementioned criteria, yet there is no evidence at the moment supporting such a hypothesis. It should be highlighted, however, that an unknown percentage of supposedly high risk drug induced long QT patients have congenital LQTS and would therefore be entitled to an ICD implantation according to current recommendations. Moreover, the study by Mönnig *et al* supported the need for a more aggressive preventive strategy in ALQTS patients surviving cardiac arrest.[26] This study suggested the proarrhythmic risk in this study population is not due solely to a transient trigger but an underlying persistent predisposition or exposure to other as yet unrecognised factors that cause QT prolongation. Therefore, patients surviving cardiac arrest due to ALQTS resulting from a presumably non-avoidable trigger should be considered for an ICD implantation. Patients surviving cardiac arrest resulting from an apparently avoidable trigger may still, under exceptional circumstances, be considered for an ICD implantation if carrying additional high risk features. These include significant transmural dispersion of repolarisation (estimated by the T wave peak to T wave end interval divided by the QT interval—a value above 0.28 has been shown to predict the occurrence of TdP[43]) or beat to beat QT variability, family history of drug induced or unexplained sudden cardiac arrest, and mutations in genes or polymorphisms associated with a higher risk of prolonged QT interval and TdP. Regarding the latter, discussion with an expert in cardiovascular genetics would be invaluable. If an ICD is implanted, short detection times should be avoided in most patients to avert unnecessary therapy, and consideration should be given to the programming of a relatively fast lower rate limit and use of pause prevention algorithms.[26]

What about pacemaker implantation?

Cardiac pacing with a dual chamber device at a relatively fast lower rate limit and use of pause prevention programming, such as rate smoothing algorithms, are effective in preventing TdP in LQTS.[24] Although a minimal protective pacing rate has not been clearly identified, a study by Pinski *et al* demonstrated that programmed lower rates < 70 beats/min would not be protective, and TdP would be mostly unlikely with an effective pacing rate >70 beats/min, unless facilitated by programmable pause promoting features or oversensing.[51] Besides patients with bradycardia dependent TdP or polymorphic VT (defined as the occurrence of these arrhythmias in the context of severe bradycardia with prolonged QT interval or as a result of a long-short sequence), those with significant, albeit asymptomatic, drug induced QT prolongation should also be considered for pacemaker implantation if severe and persistent bradycardia occurs concurrently and there is no alternative non-QT prolonging drug. It is noteworthy that, in patients with congenital LQTS implanted with an ICD, the frequency of shocks can be reduced after increase of antibradycardia pacing rate, by adding a β blocker or starting the rate smoothing algorithm (average 7.1 shocks before to 0.75 shocks afterwards).[27] Prospective randomised controlled studies comparing dual chamber pacemakers to dual chamber ICDs in high risk patients with ALQTS would be welcome.

What is the role of β blockers in the management of ALQTS?

Given the indisputable evidence supporting the use of β blockers in congenital LQTS patients and the recognised overlap between the acquired and congenital forms of LQTS, we would expect β blockers to be of benefit in patients with ALQTS without bradycardia or pause dependent TdP, or contraindications for its use. However, Tan *et al* have shown that the onset of TdP may differ among congenital LQTS patients, pointing to different arrhythmia mechanisms and possibly different therapy strategies.[52] In their study, pause dependence of TdP onset was predominant in type 2 LQTS but absent or rare in type 1

Table 1 Main findings of our review of scientific data

Topic	Relevant findings	Author, year
Epidemiology	QT prolongation common in hospitalised patients	Pickham 2012[4]
	QT prolonging drugs frequently prescribed to patients with baseline QT prolongation	Baptista 2011[1]; Allen LaPointe 2006[2]; Curtis 2003[3]
	Drug induced TdP with non-antiarrhythmic drugs is 1 case in 10 000–100 000 drug exposures, easily dodging detection in pre-release trials	Haverkamp 2000[7]
QT interval measurement	High percentage of clinicians unable to correctly measure the QT interval	Viskin 2005[8]
	QT intervals vary according to ECG acquisition technique, electrolyte imbalance, sympathovagal activity, intra and interobserver variability, normal circadian variation, autonomic nervous system impulses and postprandial status	Morganroth 1991[9]; Molnar 1996[10]
	Corrected QT intervals ≥460 ms in men and ≥470 ms in women considered prolonged	Drew 2010[16]
	QT interval measured from beginning of QRS complex to T wave termination and averaged over 3–5 beats in a single lead, preferably V3 or V4	Sadanaga 2006[11]
	Prominent U waves included if merging into T wave, and RR interval preceding the QT interval measured for rate correction	
Risk stratification	Main clinical risk factors: older age, female gender, bradycardia, hypokalaemia, hypomagnesaemia, exposure to drugs with QT or metabolic liability, heart failure, left ventricular hypertrophy, history of thyroid disease or myocardial infarction and polymorphisms or mutations in genes regulating ventricular repolarisation	Benoit 2005[36]; Roden 2006[37]; Makkar 1993[38]; Kannankeril 2011[39]
	Electrophysiological or electrocardiographic risk markers: TDR, configuration of cardiac AP*, beat to beat variability of repolarisation, baseline QT prolongation, short-long-short RR sequences, fragmented QRS, long QT waves with abnormal T-U complex, giant T-U waves, macroscopic T wave alternans, bradycardia or frequent pauses and premature ventricular complexes	Topilski 2007[44]; Yamaguchi 2003[31]; Thomsen 2007[45]; Haraoka 2010[46]; Kirchhof 2009[47]
β Blockers	While LQT1 is particularly sensitive to β blocker therapy, sudden heart rate slowing is more arrhythmogenic in LQT2/LQT3, and clinical arrhythmias are pause dependent in LQT2	Tan 2006[52]
	β Blockers may reduce the arrhythmic risk in LQT2, even if to a lower extent than in LQT1	Goldenberg 2008[54]
	Loss of function mutations of the HERG gene resulting in I_{kr} channel inhibition is the mainstay abnormality in type 2 LQTS, but ALQTS patients share the same pathophysiological QT prolonging mechanism (I_{kr} channel inhibition)	
	Given the similarities between congenital LQT2 and ALQTS, β blockers alone might not be the wisest strategy, but could be of benefit if added to cardiac pacing (inference)	Viskin 2000[55]; Priori 2004[56]
Pacing	Guidelines support pacing to prevent pause dependent TdP in ALQTS patients (class IIa, level of evidence B)	Zipes 2006[24]
	Patients with bradycardia dependent TdP or polymorphic VT should receive a permanent pacemaker set at a relatively fast lower rate limit and using pause prevention programming	Pinski 2002[51]
	In patients with acquired LQTS implanted with an ICD, the frequency of shocks might be reduced after increase of antibradycardia pacing rate, by adding a β blocker or starting the rate smoothing algorithm (inference)	Mönnig 2005[27]
Defibrillators	Patients with a history of sudden cardiac arrest due to apparently unequivocal acquired proarrhythmia seem to be at ongoing risk of further life threatening events	Mönnig 2012[26]
	Patients surviving cardiac arrest resulting from a non-avoidable trigger should be considered for an ICD implantation	
	Highly selected patients surviving cardiac arrest resulting from an apparently avoidable trigger may still be considered for an ICD implantation if carrying additional high risk features (*inference*)	Schwartz 2010[50]
	Short detection times should be avoided to avert unnecessary therapy	Mönnig 2012[26]
Genetic testing	10–15% of the general population possesses either subclinical genetic polymorphisms or mutations in LQTS genes which encode for the ion channels that predispose individuals to QT interval prolongation	Yang 2002[22]; Paulussen 2004[21]; Itoh 2009[28]
	Genetic variations or polymorphisms in *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *SCN5A* and *ANKB* have been identified in some patients with drug induced TdP	Paulussen 2004[21]
Family screening	Molecular screening may allow identification of family members of gene carriers potentially at risk of life threatening arrhythmias if treated with I_{kr} blockers	
	First degree relatives of patients with ALQTS display a more pronounced transmural dispersion of repolarisation after intravenous quinidine administration compared to controls	Kannankeril 2005[20]
	Intravenous DL-sotalol has been shown to unmask susceptibility to drug induced LQTS and TdP	Letsas 2008[58]; Kaab 2003[59]

*Triangulation, such as that caused by DL-sotalol, is usually proarrhythmic.
ALQTS, Acquired Long QT Syndrome; AP, action potential; ECG, electrocardiogram; HERG, human ether-à-go-go-related gene; ICD, implantable cardioverter defibrillator; LQTS, Long QT Syndrome; TdP, torsade de pointes; TDR, transmural dispersion of repolarisation (traducing differences in action potential durations across the ventricular wall and measured by the difference between the T wave peaks and ends, or the T wave peak to end interval divided by the QT interval); VF, ventricular fibrillation; VT, ventricular tachycardia.

LQT1. While LQT1 is particularly sensitive to β blocker therapy due to the fact that the affected ion channel is responsible for the predominant repolarising current during high sympathetic activity and faster heart rates,[53] sudden heart rate slowing is more arrhythmogenic in LQT2 and LQT3, and clinical arrhythmias are pause dependent in LQT2. As previous data have shown that β blockers may reduce the arrhythmic risk in LQT2, even if to a lower extent than in LQT1,[54] cardiac pacing in addition to β blocker therapy, rather than β blockers alone, would be a better choice in LQT2.[55 56] Loss of function mutation of the HERG gene resulting in I_{kr} channel inhibition is the mainstay abnormality in type 2 LQTS. ALQTS patients share the same QT prolonging mechanism (I_{kr} channel inhibition) and may also show a pause dependence of TdP onset which would make them less ideal candidates for β blockers. In these patients, TdP is frequently triggered by short-long-short sequences or pauses. Given the similarities between congenital LQT2 and ALQTS, we can speculate that β blockers alone might not be the

safest strategy, but could be of benefit if added to cardiac pacing. Identification of those with the forme fruste of congenital LQTS (rather than true ALQTS) would also identify a subgroup of patients potentially entitled to treatment with β blockers.

Should we treat asymptomatic individuals with acquired long QT interval?

No studies have addressed the long term management of asymptomatic patients with acquired long QT interval. Persistently prolonged QT intervals despite removal of triggers should raise suspicion for a congenital form of LQTS and suggests the need for genetic testing, especially when there is a family history of sudden cardiac death or unexplained QT interval prolongation (mutations associated with congenital LQTS 1–3 should be given particular attention). History of severe, albeit reversible, prolongation of the QT interval (QTc >500 ms) due to pharmacological I_{kr} blockade suggests the need for periodic ECG screening and strongly advises against recurrent use of the offending drug. If scheduled for major surgery, asymptomatic patients with prolonged QT interval could be considered for automatic continuous perioperative monitoring of the QT interval.[57] (This recommendation also includes, of course, those with symptomatic ALQTS.) There does not seem to be any role for β blockers, pacemaker or ICD implantation in individuals with drug induced QT prolongation but no ventricular arrhythmias or significant bradycardia, unless a different indication exists. Conversely, it is the opinion of the authors that asymptomatic patients with drug induced sustained TdP (an unlikely phenomenon, as TdP lasting for > 30 s is rarely asymptomatic) should be managed similarly to symptomatic individuals.

Table 1 summarises the main findings of our review of scientific data. Figure 5 suggests a potential decision algorithm for the management of ALQTS patients. This algorithm requires validation in prospective studies and should supplement, but not replace, clinical judgment. When in doubt, patients should be referred to a cardiac electrophysiology outpatient clinic.

Main messages

- QT prolonging drugs are widely used in hospital clinical practice despite the high prevalence of baseline QT interval prolongation.
- Survivors of drug induced torsade de pointes and first degree family members of drug induced case fatalities should be entitled to exhaustive scrutiny and eventually genetic testing.
- There is a partial dissociation between the QT prolonging effect of a specific drug and its torsadogenic potential.
- Markers of risk include short-long-short sequences, giant T-U waves, T wave alternans, beat to beat variability of repolarisation duration, notched T waves in patients with severe bradycardia and a long T[peak] to T[end] interval.
- Patients with bradycardia dependent torsade de pointes should receive a pacemaker set at a relatively fast lower rate limit and using pause prevention programming.
- Patients surviving cardiac arrest due to acquired LQTS resulting from a presumably non-avoidable trigger should be considered for cardioverter defibrillator implantation.

CONCLUSIONS

ALQTS is a potentially fatal and increasingly frequent condition. Its post-acute management has received scarce attention before, probably due to the fact that this is considered a reversible phenomenon in most cases. Avoidance of offending triggers, electrocardiographic screening, pacing at a relatively fast lower rate limit and using pause prevention programming (with or without β blocker treatment), implantable defibrillators in the highest risk patients, and genetic counselling and testing in selected cases are among the strategies potentially applicable to this cohort of patients. Further research is needed in order to optimise preventive and treatment strategies.

Current research questions

- Could a treadmill or epinephrine stress test unmask the congenital form of LQTS in a patient deemed to have the acquired version?
- Could a drug challenge with a QT prolonging drug[58 59] unmask a malignant phenotype in asymptomatic patients carrying a QT prolonging associated mutation?
- Should compounds selected for development also be examined for I_{ks} liability, in addition to I_{kr}, before testing in humans?[60 61]
- What is the efficacy of new approaches, such as a carvedilol analogue,[62] I_{kr} activating drug therapy,[63 64] verapamil[65] and left cardiac sympathetic denervation?[66]

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Self assessment questions

1. Strategies for the prevention of drug induced torsade de pointes should be considered by all healthcare professionals because:
   A. QT prolonging drugs are widely used in hospital clinical practice.
   B. There is a high prevalence of QT interval prolongation in patients admitted to hospital.
   C. There is a high rate of prescription of QT interval prolonging drugs to patients presenting with QT interval prolongation.
   D. All of the above.
2. Drug induced torsade de pointes involves such steps as:
   A. Inhibition of a specific potassium current, the rapid component of the delayed rectifier current I_{kr}, generated by expression of the human ether-à-go-go-related gene (HERG).
   B. Occurrence of early afterdepolarisations during a prolonged repolarisation phase.
   C. Generation of premature ventricular complexes when early afterdepolarisations reach threshold potentials, encroaching on the underlying substrate of heterogeneous repolarisation to initiate torsade de pointes or re-entrant polymorphic ventricular tachycardia.
   D. All of the above.
3. The importance of the genetic modulation of repolarisation reserve has been suggested by such findings as:
   A. First degree relatives of patients with the Acquired Long QT Syndrome display a more pronounced transmural dispersion of repolarisation after intravenous quinidine administration compared with controls.
   B. Genetic variations or polymorphisms in *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *SCN5A* and *ANKB* have been identified in some patients with drug induced torsade de pointes.
   C. 10–15% of the general population possess either subclinical genetic polymorphisms or mutations in Long QT Syndrome genes which encode for the ion channels that predispose individuals to QT interval prolongation.
   D. All of the above.
4. Identification of patients at high risk for drug induced torsade de pointes is a fundamental step in the prevention of the Acquired Long QT Syndrome. Which characteristics suggest a higher risk?
   A. Epidemiological and clinical risk factors such as older age, female gender, hypokalaemia, hypocalcaemia, hypomagnesaemia, baseline QT prolongation, exposure to drugs with QT liability or metabolic liability, heart failure, left ventricular hypertrophy and polymorphisms or mutations in genes regulating cardiac ion channel expression and ventricular repolarisation.
   B. Electrophysiological markers such as transmural dispersion of repolarisation, the configuration of the cardiac action potential and the beat to beat variability of repolarisation.
   C. Electrocardiographic markers such as short-long-short RR sequences, fragmented QRS, long QT waves with abnormal T-U complex, giant T-U waves, macroscopic T wave alternans, bradycardia or frequent pauses and premature ventricular complexes.
   D. All of the above.
5. Treatment of the Acquired Long QT Syndrome and prevention of future arrhythmic episodes may involve the following measures:
   A. Avoidance of QT prolonging drugs in all patients with drug induced torsade de pointes or at high risk for such events.
   B. Permanent pacemaker implantation (set at a relatively fast lower rate limit and using pause prevention programming) in patients with bradycardia dependent torsade de pointes or polymorphic ventricular tachycardia.
   C. Implantable defibrillator in patients surviving cardiac arrest due to Acquired Long QT Syndrome resulting from a presumably non-avoidable trigger.
   D. All of the above.

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Answers

1. D
2. D
3. D
4. D
5. D

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Notes