CASE REPORT

Hereditary Long Q-T Without Congenital Deafness (Romano-Ward) Syndrome

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Abstract. We report a case of hereditary long Q-T syndrome without congenital deafness (Romano-Ward syndrome). In four members of a family, a father and his three daughters, the Q-T intervals on the EKG were found to be prolonged. There were no other accompanying familial anomalies such as deafness or a tendency to extracellular hypokalemia. The youngest daughter which had the longest Q-T interval had several Adams-Stokes attacks, and died in the last attack at the age of 23 months. Her two older siblings died at the age of 15 and 10 months with the same typical clinical histories. The eldest daughter, a 12-year old girl, has no clinical symptoms at all, while the fourth child, 5-year old girl has several occasions of near fainting attacks. The EKG of the father showed several runs of supraventricular premature contractions that ceased spontaneously, besides evidence of the prolongation of Q-T interval. The beta-adrenergic blocking drug (propranalol) given in a relatively small maintenance dose, proved to be effective in preventing attacks of the father and the fourth child, despite the unchanged prolongation of the Q-T interval. **[Paediatr Indones 1994; 34:221-230]**

Introduction

Prolongation of the QT interval associated with syncopal attacks can be encountered in two different situations: (1) the long QT syndrome of congenital origin; and (2) the acquired form.[1] There are three forms of congenital long QT syndrome: (1) the Jervell-Lange-Nielsen syndrome, associated with congenital deafness;[2,3,4] (2) the Romano-Ward syndrome, associated with normal hearing;[5,6] and (3) cases reported by Gamstrop, Nilsen and Westling with tendencies of low serum potassium in some families.[7] The acquired form may be found in association with various con-

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ditions such as atrioventricular block, sinus bradycardia or the use of which quinidine, phenothiazines, and amiodarone are examples.[1,8]

Although the incidence of hereditary long QT syndrome (LQTS) is very rare, the syndrome should be recognized well, because of the serious major impact and poor prognosis, which is characterized by recurrent episodes of loss of consciousness, some of which end fatally, represents a unique clinical example of stress-related sudden cardiac death.[9,10] According to the medical record data of the Department of Child Health, Cipto Mangunkusumo Hospital, there was no such a case within the last two decades.

The purpose of this paper is to report a family with Romano-Ward syndrome, with a history of sudden death in some members of the family without evidence of congenital deafness.

Case Report

The pedigree of the family showed that the LQTS affected the father and all his daughters and son (Figure 1).

Case 1

This patient was the fifth child of the family. She was a 23-month old girl. She was brought to a pediatrician because her parents were very concerned about the several syncopal attacks after she was crying or disappointing. Her two older siblings (a boy and a girl) died previously at the age of 15 and 10 months with the same typical clinical histories (Figure 1). She was then referred to the Outpatient Clinic of the Cardiology Division, Department of Child Health, Cipto Mangunkusumo Hospital for further ambulatory examination. However, sudden unexpected death occurred at home due to the last syncopal attack, one day after the electrocardiographic and echocardiographic examination. Unfortunately prophylaxis treatment with beta-adrenergic blocking agent was not yet be given. In spite of normal routine laboratory findings and serum electrolyte concentration, normal chest X-ray and echocardiogram, her electrocardiogram showed marked prolongation of Q-T interval with bizarre T and U wave. The corrected Q-T (QTc) interval was 500 msec (Figure 2). Based on those findings, we made electrocardigraphic examination to her parents and her two older sisters. It was a great surprise seeing the electrocardigram findings, that prolongation of the QT interval was present also at the electrocardiogram of the father and all his children but his wife.

Case 2

The father was 36 years old. There was no definite information on syncopal attacks and angina pectoris. Physical examination revealed normal findings. The heart rate was 80 per minute, blood pressure 120/80 mm Hg. Routine laboratory examination, serum calcium, and serum potassium determination were normal. The chest X-ray was normal. But his electrocardiogram showed prolongation of Q-T interval (the QTc interval was 450 msec) with several occasions of run of supraventricular premature contraction that ceased spontaneously (Figure 3). The dysrythmia was diminished after treated with oral propranolol 10 mg twice daily.

Case 3

She was the oldest child of the family, aged 12 years old. There was no history of dizziness or syncopal attacks. Physical examination showed essential normal findings. Laboratory test was normal. Her chest X-ray and echocardiogram were normal. The only abnormality was prolongation of the Q-T interval on the electrocardiogram. The QTc was 460 msec (Figure 4). She got no treatment.

Case 4

This is the fourth child of the family, she was a 5-year old girl. She had a history of several occasions of cold sweating, pale and near fainting attacks. There was no history of convulsion. Physical examination showed normal findings. The heart rate was 100 beats per minute, respiratory rate 28/minute, blood pressure 100/60 mmHG, no murmur, no rales. The laboratory data were as follows: hemoglobin 11.6 g/dl, erythrocyte sedimentation rate per 1 hour 23 mm, leukocytes 6800/µl, hematocrit 34 vol%, platelets 367 000/µl. Differential count: eosinophil 0%, stab 2%, segment 58%, lymphocytes 38% and monocytes 2%. ASTO < 222 Todds unit, C-reactive protein was negative. Serum electrolytes: sodium 140 mEq/L, potassium 3.8 mEq/L, chloride 102 mEq/L, calcium 8,9 mEq/L, magnesium 1.8 mg/dl and phosphate 3.9 mg/dl. The electrocardiogram showed prolongation of the QT interval, the QTc was 455 msec (Figure 5). Chest X-ray, echocardiogram, and electroencephalogram gave normal findings. Free field test was positive at 70 dB. Audiometry brainstem response showed no hearing disturbances. Oral propranolol given in a relatively small maintenance dose, 2 mg twice daily, diminished the attacks, but the prolongation of the Q-T interval was unchanged.

Discussion

The long Q-T syndrome (LQTS) is electrocardiographically characterized by a prolonged corrected Q-T interval and by several other, more subtle, ST-T-U wave abnormalities.[11] The corrected Q-T interval is measured by using the Bazett's formula corrected at the heart rate of 60 beats per minute. The normal range of the QTc is 390 to 480 msec, with a slightly longer QTc found in females. The frequently suggested upper limits of the normal QTc is 440 msec.[12] Although the accuracy of Bazett's formula has been question, it is still the most widely accepted.[12] Despite growing evidence that Bazett's formula overestimates the QT interval at faster heart rate, most authors continue to use it for clinical and research purposes. Recently a quantitative computer program was developed to differentiate between normal subject and patient with congenital LQTS.[11]

By using the Bazett's formula, all of our cases had prolonged QTc interval, especially the QTc of the fifth child with the history of sudden death was markedly prolonged. This markedly prolonged QT interval maybe due the prominent U

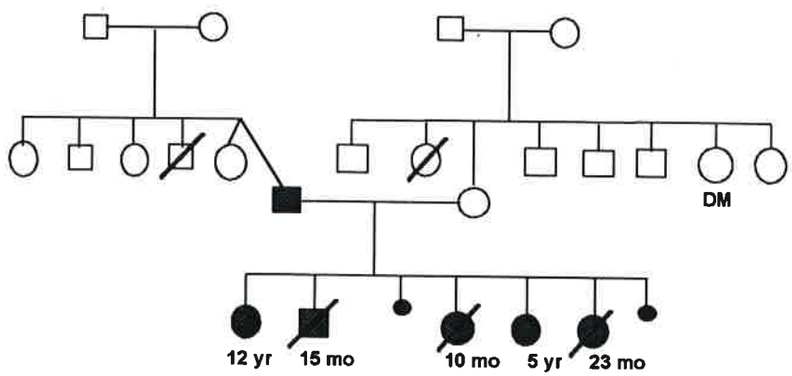
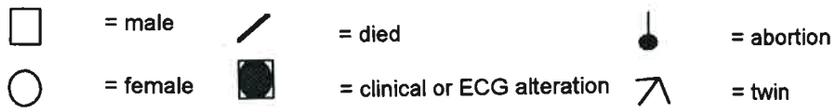


Figure 1. Pedigree of the patients.



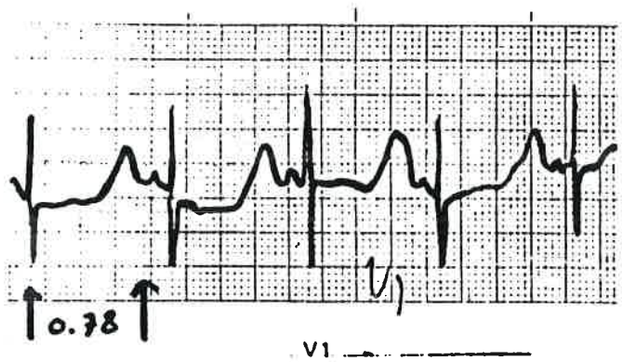


Figure 2. The electrocardiogram of the fifth child showed marked prolonged QT interval with bizarre ST-T-U wave in lead V1. The corrected Q-T (QTc) interval was 780 msec.

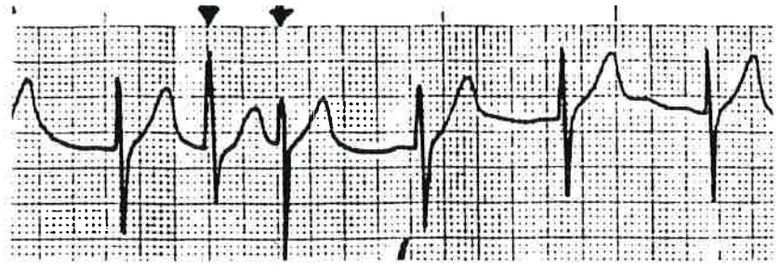


Figure 3. The electrocardiogram of the father showed prolonged Q-T interval with run of supraventricular premature contraction seen in leads V3 and V4. The QTc was 450 msec.

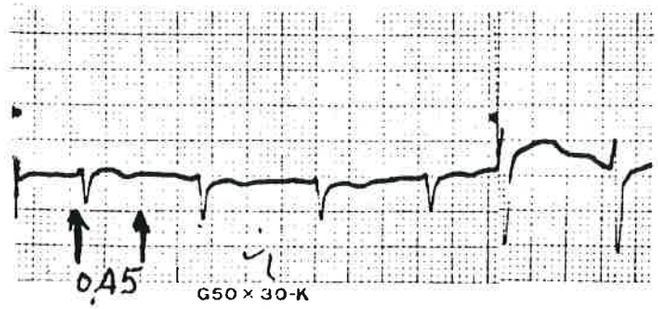


Figure 4. The electrocardiogram of the first child showed prolonged Q-T interval. The QTc was 450 msec. She has no symptoms.

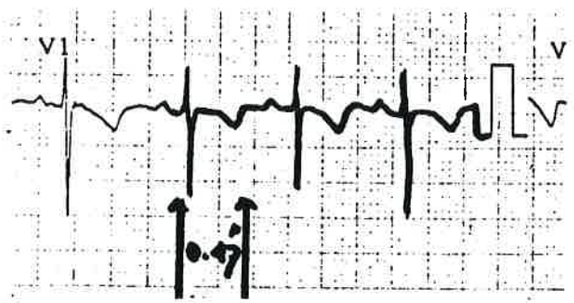


Figure 5. The electrocardiogram of the fourth child showed prolonged Q-T interval. The QTc was 470 msec. Her symtomps were cold sweating, pale and near fainting attacks.

which is consistent with recently developed concept that a prominent U wave rather than a prolonged QT interval may be responsible for paroxysmal ventricular tachycardia in patients with LQTS.[12]

The inheritable prolongation of the Q-T interval on the electrocardiogram, associated with congenital deafness, was first described by Jervel and Lange-Nielsen in 1957.[2] Since then the number of reported cases increased and some authors have named the disease the Jervell-Lange-Nielsen syndrome.[13] The main characteristics of this syndrome are as follows: (1) attacks resembling angina pectoris and/or syncopal attacks and/or sudden death; (2) a prolonged QT interval in the electrocardiogram; (3) congenital neural deafness; and (4) familial incidence.[13] Some authors suggested the name surdo-cardiac syndrome in order to sharply distinguish this autosomal recessive heredity syndrome from other familial diseases accompanied by Q-T prolongation.[4,13]

The second form of Q-T prolongation was reported by Romano, Gemme and Pongiglione, and independently by Ward, in several members of family the Q-T interval was prolonged and the T and U waves were bizarre-shaped. The hearing of the affected members of the family was normal, and extracellular hypokalemia could not be detected either.[5] An additional case has been reported by Csanady and Kiss in 1973.[6] The syndrome has an autosomal dominant inheritance and has recently been named the Romano-Ward syndrome.[5,6]

Gamstrop, Nilsen and Westling described the third form of Q-T prolongation; in the family reported by them, the affected members were hypokalemic. After administration of potassium, the electrocardiographic abnormalities was diminished, and the Adams-Stokes attack ceased.[7]

The syndrome observed by us can be classified as a Romano-Ward syndrome, because the Q-T prolongation of the electrocardiogram was not accompanied by either hearing disturbance or extracellular hypokalemia and hypocalcemia. Moreover the prolongation of the Q-T interval affected the father and all his three daughters, suggested that the syndrome was inherited probably in an autosomal manner as those in Romano-Ward syndrome.

The results of examinations and the clinical manifestations in our patients did not differ from previous case reports of hereditary Q-T prolongation. The longest Q-T interval was observed in case 1 (the fifth child) which died due to the last attack at the age of 23 months. Sudden death occurred unexpectedly after electrocardiography and echocardiographic examination. The last attack was probably triggered by strong emotional or physical stimuli. The oldest daughter has no symptoms at all, while the fourth child has several mild near syncopal attacks. Several attacks of tachycardia were recorded for case 2 (the father) without clinical symptoms. The lack of symptoms in those cases were probably due to the briefness of the attacks.

The syncopal episodes result from torsades de pointes, often degenerating into ventricular fibrillation. Prolongation of the QT interval increases the chance of an ectopic beat falling on the vulnerable

period of the preceding T wave and thus precipitating ventricular fibrillation.[14] An unobserved ventricular fibrillation preceded the observation, could explain the mechanism of the attack, in those patients with normal pulse during the syncopal attack.[14]

It is important to remember that just because patients with the long Q-T syndrome have increased risk for developing ventricular tachyarrhythmias, that does not mean that all other states characterized by Q-T prolongation confer a similar risk.[9]Whether such dispersion in recovery of excitability causes arrhythmias in patients with long Q-T syndrome is not clear.

The fundamental nature of the disorder remains unknown.[14] (Gale). Atrioventricular conduction and the duration of mechanical systole are normal. According to Gravrilescu, the electrophysiological basis in long QT syndrome were as followed: (1) right ventricular monophasic action potentials were excessively prolonged and of varying shapes in different recording sites; and (2) in addition, effective refractory periods of ventricular muscle were abnormally long.[1] It has been postulated (Ward, 1964) that an abnormality of myocardial metabolism prolongs repolarization after systole. Sympathetic stimulation sometimes prolongs the QT interval and it is possible that the myocardium in these patients is unduly sensitive to catecholamine release. Of the several hypothesis proposed, cardiac sympathetic imbalance and an intrinsic myocardial abnormality of repolarization appear most plausible. Other neurocardiological mechanism may be operative in occasional patients.[9]

Sympathetic imbalance has been invoked to explain the arrhythmogenic potential of the long Q-T syndrome on the basis reflex increased left sympathetic activity. Normally the left stellate ganglion exerts a quantitatively greater adrenergic influence on the ventricles than does the right stellate ganglion. This phenomenon may be the basis for the greater arrhythmogenic potential of left stellate ganglion stimulation compared with right.[10] Clinical studies suggest that some of the sudden infant death victims may have a reduced cardiac electrical stability may be provoked by a developmental imbalance in sympathetic innervation such to create a dominance of left-sided nerves.[15,16]

The second hypothesis, that of an intrinsic abnormality in myocardial repolarization, can explain the QT prolongation, prominent and peculiar T and U waves, T wave alternans, and ventricular tachyarrhythmias. In addition, it can serve as the mechanism for the acquired LQTS, which the sympathetic imbalance concept cannot.[9] It has been suggested that in this syndrome there is a state of inequality of the QT interval in different part of the myocardium and that asynchronous refractoriness predisposes the myocardium to ventricular fibrillation by a critically timed early impulse occurring during a vulnerable out-of-phase state.[10] This hypothesis assumes that the cause of abnormal repolarization, lies within the heart itself, perhaps an abnormal channel protein reducing or blocking an outward repolarizing potassium current or increasing an inward depolarizing calcium or sodium current.[9]

These two hypothesis are not mutually exclusive because recent evidence suggests that incomplete developement of cardiac sympathetic innervation may prolong the QT interval and alter the intracellular function. The high arrhythmogenic potential of the left cardiac sympathetic nerves leaves entirely open the possibilty that the basic defect in LQTS is a molecular cardiac membrane disorder that decreases electrical stablility and make the myocardium more vulnerable to the effect of sympathetic activation.[10]

Effective therapy for LQTS to prevent ventricular arrhythmias and sudden cardiac death continues to elude. Several pharmacologic agents such as beta-adrenergic blocking agents,[14] digitalis,[17] diphenylhydantoin,[18] and primidone,[19] have been reported. Though medical treatment is generally unsatisfactory, beta-adrenergic blocking agents may be the most value in long QT syndrome. It may reduce the incidence, intensity, and duration of attack. Propranalol given in a relatively small maintenance dose, proved to be an effective agent in preventing attacks of the father and the fourth child, despite the unchanged prolongation of the Q-T interval. Besides propranolol, another beta-adrenergic that is more cardiac selective could be used in such cases. It is in accordance with the experience of Schwartz and other authors that beta-adrenergic-blocking agents are the best of choice.[10,15]

Surgical treatment with left cervicothoracic sympathetic ganglionectomy has also been used in LQTS patients with recurrent syncope. There fore, when beta-adrenergic blocking agents fail, left cardiac sympathetic denervation has also proven to be very effective. The latter result suggests a role for alpha-adrenergic mechanisms in the arrythmias of long QT syndrome.[10]

The efficacy of pacemakers as a treatment option for long QT syndrome has been reported. The beneficial effect of pacing in high-risk long QT syndrome patients probably relate to the prevention of bradycardia, pauses, and the shortening of long QT intervals-factors that are known to be arrhythmogenic in this syndrome. Permanent cardiac pacing reduces the rate of recurrent syncopal events in high-risk long QT syndrome patients, but it does not provide complete protection.[20] For some patients implantation of a cardioverter-defibrillator may be necessary.[9]

Recently, a DNA marker at the Harvey ras-1 locus was shown to be linked to the long QT syndrome. This finding confirms the disorder and localizes this gene to the short arm of chromosome. The protein encoded by the gene is one of the G proteins and may help control the passage of potassium ions through membrane channels. So in the future one can identify precisely the repolarization abnormality and possibly direct therapy with more specificity than producing left sided sympathetic denervation of the heart.[9]

The fundamental question is whether the QTc can identify a patient at higher risk for sudden death. There are still some indications that patients with longer QTc as a group have a worse outcome. Two recent longitudinal studies have suggested a correlation between Q-T prolongation and mortality in the general population with and without heart disease.[12,21,22] Although the very marked prolongation of the QT interval was seen only in the fifth child with the history of sudden death, the prognosis of the father and his fourth daughter is still dubious. We should explain the parents regarding the potential of sudden death recurrence in their family and promote the compliance in using the propranolol as prophylactic treatment.

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