Short QT syndrome: A case report and review of literature

Li Xiong Lu*, Wei Zhou, Xingyu Zhang, Qin Cao, Kanglong Yu, Changqing Zhu

Department of Emergency and critical care, Renji Hospital, Shanghai Jiaotong University School of Medicine, 1630 Dongfang Road, Shanghai 200127, China

Received 21 December 2005; received in revised form 15 March 2006; accepted 20 March 2006

KEYWORDS
Tachycardia; Ventricular; Genetics; Death; Sudden cardiac; Syncope; Short QT syndrome; Channelopathy

Summary The short QT syndrome has been recently recognised as a genetic ion channel dysfunction. This new clinical entity is associated with an incidence of sudden cardiac death, syncope, and atrial fibrillation in otherwise healthy individuals. The distinctive ECG pattern consists of an abnormally short QT interval, a short or even absent ST segment and narrow T waves. A 30-year-old resuscitated woman with short QT syndrome is described together with an example of the classic ECG characteristics. A short-coupled variant of torsade de pointes was reveal on Holter recordings. The implantable cardioverter defibrillator seems to be the therapy of choice to prevent from sudden cardiac death. Quinidine proved to be efficient in prolonging the QT interval and rendering ventricular tachyarrhythmias non-inducible in patients with a mutation in KCNH2 (HERG). Our preliminary data suggest amiodarone combined with /H9252 blocker may be helpful in treating episodes of polymorphic ventricular tachycardia for patients with an unknown genotype. Because the short QT syndrome often involves young patients with an apparently normal heart, it is imperative for physicians to recognize the clinical features of the short QT syndrome in making a timely correct diagnosis.

Introduction

Syncope is a common disorder, constituting up to 3% of all visits to emergency department. Cardiac syncope patients are often associated with a risk of recurrent life-threatening events and require more attention from the emergency physician. In the majority of cardiac syncope patients, a structural or functional abnormality can be identified, but in 5–10% of sudden cardiac death patients, the heart is apparently normal, so-called ion channel disease or ion channelopathy.1,2 Because the symptoms of syncope or palpitation are transient and may escape detection, and no identifiable heart disease can be detected despite thorough clinic examination, it is a challenge for emergency physicians to recognise...
ion channel disease. As yet, a few families affected with the short QT syndrome have been identified but other cases have probably been overlooked.3,4 We report a case of short QT syndrome and the knowledge to date on this little recognised disorder is presented.

Case presentation

At approximately 21:00 h, a 30-year-old Chinese female developed rapid palpitations and chest tightness, followed by a witnessed episode of syncope with urinary incontinence. She regained consciousness immediately with no neurological sequelae. After three similar syncopal attacks within 3 h she was taken to the nearest hospital by her family members.

She had palpitations and chest tightness on exertion 3 months ago.

The patient had no history of cardiovascular disease and rheumatic fever. There was no history of sudden death in her family. She had no other medical history and was receiving no regular medication. She is the youngest of six siblings. No electrolytes abnormalities were detected. The patient had an urgent computed tomography scan of the head, which was normal. On the second day, after a total of five syncopal or presyncope episodes the patient was transferred to our hospital for further treatment.

During the transfer to our hospital she suffered a cardiac arrest with ventricular fibrillation and was resuscitated with an external defibrillator in the ambulance (Figure 1).

The patient did not have continuous ECG monitoring in the ambulance

- A: The left part of the rhythm strip was obtained in lead II as a routine evaluation in ambulance.
- B: It happened that the patient developed an episode of syncope and seizure like activity just after the routine ECG was completed, so the ECG was restarted promptly and showed ventricular tachycardia. She was successfully resuscitated by cardioversion. Thus, the recording paper in Figure 1 is continuous but there was a break in the ECG trace and the onset of arrhythmia was not recorded, but the QRS morphology of the initial episode of ventricular fibrillation suggested it may be a deterioration from polymorphic ventricular tachycardia.

On arrival in the emergency department she was alert. General physical examination revealed a puffy woman, mildly dyspnoeic, and pink in colour. Temperature was normal, respiratory rate was 22/min. Her oxygen saturation, as measured by pulse oximetry, was 98%. Pulse rate was 64/min and regular. Blood pressure was 110/60 mmHg in the right upper arm. She had no jugular venous distention. Precordial examination revealed no chest deformity, with quiet precordium, and no thrill. Cardiac examination revealed a regular rate and rhythm without murmurs, rubs or gallops. The lung fields were clear with equal air entry. Neurological examination and the remaining physical examination was unremarkable.

No clinical or laboratory evidence of rheumatic fever was found. All laboratory investigations including three sets of cardiac enzymes were normal. Two-dimensional echocardiography showed no structural abnormality and a normal ejection fraction. Chest radiography was normal.

A routine 12-lead electrocardiogram showed sinus rhythm with a heart rate of 70, a QT interval of 270 ms (Bazzett-corrected QT interval of 292 ms), and a peaked T waves (Figure 2).

On the evening of hospital admission, the patient underwent Holter monitoring for 24 h during which she complained several episodes of rapid palpitations. Coinciding with the attack, monitoring revealed episodes of 6- to 12-beat runs of torsade de pointes with very short coupling intervals. A 24-h Holter monitor recorded 57 ventricular ectopic beats/24h, 10 episodes of self-terminating polymorphic ventricular tachycardia (Figure 3).

She was diagnosed to be suffering from short QT syndrome.

After documented episodes of ventricular tachycardia, it was treated with metoprolol, amiodarone, and magnesium. Metoprolol (12.5 mg b.d.) was stopped the next morning because of concern about bradycardia developing. Amiodarone was given as a 150 mg bolus IV over 10 min, followed by a continuous infusion of 800 µg/min for 24h, reducing to 400 µg/min for 24h. Finally oral amiodarone was given. Over the next few days,

Figure 1  Rhythm strip showing ventricular fibrillation recorded during seizure in ambulance.
she did not have any further episodes of ventricular tachycardia. The QT interval remained short, however, and small fluctuations of QTc interval was documented which could not be explained by the variation of the heart rate, the use of drugs and other probable factors influencing the QT interval. For economic considerations, she did not have electrophysiological testing and an ICD implant. Two weeks later, she was discharged on amiodarone. During the 12-month follow-up period, the patient did not have any further syncpe or palpitations.

Discussion

Long QT intervals in the ECG have been associated with sudden cardiac death. Little is known about the clinical implication of a short QT interval. Tremendous strides have been made in recent years in the diagnosis and treatment of sudden cardiac death in individuals with an apparently normal heart. Algra et al. first suggested that patients with a short QT interval had an increased risk of sudden death by analyzing Holter recordings retrospectively in 1993. It was not until 2000 that Gussak et al. proposed a short QT syndrome as a new inherited clinical syndrome. In 2003, the definitive familial link between short QT syndrome and sudden death was demonstrated by Gaita et al.7

The short QT syndrome forms a distinct clinical entity. It is characterized by a short QT interval, a short or even absent ST segment and tall, narrow and peaked T waves in the precordial leads, and sudden cardiac death in individuals with an apparently normal heart. These subjects also had a high incidence of atrial arrhythmia. Individuals with short QT syndrome frequently complain of palpitations and may have syncope. Short QT syndrome is associated with an increased risk of sudden cardiac death, most likely due to ventricular fibrillation. Most individuals will have a family history of unexplained or sudden death at a young age, palpitations, or atrial fibrillation. The electrocardiographic characteristics of short QT syndrome are a short QT interval, typically \( \leq 320 \text{ ms} \), that does not change significantly with the heart rate. Sometimes a lack of adaptation or paradoxical behavior of the QT interval with various heart rates was
Holter monitoring showed self-terminating polymorphic ventricular tachycardia and short QT interval. The coupling interval of the first beat of the polymorphic ventricular tachycardia was very short.

Figure 3  Holter monitoring showed self-terminating polymorphic ventricular tachycardia and short QT interval. The coupling interval of the first beat of the polymorphic ventricular tachycardia was very short.

observed. Tall, symmetrical and peaked T waves often also are noted. Individuals may also have an underlying atrial fibrillation. In the electrophysiological study, individuals with short QT syndrome are noted to have short refractory periods, both in the atria as well as in the ventricles. Also, ventricular fibrillation is frequently induced on programmed stimulation.6,7,9 The diagnosis of short QT syndrome is made up of a characteristic history and findings on ECG and electrophysiological testing. There are currently no guidelines for the diagnosis of short QT syndrome.

Even if ion channel disease is rare, its clinical impact is high because it often concerns young, active and otherwise healthy individuals.1,2,10 In contrast to the other types of ion channelopathies, the electrocardiologic characteristics of the short QT syndrome are less remarkable. The incidence of ion channelopathies may have been underestimated. It is essential for the emergency physician
to be aware of this syndrome so that an accurate
diagnosis can be made.

It is noteworthy that the short QT interval is dif-
ficult to record when the heart rate exceeds
100 beats/min. Special attention should be given
in cases when the patients have fever, anaemia,
respiratory failure, etc., particularly in the pedi-
atriatric population. Because atrial fibrillation may
be the first symptom of the short QT syndrome, the
short QT syndrome should be excluded in young
patients with lone atrial fibrillation.3,4,6,7 It should
be emphasized that some cases at risk, like our
patient, may show periods of a normal QT inter-
val, leading to underestimation of the syndrome.
Differential diagnosis of VT includes long QT syn-
drome, Wolff—Parkinson—White syndrome (WPW
syndrome), fascicular VT, arrhythmogenic right ven-
tricular dysplasia (ARVD) and myocarditis. The first
three conditions can be safely excluded after ana-
lyzing the ECG tracings. The causes of acquired
short QT interval should be kept in mind when evalu-
ating QT changes, such as increased heart rate,
hyperthermia, hypocalcaemia, hyperkalaemia, aci-
dosis, administration of digitalis preparations and
altered autonomic tone.6,7

The aetiology of short QT syndrome is unclear. A
current hypothesis is that the mutated ion channels
shorten the plateau phase of the action potential,
leading to a non-homogeneous overall shortening
of refractory periods and the QT interval. The con-
sequence is a heterogeneous abbreviation of the
action potential duration and refractoriness at both
atrial and ventricular level. Short and amplification
of transmural or other spatial heterogeneities of
refractory periods at three different cell types of
the left ventricular myocardium favour reentry and
thus arrhythmogenesis.11–14

The optimal management of arrhythmias in
patients with short QT syndrome remains a criti-
cal issue. The implantable cardioverter defibrilla-
tor (ICD) may be the only effective intervention for
preventing sudden death.3,4,15 However, drugs will
remain essential in many clinical situations. Phar-
macological therapy is important and may serve as
an adjunct to ICD therapy to suppress atrial fibril-
lation, which is a major clinical problem in short
QT syndrome, to suppress ventricular tachyarrhyth-
rias, and especially to treat electrical storm. Phar-
macological treatment is also needed and may con-
stitute an alternate treatment to ICD if a defibrilla-
tor implant is denied or impossible for any reason.

Currently, there are no specific pharmacological
treatments for preventing sudden death in indi-
viduals with short QT syndrome. One study sug-
gested that the class Ic agent propafenone could
be effective to prevent episodes of paroxysmal
atrial fibrillation in patients with a mutation in
KCNH2 (HERG),9 and in this specific patient pop-
ulation, quinidine showed it was efficient in pro-
longing the QT interval and rendered ventricular
tachycardia non-inducible.9,16 However, no corre-
lations have been identified between the magni-
tude of the QT shortening and the proclivity for
an arrhythmic event. The heterogeneity of local
refractoriness may play a more important role
in the development of the malignant ventricular
tachyarrhythmia than the shortness of refractory
period. The significance of programmed ventricular
stimulation is unclear concerning risk stratification
in patients with inherited channelopathies. More-
over, quinidine-associated mortality is high for the
treatment of other arrhythmias in the literature,
therefore, further clinical evidence with quinidine
in patients with a mutation in KCNH2 (HERG) is
needed before this therapy can be recommended
as safe and effective for patients with a mutation
in KCNH2 (HERG).

To date, three genes — KCNH2 (SQT1), KCNQ1
(SQT2) and KCNJ2 (SQT3) — encoding different
potassium ion channels involved in repolarisation
have been linked to the short QT syndrome,
which not only demonstrates the inherited het-
rogeneity of the disease, but also is likely to
make the therapeutic options unique to each
gene/mutation.3,4,8,9,16–20 Little data are available
about gene/mutation-specific pharmacologic ther-
apy of short QT syndrome. As an allelomorphic dis-
 ease to long QT syndrome, it was not surprising that
all three genes associated with short QT syndrome
are also involved in long QT syndrome. SQT1 and
LQT2 involve the same gene that encodes potassium
IKr, SQT2 and LQT1 involve the same IKs gene, SQT3
and LQT7 involve the same Kir2.1 gene. Therefore,
the treatment of the short QT syndrome may ben-
efit from the experience of treatment of the long
QT syndrome.

The long QT syndrome was the first to be dis-
covered and is the best-known channelopathy. To
date, mutations in at least eight different genes
have been associated with long QT syndrome.
The classification of the long QT syndrome into
various genetic classes has led to a number of
genotype—phenotype studies that demonstrated
that the underlying genetic defect impacts on
EGC morphology, trigger and onset of symptoms,
prognosis and, most importantly, treatment. Since
potassium ion channels are the primary contribu-
tors to the repolarisation process, the genes KCNQ1
and KCNH2 are vulnerable to mutate and up to
90% of genotyped patients with long QT syndrome
carry mutations in KCNQ1 and KCNH2. The IKs and
IKr component have been shown previously to be
under control of the sympathetic nervous system. Cardiac events in LQT2 and LQT1 patients were associated with elevated sympathetic nerve activity. In concordance with the predominant adrenergic triggers, β-blocker therapy is most effective in preventing recurrence of cardiac events and lowering the death rate in LQT1 and to some extent in LQT2 but is much less effective in other long QT syndrome. It is noteworthy that the QT prolongation alone, if not accompanied by an increase in transmural dispersion of repolarization, is not in itself sufficient to cause polymorphic ventricular tachyarrhythmia. β-Blockers have minimal effects on the QTc interval but are associated with a significant reduction in cardiac events in patients with long QT syndrome.21–24

In our patient, it is noted she experienced her cardiac events during psychological stress, and during Holter monitoring, although her mean heart rate was slow (62 beats/min), paroxysmal variations at several minutes intervals in heart rate were noticeable and there also appeared to be an increase in underlying heart rate before the onset of episode of arrhythmia, suggesting a role for adrenergic activation. These findings provide the rationale for a novel approach toward the prevention of sudden death in this patient with short QT syndrome of unknown genotype: Amiodarone plus β-blocker. Compared with other antiarrhythmic drugs, amiodarone has a distinct pharmacological profile and can inhibit both IKr and IKs potassium currents, which are most probably responsible for short QT syndrome. The concomitant modulation of IKs, IKr and adrenergic blockade may constitute a potential pharmacologic strategy for prevention of malignant ventricular arrhythmias. Meanwhile, sympathetic stimulation is known to modulate a number of currents, by virtue of its multi-channel properties and unique antiadrenergic properties, amiodarone combination with β-blocker can interact synergistically to show more effective antiadrenergic interventions and protect against malignant arrhythmia.25–27

The prognosis and natural history of short QT syndrome still remains obscure. Our patient was free from any further episodes of syncope for 1 year with such therapeutic interventions and behavioral recommendations. However, it has to be emphasized that because of the ‘‘random’’ nature of the malignant arrhythmia, the safety and efficacy of amiodarone in patients of unknown genotype with life-threatening arrhythmia that tend to be adrenergic dependent remain questionable. Confirmation of these preliminary data is required.

It may be of interest to note that the coupling interval of the first beat of the polymorphic ventricular tachycardia in our case was short. Therefore, it is possible that some patients with a short QT syndrome may be thought to have a short-coupled variant of torsade de pointes, because of little interest in short QT intervals.28

Our patient’s QT interval measured 270 ms at a heart rate of 70. Her 7-year-old daughter was asymptomatic and showed a QT interval of 290 ms at a heart rate of 68, whereas the 53 year-old mother displayed a QT interval of 290 ms (QTc 300 ms) at a heart rate of 64 and episode of paroxysmal atrial fibrillation. Her husband and her father had normal QT intervals. The family patterns suggested autosomal dominant inheritance. However, this disorder, like most other genetic conditions, has variable expression of severity (i.e. variable penetrance). An affected individual within a given family with a specific mutation may be asymptomatic, such as her daughter and her mother, whereas another family member with the same gene mutation may experience recurrent syncope and sudden cardiac death, such as the patient in our case. Three forms of the disease have been so far identified: SQT1, caused by a gain of function substitution in the HERG (IKr) channel, SQT2, caused by a gain of function substitution in the KvLQT1 (IKs) channel, and SQT3, which has a unique ECG phenotype characterized by tall and asymmetrically shaped T waves, caused by a defect in the gene coding for the inwardly rectifying Kir2.1 (IK1) channel, but the fact that no mutation was found in some patients with a short QT syndrome indicates further genetic study is necessary.3,4,7,17–20

The pedigree described herein is large enough to undertake a genome scan and provides an excellent model for the molecular mechanism of the short QT syndrome.

In recent years, many genetic causes of ion channel diseases have been revealed. The identification of the gene defects has revolutionized our understanding of the basic mechanisms underlying numerous disease processes. Identification of mutations in the HERG K+ channel as the molecular basis of congenital long QT syndrome led to the discovery that HERG is the molecular target for the vast majority of drugs that cause drug-induced arrhythmias. This has had profound implications not only for the development of antiarrhythmic agents, but also for drug development in general. Although clinical presentation is determined by complex interactions between causal genes, genetic background, and environmental factors, with increasing knowledge about identification of underlying ion channel defects and new details of the mechanisms of arrhythmogenesis, it is expected that an individually tailored approach to the basis of patient-
specific genetic information will gain more importance in the future.

References

13. Zhang H, Hancox JC. In silico study of action potential and QT interval shortening due to loss of inactivation of the cardiac rapid delayed rectifier potassium current, I(kr), and the underlying HERG ion channel. Basic Res Cardiol 2004;99:279—87.