Sudden cardiac death in nephrology: focus on acquired long QT syndrome

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Introduction

More than a half million Americans have end-stage renal diseases (ESRD), 20 millions have been diagnosed with chronic kidney disease (CKD) and another 20 millions are individuals at risk [1]. The ESRD patients population is characterized as one with the highest mortality rate (even when adjusted for age, race, sex and comorbid conditions), comparable with patients in advanced stages of breast cancer [2]. Among dialysis patients in the United States, cardiovascular disease (CVD) mortality is 30 times higher than in general population and accounts for 58% of all-cause mortality, and the risk for arrhythmogenic death is one of the highest among any other populations [3]. The situation is greatly exacerbated by the fact that there is a clinically proven lack of benefits from: (a) implantable cardioverter-defibrillators in patients with severe renal disease and heart failure [4], and (b) the statins on the risk of cardiovascular events in the advanced CKD [5]. This presents the questions: why are renal patients so vulnerable to fatal arrhythmias and what else can be done to prevent sudden cardiac death (SCD) in this population?

The main goal of this review is to bring to the attention of the nephrology community some of the latest developments in the field of experimental and clinical cardiac electrophysiology and the pharmacology of SCD. A special focus is placed on the molecular, ionic and pharmacological aspects of acquired long QT syndrome (LQTS), its clinical manifestation and prevention.

Acquired long QT syndrome in nephrology

Renal patients are at increased risk of various life-threatening cardiovascular complications, including coronary artery diseases (CAD), arterial hypertension, left ventricular hypertrophy (LVH), congestive heart failure (CHF), metabolic and uremic cardiomyopathies and diabetic cardiac autonomic neuropathy. CVDs, especially CAD, LVH and CHF, are associated with strong remodelling of cardiac ions resulting in the acquired cardiac channelopathies and increased risk of SCD. Such an adverse modulation of the cardiac electrophysiological matrix is characterized by a progressive reduction of the naturally redundant K⁺ channels (diminished ‘repolarization reserve’) and concomitant increase in sensitivity of the remaining K⁺ channel to their inhibition (acquired LQTS).

Therefore, administration of any drug that is capable of inhibiting K⁺ channel (predominantly—Iₖr current) will lead to increased time require to complete ventricular repolarization. This results in electrocardiographic QT prolongation and subsequently a substantially elevated risk of life-threatening arrhythmias (Figure 1).

The most common clinical manifestation of the acquired LQTS is Torsade de Points (TdP) polymorphic ventricular tachycardia and SCD. The risk of TdP and SCD tremendously increases when any QT-prolonging drug is co-administered with any other substance or drug known to inhibit its metabolism (e.g. CYP3A4 inhibitors such as grapefruit juice, macrolides, ketoconazole and alcohol overdose) or excretion. In patients with impaired glomerular filtration, QT-liable drugs with renal excretion can produce an unpredictable increase of the plasma concentration, leading to a significant prolongation of the QT interval and development of TdP. To avoid cardiac arrhythmogenic toxicity, dosages of drugs primarily excreted through the kidneys must be reduced. For example, antiarrhythmic sotalol should be given in a 40mg dose after dialysis (every second day), as opposed to the usual daily dose, 80–120 mg every 12 h.
Although, arrhythmogenic potential of acquired LQTS induced by non-cardiac drugs is less malignant than that associated with antiarrhythmic drugs, many non-cardiac pharmaceutical agents have been withdrawn from the market or severely restricted to specific indications, because of clinical concern over rare but unexpected and potentially fatal complications of acquired LQTS. A well-documented large population-based case-control study of 775 cases of SCD and 6297 matched controls revealed that, after adjustment for known confounding factors, current use of non-cardiac QTc-prolonging drugs in a general population was associated with almost 3-fold increased risk of SCD (adjusted OR: 2.7; 95% CI: 1.6–4.7) [6]. Based on this, it can be estimated that the annual mortality rate from the same cause could be as high as 9000 cases in Europe or 6000 cases in the USA. Lists of (a) most QT-prolonging drugs with torsadogenic potentials and appropriate illustrative materials and (b) most common drug interactions are presented on the Internet web sites: http://medicine.iupui.edu/flockhart/ and http://www.qtdrugs.org, respectively.

Despite published research on potentially lethal consequences of drug-induced LQTS, the risk and the risk/benefit ratio of QT-prolonging medications are profoundly underestimated in clinical practice. Based on the patterns of most currently prescribing medications, it appears that clear restrictions, side effects, warnings and contraindications pertinent to the QT-prolonging medications are widely ignored or even disregarded. Curtis et al. [7] from Duke University researched a large prescription claims database that included 4.8 million patients. They discovered unacceptably high rates of prescription of QT-prolonging medications and concomitant therapy with two or more QT-prolonging drugs. The analysis included 50 medications associated with QT interval prolongation and 26 agents, which inhibited hepatic or renal clearance of these medications. They showed that:

- Of the patients, 22.8% had a prescription for at least one medication associated with QT interval prolongation, 47.4% were for erythromycin or clarithromycin and 40% were for antidepressants. Among this group, 9.4% of patients filled overlapping prescriptions for at least one other QT-prolonging medication or for at least one agent that inhibits its clearance. Of these patients, 7249 (0.7%) filled overlapping prescriptions for three or more potentially interacting medications.
- Among 103 119 patients who filled two or more prescriptions for medications that may prolong QTc values, 26.9% also filled an overlapping prescription for a potentially interacting medication.

**Arrhythmogenic potentials of acquired long QT syndrome and haemodylisis**

As mentioned earlier, CAD, LVH, CHF and cardiomyopathies are among the most common CVD that are associated with acquired LQTS. One can only
Imagine how combination of those very common in nephrology practice CVD can potentiate the risk of arrhythmogenic death. The short list of non-cardiac risk factors for acquired LQTS in nephrology includes: (a) impaired drug elimination (e.g. renal or hepatic dysfunction), (b) electrolyte disturbances, (c) acute neurological events (e.g. intracranial and subarachnoid haemorrhage, stroke, trauma), (d) diabetes mellitus and (e) altered nutrition (e.g. anorexia nervosa, starvation diets, alcoholism). Female gender, elderly age, abnormal bradycardia or tachycardia are among the most common factors predisposing to aggravation or initiation of malignant arrhythmias and SCD. In general, females three times more often have abnormally prolonged QTc interval at baseline, and three times more likely to die due to drug-induced TdP.

From acquired LQTS perspective, haemodialysis (HD) procedure is associated with so-called ‘paradoxical’ QTc prolongation that many investigators associate with exaggerated risk of the occurrence of fatal arrhythmias. It is a prevailing opinion that such a ‘paradoxical’ increment in the QTc is related to the potassium fluxes induced by HD. We studied this ECG phenomenon in ESRD patients and found that the increase in QTc is not a ‘paradoxical’ ECG phenomenon, and is due to a statistically significant increase in the heart rate (most likely, secondary to the HD-induced reduction of the extracellular fluid) but not due to the changes in the absolute value of the QT interval [8]. As reminder, QTc is a function of both: (a) the heart rate and (b) the absolute value of QT interval duration, and increase in either of those parameters will ultimately result in the increase in QTc. In addition, we also noted that corrected QTc was initially prolonged (480.1 ± 32.0 ms) and ECG criteria for LVH were evident in the vast majority of our ESRD patients.

In our opinion, the arrhythmogenic mechanism underlying HD is based on a transient (even brief) intracellular hypokalaemia and/or hypomagnesaemia induced by HD. More specifically, the sharp reduction in the intracellular potassium concentration could be caused by a sharp fluctuation in the potassium kinetics induced by an aggressive HD. Of note, correlation between intracellular and extracellular potassium concentrations is pure, and brief ‘arrhythmogenic’ intracellular hypokalaemia cannot be detected by measuring of potassium concentration in the blood serum. We also believe that less aggressive HD procedure with a lesser potassium gradient between dialysate and blood potassium level, longer treatment time and slower ultrafiltration rate could have a positive impact on the procedure-related cardiac mortality. Also, the role of magnesium in the HD-related arrhythmogenesity warrants further investigation.

Conclusions

Acquired LQTS is one of the many mechanisms of SCD in nephrology. Arrhythmogenic potential of acquired LQTS in renal patients is determined and modified by: (a) electrophysiological remodelling of the heart due to concomitant CVD, such as CAD, LVH/Hypertension and CHF, and (b) excessive exposure to the multiple (often excessive and proarhythmic) medications and their abnormal excretion or metabolism.

Conflict of interest statement. None declared.

References


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