

LK Yuen 袁麗琪  
 NC Fong 方乃聰  
 PM Tang 鄧寶明  
 CC Shek 石志超  
 CB Chow 周鎮邦

## Jervell-Lange Nielsen syndrome in a Pakistani family

### 巴基斯坦裔病人患上的賈—蘭綜合徵

Congenital long QT syndrome is a rare hereditary disease that is related to the dysfunction of ion channels in cardiac cells. We report on a very rare case of its autosomal recessive form—the Jervell-Lange Nielsen syndrome—in a Pakistani family, which was diagnosed after the incidental finding of bradycardia in a newborn baby girl. We discuss the range of presentations in neonates; the importance of strong suspicion of the syndrome and family screening; the use of the diagnostic criteria and genetic tests; and the different management strategies.

先天性長QT綜合徵是一種罕見的遺傳病，與心肌細胞的離子通道機能障礙有關。本文所報告的賈—蘭綜合徵是這種遺傳病的常染色體呈隱性的發病形式，患者為一名巴裔新生女嬰，因為偶然發現出現心跳徐緩而診斷出患有賈—蘭綜合徵。本文討論了該症在新生兒身上出現的各種徵狀，指出對病人是否患上該綜合徵必須保持高度警覺以及進行家族成員檢測的重要性，也探討了斷症標準和各種基因測試的應用，以及不同的治療措施。

### Introduction

The long QT syndrome (LQTS) is characterised by a long QT interval in electrocardiography (ECG), a risk of torsades de pointes and sudden cardiac death. It can be congenital or acquired. Congenital LQTS is a rare hereditary disease that relates to the dysfunction of ion channels in cardiac cells.

### Case report

The index case was a full-term Pakistani newborn baby girl who was admitted to neonatal ward of the Princess Margaret Hospital in August 2003 because of sepsis. She had presented with repeated vomiting and abdominal distension on day 2 of life. Physical examination yielded unremarkable results, except for the soft, distended abdomen. The initial heart rate was 140 beats per minute. Investigations for sepsis showed a normal white cell count, raised C-reactive protein level of 60.0 mg/L (reference level, <6 mg/L), negative blood culture findings, and a normal abdominal X-ray. The baby was treated with intravenous ampicillin and netromycin.

On day 3 of life, the patient was found to have bradycardia: the resting heart rate was approximately 100 beats per minute, but on occasion, it dropped to approximately 80 beats per minute. Electrocardiography showed a prolonged, corrected QT interval (QTc) of 0.57 s (Fig 1). Acquired causes were excluded. The whole family was subsequently screened and found to have a strong history of long QT interval and congenital deafness (Fig 2). The baby's parents were first-degree cousins and her grandfathers were brothers. The QTc of the father was normal; although the mother's ECG scan showed atrial ectopic waves, her QTc was normal. The eldest brother was in Pakistan and was well, with normal hearing. The other older brother and the sister both had lost their hearing since birth, and both had a prolonged QTc, of 0.61 s and 0.56 s, respectively, with features of polymorphic T waves. The family had had one early neonatal death: 5 years previously, a baby boy had died shortly after birth; Potter syndrome had been diagnosed antenatally. Furthermore, 7 years previously, there had been a spontaneous abortion at approximately 20 weeks of gestation,

#### Key words:

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#### 關鍵詞：

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Department of Paediatrics and Adolescent  
 Medicine, Princess Margaret Hospital,  
 Laichikok, Hong Kong

LK Yuen, MB, BS  
 NC Fong, MMedSc, MRCP  
 PM Tang, MRCP, FHKAM (Paediatrics)  
 CC Shek, MRCP, FHKAM (Paediatrics)  
 CB Chow, MBBS, FHKAM (Paediatrics)

Correspondence to: Dr LK Yuen  
 (e-mail: keikei62@i-cable.com)



Fig 1. Electrocardiogram of index patient on day 3

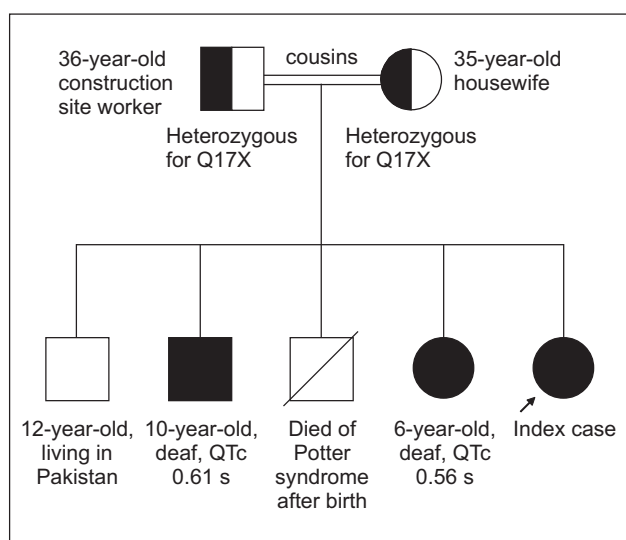


Fig 2. Family tree of index patient

and no cause had been found. No family members had experienced syncope, palpitation, epilepsy, or any episode of cardiac arrest.

Echocardiography of the baby showed a structurally normal heart and 24-hour ambulatory ECG showed no ventricular arrhythmia. Brainstem auditory evoked potential, however, revealed bilateral sensorineural deafness. Because of the strong suspicion of congenital LQTS, a genetic linkage study of the family was performed, which revealed linkage of the phenotype to the *KCNE1* gene. Both parents were heterozygous for the gene, whereas both deaf siblings and the index case were homozygous, thereby confirming the diagnosis of Jervell-Lange Nielsen (JLN) syndrome for these three individuals.

The index patient underwent daily ECG, which showed a varied but still prolonged QTc between 0.50 s and 0.57 s. The heart rate ranged from 100 to 110 beats per minute. From day 7 of life, oral  $\beta$ -blocker therapy with propranolol was started, together with careful monitoring of the heart rate and blood pressure. The QTc dropped to 0.44 s on day 10 of life, and then it remained static. The heart rate

increased to 120 to 130 beats per minute on day 13, when the mean blood pressure was 50 mm Hg. The dosage of  $\beta$ -blocker was progressively increased in an attempt to achieve maximal control of the heart rate, at 80% of the expected heart rate. However, it remained at 120 to 130 beats per minute, and the decision was thus made to maintain the previous dosage.  $\beta$ -Blocker therapy was also started for the two affected siblings.

## Discussion

The LQTS is characterised by a long QT interval in an ECG scan, a risk of atypical polymorphic ventricular tachycardia displaying features of torsades de pointes, and a high risk of sudden cardiac death. Congenital LQTS is a hereditary disease of the ion channels caused by a number of genetic defects that encode for the transmembranous sodium or potassium channel proteins. Until now, six different genes that are related to the disease have been identified (*LQT1-LQT6*).<sup>1</sup>

Clinical manifestations of LQTS vary from dizziness to syncope to sudden cardiac death; they are the result of torsades de pointes with or without degeneration into ventricular fibrillation.<sup>2</sup> These symptoms, however, cannot be reported easily in neonates, except for sudden cardiac death. Important signs of sinus node dysfunction, such as sinus bradycardia (which is also common in LQTS), would raise suspicion, as in our case.<sup>3,4</sup> Bradycardia in a neonate has several differential diagnoses, such as hypoxia, lung disease, central nervous system disease, and temperature instability. Although cardiac disorders, such as congenital heart block or congenital LQTS, are rare, they necessitate consideration. In our case, the presentation was incidental, but the family history of congenital deafness was strong—a feature that confirmed suspicion of JLN. Hence, an ECG study in a neonate with relative bradycardia or a family history of congenital deafness is essential.

One should note that QT prolongation in a neonate may be transient or an early indicator of congenital LQTS. A transient prolonged QT interval in the first year of life may be due to transient sympathetic imbalance or electrical instability, and it will disappear after the first year of life.<sup>5</sup> Thus, a prolonged QT interval in a neonate requires further confirmation for the diagnosis of congenital LQTS.

To distinguish between whether it is a transient long QT or congenital LQTS in our case, we used the diagnostic criteria for LQTS proposed by Schwartz et al (Table).<sup>6</sup> The set of criteria depends on the patient's clinical features, the family history, and the characteristics of the ECG scan. Individual criteria are assigned point values that reflect their relative importance, and the total score is classified according to probability category: a score of one point or less implies a low probability; a score of two to three points implies intermediate probability, and a score of four or more points implies a high probability of having LQTS. In our

**Table. Diagnostic criteria of QT syndrome<sup>6</sup>**

Criteria	Points
ECG <sup>*</sup> findings <sup>†</sup>	
QTc <sup>‡</sup>	
≥ 480 ms	3
460-470 ms	2
450 ms (in males)	1
Torsade de pointes	2
T-wave alternans	1
Notched T-wave in three leads	1
Low heart rate for age (<2nd percentile)	0.5
Clinical features	
Syncope with stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history <sup>§</sup>	
Family history of definite long QT	1
Unexplained sudden cardiac death at age <30 years among immediate family members	0.5

\* ECG electrocardiogram/electrocardiography

† In the absence of drug therapy affecting these features

‡ QTc corrected QT interval

§ Same family member cannot count twice

index case, the patient had a total score of 5, whereas her two deaf siblings each had a score of 4.5; all three individuals thus had a high probability of having LQTS.

The diagnosis of congenital LQTS was further confirmed by genetic linkage studies in our case. These studies demonstrated a typical autosomal recessive inheritance of the *KCNE1* gene—that is, the *JLN2* gene. This finding illustrates the importance of family screening when a new case of LQTS is diagnosed. So far, six genes have been identified for LQTS. Different genotypes give rise to six types of Romano-Ward syndrome and two types of JLN syndrome.<sup>1</sup> Jervell-Lange Nielsen syndrome accounts for fewer than 1% of the total cases of LQTS, although JLN-2 is much rarer than JLN-1. Genetic studies require special arrangement in Hong Kong, however, only approximately 60% of patients with LQTS have a known mutation.<sup>7</sup> Therefore, the diagnosis of LQTS still depends on the diagnostic criteria rather than on a genetic test. Still, it is valuable to perform genetic studies to confirm the diagnosis and the fact that genetic counselling is needed for the family.

Long-term management strategies include medical treatment, patient and family education, and cardiac pacing if necessary. Because stress and exercise are strong triggers of cardiac events in patients with congenital LQTS,  $\beta$ -blockers are used to prevent such triggers, by suppressing the adrenergic system.  $\beta$ -Blockers significantly reduce mortality among symptomatic patient—from 50% to less than 5%.<sup>8</sup> For asymptomatic patients, as in the Pakistani family in our case, treatment is controversial. Some physicians believe that most patients will never experience symptoms and that lifelong treatment is inconvenient and cost ineffective. Garson et al,<sup>2</sup> however, showed that 12% of untreated asymptomatic patients later developed symptoms, and that 4% had sudden death as the first symptom; the authors concluded that treatment is beneficial.

Wehrens et al<sup>9</sup> quoted that while waiting for more definitive data, treatment should be initiated for the following asymptomatic patients: those with congenital deafness; infants younger than 1 year because of an increased risk of events in first few months of life; those with siblings who had died suddenly; those with an ECG trace showing T-wave alternans; those with QTc of more than 600 ms; and those with anxiety who ask for treatment. Our index case had symptoms of bradycardia and therefore,  $\beta$ -blocker therapy was started.

The appropriate or optimal dose of  $\beta$ -blocker is still uncertain. Moss et al<sup>10</sup> demonstrated a lack of a dose-response effect. Most authorities, however, assess the adequacy of  $\beta$ -blocker treatment by setting the target heart rate at 80% of the expected rate, using ambulatory ECG or exercise testing to monitor the rate.<sup>11</sup> Rather than decreasing, the heart rate of the patient in our index case increased; however, the QTc did eventually return to normal and the heart rate remained constant even after we increased the dosage of  $\beta$ -blocker. Hence, we decided to revert to the usual recommended dosage. This case thus illustrated the limitation of the current method of assessing the adequacy of the  $\beta$ -blocker dosage. Although Moss et al<sup>10</sup> showed that  $\beta$ -blocker therapy is associated with a small but significant reduction in QTc, whether a shortened QTc is associated with a decreased risk of cardiac death is not well studied.

Other types of triggers have been found to be associated with different types of LQTS: sleep with LQT3, loud noise with LQT2, and diving with LQT1.<sup>9</sup> These findings indicate that  $\beta$ -blocker treatment is not universally applicable; yet, it is generally prescribed. Treatment may instead involve cardiac pacing in patients with significant bradycardia or atrioventricular conduction disturbances. Cardiac pacing is also an important adjuvant therapy in patient whom  $\beta$ -blockers have proven ineffective.<sup>3,9</sup>

The main challenge we faced was the long-term care of the index patient's whole family, including their compliance to drug therapy, lifelong avoidance of exercise, and avoidance of a long list of drugs.<sup>12</sup> Rapport between physicians and family is very important for successful care.

## Conclusion

We report a very rare JLN syndrome in a Pakistani family. Our case illustrated the importance of strong suspicion of the syndrome in neonates, as well as the importance of diagnostic criteria and genetic testing for establishing the diagnosis of LQTS. It also demonstrated the difference in heart rate response to  $\beta$ -blocker as the treatment for JLN.

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