Case Report

Acute respiratory distress syndrome with transiently impaired left ventricular function and Torsades de Pointes arrhythmia unmasking congenital long QT syndrome in a 25-yr-old woman

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We report a case of recurrent episodes of Torsades de Pointes arrhythmia in the setting of transiently impaired left ventricular ejection fraction, acute respiratory distress syndrome, transient hypokalaemia and QT-prolonging drugs, in a previously healthy 25-yr-old female patient. In the course of the clinical and genetic work-up this patient was newly diagnosed with a mutation in KCNH2 encoding the α-subunit of the human repolarizing potassium channel Kr. This case report illustrates the multivariate nature of long-QT syndrome, and emphasizes the usefulness of a pharmacological test for repolarization abnormalities.

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In critically ill patients, multi-drug treatment, electrolyte disturbance and impaired cardiac function are a common coincidence. However, clinicians in critical care settings are often not aware of their implications for an increased risk of arrhythmias in the context of QT-prolongation.1 2

Case report

We present the case of a 25-yr-old female patient, who was referred to our intensive care unit (ICU) for the management of acute respiratory distress syndrome. Five weeks before onset of symptoms the patient had delivered her third child by Caesarean section. Medical history included a respiratory infection with cough and fever 1 week before admission.

At arrival in our ICU the patient presented with septic shock and multiple organ failure (temp. 40°C, PaO2/FIO2 ratio 7.6 kPa, INR 2.1, C-reactive protein 255 mg litre−1, procalcitonin 160 ng litre−1, white cell count 38.3x109 litre−1). A chest radiograph revealed diffuse bilateral pulmonary infiltrates. The patient was endotracheally intubated and mechanically ventilated. Antibiotic treatment with i.v. erythromycin had been initiated. I.V. cefotiam and gentamicin were added on admission to intensive care. To maintain an adequate systemic perfusion pressure, norepinephrine was infused at 1.3 mg kg−1 min−1 and 2500 ml of colloid was infused. Initial therapy included physical cooling and prescription of hydrocortisone. A urine test for pneumococcal antigen was positive.

On day 2 after admission, the patient’s temperature had come down to 37.5°C, the PaO2/FIO2 ratio had improved to 170 22.7 kPa and laboratory inflammation markers had decreased. Norepinephrine 0.2 µg kg−1 min−1 was sufficient to maintain a mean arterial blood pressure of 80–90 mm Hg and a cardiac index of 3.5 litre min−1 m2−1. However, transthoracic and transoesophageal echocardiography revealed a dilated left ventricle with severely impaired left ventricular function. The left ventricular end-diastolic diameter was 56–60 mm and the fractional shortening <10 %.

On day 3 after admission to our ICU the patient presented with Torsades de Pointes (TdP) tachycardia (Fig. 1). At that time the serum potassium level was 3.5 mmol litre−1.
the serum magnesium level was 0.50 mmol litre\(^{-1}\) and QTc-interval was 485 ms. Magnesium sulphate (1 g i.v.) and potassium were administered. In the following course of 4 weeks on intensive care, left ventricular dysfunction persisted and the patient developed two additional episodes of TdP, on day 8 while the patient was being treated with erythromycin 4 g per day with a QTc-interval of 510 ms, and on day 25 while the patient was being treated with fluconazol 400 mg per day with a QTc-interval of 489 ms. Both episodes rapidly degenerated into ventricular fibrillation and had to be terminated by external defibrillation.

With continuing treatment with an angiotensin-converting enzyme inhibitor and diuretics the patient could be transferred to a regular ward on day 30. By day 32, transthoracic and transoesophageal echocardiography showed a normal left ventricular diameter with normal contractile function and a QTc-interval of 430 ms. Further clinical evaluation including left and right heart catheterization, coronary angiography, echocardiography and cardiac magnetic resonance imaging revealed no signs of structural heart disease. No sustained ventricular tachycardia was inducible with programmed electrical stimulation during an electrophysiological study. In order to evaluate the pathogenetic mechanism of QT-prolongation in this patient, provocative i.v. sotalol test (2 mg kg\(^{-1}\) i.v. over 20 min) was performed to reveal an intrinsic myocardial predisposition to disproportional QT-prolongation and cardiac arrhythmias upon extrinsic triggers. With normal cardiac structure and function, serum potassium within reference limits and in the absence of any other QT-prolonging medication, the patient displayed a marked increase in QTc-interval upon challenge with DL-sotalol (from 433 ms at baseline to 515 ms) which is consistent with an abnormal repolarization reserve (Fig. 2).

Based on this finding, sequencing major long-QT (LQT) disease genes encoding \(\alpha\)- and \(\beta\)-subunits of the myocardial delayed rectifier potassium channels IKs and IKr (KCNQ1, KCNH2, KCNE1 and KCNE2) and the \(\alpha\)-subunit of the myocardial sodium channel (SCN5A) revealed a missense mutation (CGC\(\rightarrow\)TGC, nucleotide change C982T, accounting for amino acid change R328C) in KCNH2, the gene encoding the \(\alpha\)-subunit of the human repolarizing potassium channel I\textsubscript{Kr}. Genetic testing of family members revealed an affected twin sister, one affected niece, and two affected sons all without clinical manifestations of LQTS. The patient has been genetically counselled and all identified carriers of the mutation KCNH2 (R328C) have been started on \(\beta\)-blocker therapy (metoprolol 2 mg kg\(^{-1}\)) or atenolol 2 mg kg\(^{-1}\), respectively). The patient was advised to avoid all substances with potentially QT-prolonging effects and to avoid hypokalaemic states. In a 18-month follow-up no cardiac arrhythmias, syncopal events or other clinical manifestations were observed in any of the mutation carriers.

**Discussion**

Several reports of significant QT-prolongation and life-threatening TdP arrhythmias during the care of critically ill patients and recent advances in our understanding of the pathogenetic mechanism of LQTS require an increase in clinical attention towards this condition. Reliable diagnosis and risk stratification of the individual patient in an ICU setting are complicated by the multitude of mechanisms involved in QT-prolongation. In addition, a vast number of drugs directly prolong QT-interval in a dose-dependent fashion, although not all drugs that prolong QT-interval induce Tdp. The additive effect of several components, as seen in our case, may destabilize myocardial repolarization in an unpredictable way. The
individual response to drugs that potentially prolong QT-intervals has led to the concept of repolarization reserve. Assessing individual repolarization reserve and thereby unmasking a latent repolarization disorder is helpful in identifying patients at risk for arrhythmias in the context of QT-prolonging drugs. Factors predisposing to QT-prolongation and higher risk of TdP include older age, female sex, myocardial dysfunction, left ventricular hypertrophy, ischaemia, slow heart rate, electrolyte abnormalities (hypokalaemia, hypomagnesemia), and genetic predisposition. Reversible myocardial dysfunction as seen in our patient could have been a complication of sepsis or postpartum cardiomyopathy. The pathogenetic mechanism of this complication in both settings is not well understood. Ventricular dilatation and impaired contractile function independent of their aetiology are accompanied by down-regulation of repolarizing myocardial potassium channels inducing a form of acquired LQTS. More recently, increasing awareness of drug-induced arrhythmias has pointed to the QT-prolonging and arrhythmogenic potential of a wide variety of non-antiarrhythmic drugs, expanding the population at risk and prompting the need to identify factors determining susceptibility for drug-induced LQTS in the individual patient.

Experimental evidence demonstrates that QT-prolongation caused by class III antiarrhythmic agents and non-antiarrhythmic drugs is primarily affected by blockade of the rapidly activating component of the delayed rectifier potassium current, . The effects of erythromycin on and on QT-interval are well documented and accepted, while mechanisms and absolute risk are less established for fluconazol. In the presence of QT-prolonging medication, hypokalaemia may further increase labile repolarization both by reducing and by increasing drug binding to the channel, resulting in excessive prolongation of repolarization. Hypomagnesemia significantly prolongs the action potential in experimental heart failure, which also may contribute to the increase in variability of repolarization. Besides these extrinsic factors, an individual’s response to QT-prolongation upon exposure to QT-prolonging drugs depends on genetic disposition controlling intrinsic myocardial properties or signalling pathways. To substantiate the diagnosis of suspected drug-induced LQTS and support the hypothesis of reduced myocardial repolarization reserve as an intrinsic mechanism in our patient, we used a pharmacological test, a specific block of by D-l-sotalol. In a former matched pair case–control study we were able to unmask altered repolarization by inducing disproportional QT-prolongation in patients with a history of drug-induced LQTS. This approach was useful in this patient to support the diagnosis of an intrinsic repolarization disorder before results from genetic testing become available. Attempts to explain the individual predisposition to inducible forms of LQTS by mutations in KCNH2 or KCNE2, the a- and b-subunit encoding the human , or by mutations in other genes known to cause congenital LQTS, have revealed apparent genetic predisposition only in a small fraction of patients in the past. This may be because of heterogeneous patient populations and the multifactorial pathophysiology of drug-induced LQTS.

In this patient with a very specific phenotype, genetic testing revealed the diagnosis of congenital LQTS with a mutation in KCNH2 (R328C). This mutation was originally found in a family with a compound heterozygous mutation in the KCNQ1 and KCNH2 gene. In this study, all family members with the KCNH2 mutations alone appeared to have no arrhythmic events. In our patient we did not find any additive mutation in KCNQ1, SCN5A, KCNE1 or KCNE2. A monozygous twin sister, a niece, and two sons carrying the same mutation with varying QT-intervals and no symptoms emphasize the role of multiple intrinsic and extrinsic factors to cause life-threatening arrhythmias on the grounds of genetic disposition. Further studies are needed to investigate the role of common gene variants that by themselves or in addition to causal mutations modify susceptibility to arrhythmia in the context of QT-prolonging drugs. Meanwhile provocative drug-testing using i.v. sotalol seems to be a useful additive tool to confirm the diagnosis of intrinsic repolarization disorder, even in the absence of genetic proof. Our awareness and understanding of the mechanisms of LQTS will help to identify patients at risk and reduce their exposure to risk factors.

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