Congenital long QT syndrome presenting as unexplained bradycardia

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SUMMARY

Congenital long QT syndrome (LQTS) is a genetically autosomal heterogeneous disorder of the ion channels and causes about 10% of sudden death infant syndrome in newborns. Its estimated prevalence is approximately 1 in 2500, probably underestimated because of its clinical heterogenicity. Few cases of neonatal LQTS have been reported. In 4% of them, life-threatening arrhythmic events can be the first manifestation of LQTS. The authors report two cases of neonatal LQTS with heterogeneous genetic mutations. Both manifested by bradycardia, one since fetal life. One case had serious arrhythmias during beta blocker therapeutic establishment needing a pacemaker implantation. Genetic mutations found were not the most frequently described in association with neonatal bradycardia, thus the importance of this report. Presentation with bradycardia is relatively frequent in neonatal period, thus LQTS should be actively investigated in neonates with unexplained bradycardia. Beta blocker therapy reduces QTc and avoids arrhythmic events and sudden death.

BACKGROUND

Congenital long QT syndrome (LQTS) is a genetically autosomal heterogeneous disorder of the ion channels[1] and is the cause of about 10% of cases of sudden death infant syndrome in newborns.[2] Its estimated prevalence is approximately 1 in 2500, probably underestimated because of its clinical lifelong heterogenicity.[3] Prolongation of the QT interval in neonates may be transient but it can also represent an early form of LQTS .[4] Even transient QTc prolongation has been associated with life-threatening events.[5] Specific risk factors for life-threatening arrhythmic events in infants with congenital LQTS are: QTc >600 ms, T wave alternans, 2:1 atrioventricular (AV) block and sensorineural hearing loss.[6] Few cases of neonatal LQTS have been reported. In 4% of them, life-threatening arrhythmic events can be the first manifestation of LQTS.[6] The authors report two cases of neonatal LQTS that presented with bradycardia.

CASE PRESENTATION

Case 1: a female newborn was delivered at 38 weeks' gestation. Pregnancy and labour were uneventful. The newborn was evaluated on day 1 of life for asymptomatic sinus bradycardia observed in the nursery. ECG recording showed a prolonged QT interval (QTc of 555 ms) and was otherwise normal (figure 1). The newborn had a short period of supraventricular tachycardia during the first week of life with spontaneous resolution. Oral propranolol was initiated and titrated to 3 mg/kg/day. Otoacoustic emissions excluded neurosensorial deafness. Genetic testing revealed an heterozygous variant in the KCNH2 gene NM_000238.4: c.772C>T, p.(Pro241Leu) in exon 4 which has been reported in individuals with LQTS. First-degree relatives were asymptomatic and had normal QTc on ECG recording. Their genetic testing is underway.

Case 2: a male newborn was delivered at 33 weeks of gestation. Fetal bradycardia was identified during week 22 of gestation. On week 25 the fetus had a heart rate of 80 beats per minute with second-degree AV block. Regular monitoring of the fetus showed no signs of heart failure. He was born by caesarean section and birth weight was 1575 g. Heart rate was 120–145 beats per minute after birth. The newborn was admitted to the neonatal unit and ECG recordings documented prolonged QTc interval (550–650 ms) with 2:1 AV block and T wave alternans (figure 2). During the first month of life he remained in sinus rhythm with occasional ventricular extrasystolic beats. After the first month, he had recurrent episodes of non-sustained ventricular tachycardia (VT) and polymorphic VT (torsade de pointes type at 300 beats per minute) with short duration and spontaneous resolution. He was started on propranolol with gradual dose increase, but, due to a low heart rate while still having arrhythmic events, an epicardial pacemaker was implanted and programmed as VVI mode (ventricular demand pacing). Rescue HR of 70 beats per minute, allowed propranolol titration to 4 mg/kg/day and control of arrhythmias. Two heterozygous variants in SCN5A gene NM_198056.2: c.5315T>G, p.(Leuc1772Arg) and c.393–5C>T were identified by genetic testing. The first variant has not been reported in previous studies and is localised in a functional domain where several other variants causing LQTS have been described. The second variant is rare but has also been reported previously as a pathogenic variant in patients with arrhythmia. Parents were asymptomatic and had normal QTc on ECG recording. Despite proper information regarding disease severity, parents refused genetic testing and have missed several appointments.

OUTCOME AND FOLLOW-UP

Case 1

The infant remained under oral propranolol and is now 19 months old. QTc reduced to 436 ms. On serial 24 hours ECG monitoring no life-threatening arrhythmic events have been recorded.

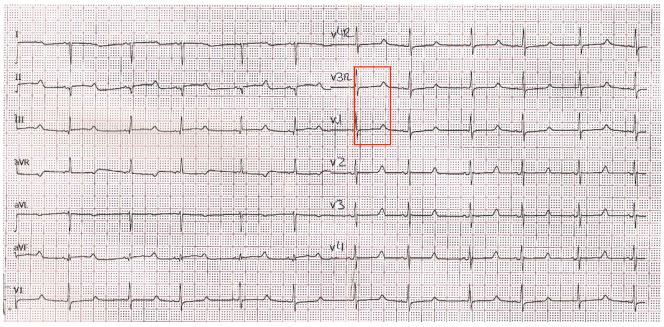

Figure 1 QT prolongation (QTc 555 ms) in the setting of bradycardia (square).

Case 2

The infant is now 16 months old and remains stable on beta blocker therapy with no evidence of arrhythmic events. QTc was 413 ms at his last clinical appointment.

DISCUSSION

Few reports of early onset LQTS are known. In both of our newborns the initial symptom was sinus bradycardia (already noted in utero for one of the patients) which is considered a diagnostic criterion and is associated with an increased risk of cardiac events.[7 8] Presentation with bradycardia is also documented in other published reports of neonatal LQTS.[1 6] Nevertheless, bradycardia and transient QTc prolongation (<500 mseg) can coexist during a healthy neonatal period. Thus, serial electrocardiographic QTc evaluation was performed in order to correctly diagnose LQTS in both patients.

None of the patients had a positive family history. Comprehensive targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval on serial 12-lead ECGs.[9] Mutations in at least 17 LQTS-susceptibility genes have been identified thus far. These two newborns had mutations in one of the three genes (KCNQ1, KCNH2 and SCN5A) that account for at least 75 per cent of all LQTS.[10] Sinus bradycardia with 2:1 AV block (pseudoblock) associated with LQTS is rare and usually presents before birth or during the neonatal period. This phenomenon occurs when sinus intervals are shorter than the ventricular refractory period and relates do the extreme prolongation of ventricular refractoriness.[11] Most of these cases have been associated with KCNH2 mutations, but the newborn in our series, with 2:1 AV block, had a SCN5A mutation.[12] Prognosis in these cases is poor, with a 50% death rate before 6 months in untreated patients.[9]

Neonatal sinus bradycardia with QTc prolongation has been associated with KCNQ1 mutations.[6] However, our patient presenting with neonatal bradycardia (case 1) had a KCNH2 mutation. The mutation detected in this patient, KCNH2 (NM_000238.4): c.772C>T, p.(Pro241Leu)), is a non-pore mutation so possesses a lower risk of arrhythmia-associated cardiac events than pore mutations.[13]

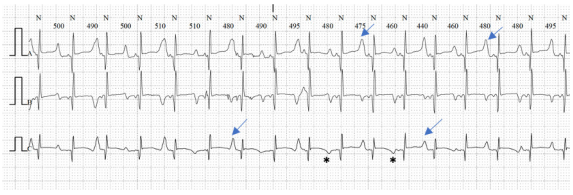

Figure 2 QT prolongation (QTc 550 ms) and T wave alternans.

Propranolol has been shown to be effective in controlling arrhythmic events in newborns with LQTS,[6] as was true in these two cases. Regarding patients' phenotype-genotype, case 1 is suggestive of LQTS 2 and patient 2 of LTQS type 3. Further familial genetic testing would help to reassure its variants' pathogenicity.

Learning points

- Although there are few reported cases of newborn long QT syndrome (LQTS), this diagnosis is crucial as it is an important cause of sudden death in this population.
- Presentation with bradycardia seems to be relatively frequent in the neonatal period, thus LQTS should be actively investigated on its grounds.
- Beta blocker therapy reduces QTc and has been shown to prevent arrhythmic events and sudden death in newborns with different types of LQTS.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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