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Long QT Syndrome in Neonates

Conduction Disorders Associated With *HERG* Mutations and Sinus Bradycardia With *KCNQ1* Mutations

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OBJECTIVES We hypothesized that neonatal long QT syndrome (LQTS) with 2:1 atrioventricular block (AVB) could be related to *HERG* mutations.

BACKGROUND Early onset of LQTS is rare but carries a high risk of life-threatening events such as ventricular arrhythmias and conduction disorders. There are no data on possible gene specificity.

METHODS We analyzed the characteristics and outcomes of 23 neonate probands from our LQTS population. Samples of DNA were available in 18 cases.

RESULTS Long QT syndrome was diagnosed because of corrected QT interval (QTc) prolongation (mean QTc of 558 ± 62 ms) and neonatal bradycardia attributable to sinus bradycardia (n = 8) or 2:1 AVB (n = 15). Symptoms included syncope (n = 2), torsades de pointes (n = 7), and hemodynamic failure (n = 6). Three infants with 2:1 AVB died during the first month of life. During the neonatal period, all living patients received beta-blockers (BB) and 13 had a combination of BB and permanent cardiac pacing. Under treatment, patients remained asymptomatic, with a mean follow-up of seven years. Mutations were identified in *HERG* (n = 8) and *KCNQ1* (n = 8), and one child had three mutations (*HERG*, *KCNQ1*, and *SCN5A*). Conduction disorders were associated with LQT2, whereas sinus bradycardia was associated with LQT1.

CONCLUSIONS Two-to-one AVB seems preferentially associated with *HERG* mutations, either isolated or combined. Long QT syndrome with relative bradycardia attributable to 2:1 AVB has a poor prognosis during the first month of life. In contrast, sinus bradycardia seems to be associated with *KCNQ1* mutations, with a good short-term prognosis under BB therapy. (J Am Coll Cardiol 2004;43:826–30) © 2004 by the American College of Cardiology Foundation

The congenital long QT syndrome (LQTS) is a potentially lethal cardiac disease caused by mutations in specific ion channels (1). Bradycardia is considered as a diagnostic criterion (2) and is also associated with a risk of cardiac events (3). A lower than normal heart rate can be caused by slow sinus rhythm or impaired atrioventricular (AV) conduction, mainly 2:1 AV block (AVB). This latter form is rare and usually manifests itself before birth or during the neonatal period (4–9). The prognosis is poor, with a 50% death rate before six months (5,7). So far, three cases of neonatal LQTS with 2:1 AVB have been related to homozygous *HERG* mutations (8–11). We hypothesized that neonatal LQTS with 2:1 AVB could be related to *HERG* mutations.

METHODS

Study population. From our LQTS population, we identified 23 neonate probands with ventricular rates <110 beats/min. Long QT syndrome was diagnosed on the basis of prolongation of ventricular repolarization (corrected QT interval [QTc] >460 ms, according to Bazett's formula) (12). Each patient underwent a clinical evaluation and cardiovascular examination, including a 12-lead electrocardiogram (ECG) and 24-h Holter recording. At the time of the study, none of the parents were known to have LQTS. In 18 cases, blood samples were obtained for genotyping after written consent from the parents, in accordance with the protocol, as approved by the local Ethics Committee.

Mutation analysis. Genomic deoxyribonucleic acid was extracted from blood samples using the standard procedure. Previously published primer pairs were used to amplify all exons of *KCNQ1*, *HERG*, *KCNE1*, and *SCN5A* from genomic DNA (13). Abnormal conformers were identified either by polymerase chain reaction–single strand conformation polymorphism or by using denaturing high-performance liquid chromatography in case of negative results. The corresponding exons were reamplified and sequenced by the dideoxynucleotide chain termination method with fluorescent dideoxynucleotides on an ABI-Prism 377 DNA sequencer (Applera, Applied Biosystems). When a mutation in one LQTS gene was identified, the other LQTS genes were also screened to eliminate associated mutations. In case of de novo mutations, biologic paternity was confirmed by DNA analysis. A control group

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Abbreviations and Acronyms

AV = atrioventricular
AVB = atrioventricular block
BB = beta-blocker/blocking
QTc = corrected QT interval
ECG = electrocardiogram
LQTS = long QT syndrome

of 100 healthy and unrelated subjects was used to exclude the possibility of the novel detected mutations being DNA polymorphisms.

Statistical analysis. Data are expressed as the mean value ± SD. Mean QTc and sinus rate values were compared using the unpaired Student *t* test, with $p < 0.05$ considered as statistically significant.

RESULTS

Clinical results. Long QT syndrome was diagnosed at a mean age of 4 ± 2 days in full-term infants (14 males) on the grounds of isolated bradycardia (n = 13 [57%]) or torsades de pointes (n = 7). In 10 other cases, QT prolongation was evidenced on the surface ECG in neonates referred for loss of conscious (n = 2), cardiac arrest (n = 1), or hemodynamic failure (n = 5) (Table 1). In contrast to neonates with relative bradycardia attributable to AVB, all neonates with sinus bradycardia were asymptomatic (Table 2). Electrocardiography was performed because of a lower than normal heart rate at birth and evidenced a prolonged QTc (mean 558 ± 62 ms). The QTc, according to Fredericia's formula, was 510 ± 56 ms. At the time of diagnosis, before any therapy, the mean ventricular rate was slow (110 ± 23 beats/min), compared with healthy newborns (12), because of sinus bradycardia (n = 8) or 2:1 AVB (n = 15). In 12 cases, bradycardia was also detected prenatally at a mean gestational age of 30 weeks during systematic cardiofetal monitoring. Fetal echocardiography was subsequently performed in only two cases showing 2:1 conduction associated with fast, irregular ventricular activity, suggesting ventricular tachycardia in Patient 12 and a slow, regular 1:1 rhythm in Patient 21. In patients with AV conduction disorders, Holter recordings revealed frequency-dependent conduction anomalies with episodes of 2:1 AVB occurring

Table 1. Clinical and Genetic Characteristics of Neonates With 2:1 Atrioventricular Block

Patient Number/Gender	Circumstances of Diagnosis	ECG QTc (ms) AR/VR (beats/min)	Initial Therapy	Outcome Follow-Up	Genotype
1/M	Syncope	620 110/55	Propranolol and PM	Death at 3 weeks of sepsis	No DNA
2/M	Fetal bradycardia	520 120/60	Propranolol	AS at 14 years	No mutation identified
3/M	Syncope	630 120/60	Acebutolol	AS at 10 years	No DNA
4/F	Fetal bradycardia, TDP	530 150/75	Propranolol	Lost to follow-up at 9 months	No DNA
5/M	Neonatal bradycardia	640 120/60	Propranolol and PM	AS at 17 years	No DNA
6/F	Fetal bradycardia, TDP	560 120/60	None	SD at 1 month	No DNA
7/M	Heart failure	560 120/60	Propranolol and PM	SD at 9 days, 3 days after withdrawal	*HERG* G604S by MT
8/F	Fetal bradycardia, collapse TDP	580 140/70	Propranolol and PM	AS without PM at 23 years	*HERG* T613M by MT
9/M	Neonatal bradycardia	520 120/60	Propranolol	AS at 21 years	*HERG* T613M by MT
10/F	Fetal bradycardia, VF, cardiac arrest at day 1	527 140/70	Propranolol and PM	AS without PM at 10 years	*HERG* S621N by MT
11/F	Neonatal bradycardia	490 140/70	Propranolol and PM	AS at 1 year	*HERG* D501N by MT
12/M	Fetal arrhythmia, collapse TDP, VT	700 90/45	Propranolol	10-year runs of TDP under nadolol and PM	*KCNQ1* R555H, *HERG* R835W, *SCN5A* L619F
13/F	Neonatal bradycardia, heart failure, collapse, VT	600 100/50	Propranolol and PM	AS at 6 months	*HERG* M645V (de novo mutation)
14/F	Fetal bradycardia, TDP, heart failure	544 140/70	Propranolol and PM	AS at 3 months	*HERG* G628S (de novo mutation)
15/M	Fetal bradycardia	680 110/55	Propranolol and PM	AS without PM at 9 years	*HERG* Y493C (de novo mutation)

AR = atrial rate; AS = asymptomatic; AVB = atrioventricular block; ECG = electrocardiographic; F = female; M = male; MT = maternal transmission; PM = pacemaker; QTc = corrected QT interval; SD = sudden death; TDP = torsades de pointes; VF = ventricular fibrillation; VR = ventricular rate; VT = ventricular tachycardia.

Table 2. Clinical and Genetic Characteristics of Neonates With Sinus Bradycardia

Patient Number/Gender	Circumstances of Diagnosis	ECG QTc (ms) VR (beats/min)	Initial Therapy	Outcome Follow-Up	Genotype
16/M	Fetal bradycardia	527 65	Propranolol	AS at 8 yrs	*KCNQ1* R231C (de novo mutation)
17/M	Neonatal bradycardia	500 90	Propranolol	AS at 7 yrs	*KCNQ1* R174H by MT
18/F	Fetal bradycardia	480 90	Propranolol	AS at 4 yrs	*KCNQ1* g.1258 ins A by MT
19/M	Neonatal bradycardia	460 95	Propranolol	AS at 6 yrs	*KCNQ1* A590T by MT
20/F	Fetal bradycardia	550 90	Propranolol	AS at 2 yrs	*KCNQ1* G325R by MT
21/M	Fetal bradycardia	545 94	Propranolol	AS at 2 months	*KCNQ1* R231C by MT
22/M	Neonatal bradycardia	560 95	Propranolol	AS at 3 yrs	*KCNQ1* g.dup524–534 by MT
23/M	Fetal bradycardia	503 69	Acebutolol	AS at 2 yrs	*KCNQ1* R231C by MT

g = genomic; ins = insertion; other abbreviations as in Table 1.

when the atrial rate increased above 150 beats/min without any ventricular arrhythmia (Fig. 1). During sequences of 1:1 conduction, a notched T-wave morphology was demonstrated. Compared with neonates with sinus bradycardia, neonates with 2:1 AVB had a significantly higher sinus rate (86 ± 12 beats/min vs. 117 ± 18 beats/min, respectively; $p < 0.001$) and a significantly longer mean QTc (516 ± 36 ms vs. 580 ± 63 ms, respectively; $p < 0.05$). Families of LQTS neonate probands were screened for LQTS. A family history was available in all cases of LQTS with sinus bradycardia. In seven cases, a prolonged QTc (mean 458 ± 13 ms) was discovered in one of the parents, which was always the mother. Only one woman had experienced syncope during childhood. A familial history was available in 10 of 15 cases of 2:1 AVB and was negative in parents and siblings of patient nos. 2, 13, 14, and 15 with normal QTc intervals. In six families, a prolonged QTc (mean 492 ± 24 ms; n = 5) was discovered in the mother, asymptomatic in all cases. However, the maternal aunt of Patient 11 died suddenly at the age of 16 years.

Treatment and follow-up. Three infants with 2:1 AVB died before one month of age: one case of sepsis in a child with a pacemaker; one case after interruption of pacing due to a loss of capture; and the last case in the absence of treatment because of parent refusal. Beta-blocking (BB) therapy was initiated with propranolol at a mean dosage of 1 mg/kg per day in all neonates and was titrated to 3 mg/kg per day. In patients with 2:1 AVB, there was a mean 20% decrease in sinus rate, and maximal heart rates were below 150 beats/min. In nine of the patients with 2:1 AVB, propranolol was combined with permanent cardiac pacing. The mode of pacing was VVI for seven of nine cases and DDD for two of nine cases. None of the neonates with sinus bradycardia required a pacemaker under propranolol at a mean dose of 3 mg/kg. Sinus rhythm decreased from 86 ± 12 to 80 ± 10 beats/min during the first month of life. During follow-up, propranolol was switched to nadolol by the age two years, and the dosage was adjusted to reach a maximal heart rate <150 beats/min in children under 10 years and <130 beats/min in children older than 10 years. All living children were asymptomatic under nadolol (50 mg/m2/day) during a mean follow-up of seven years.

Genetic results. We identified eight mutations in *KCNQ1* and eight mutations in *HERG* (Tables 1 and 2). In one child presenting initially with 2:1 AVB and severe ventricular arrhythmias, three mutations were identified: one in *KCNQ1* (R555C) and one in *SCN5A* (L619F), both inherited from the mother, and the third in *HERG* (R835W), inherited from the father. Mutations were de novo in five cases *(HERG*: n = 4; *KCNQ1*: n = 1). A novel hot spot in *KCNQ1* with R231C was identified in three patients. Two novel nonsense mutations were identified in *KCNQ1* (K422fsX and L175fsX), as well as a novel missense mutation (A590T). Mutations in *HERG* were known in six cases and novel in two cases (D501R and R835W). In the 15 cases of AVB, DNA samples were available in 10 infants, with mutations identified in *HERG* in nine of 10 cases. Samples of DNA were available in all neonates with sinus bradycardia, and mutations in *KCNQ1* were identified in all eight cases. Interestingly, all *HERG* mutations were found in cases with relative bradycardia attributable to AV conduction disorders, whereas isolated mutations in *KCNQ1* were found in neonates with sinus bradycardia.

DISCUSSION

We provide evidence that AV conduction disorders in neonatal forms of LQTS are preferentially associated with a *HERG* mutation, either isolated or combined, whereas persistent sinus bradycardia is associated with *KCNQ1* mutations. We confirm that neonatal LQTS with brady-

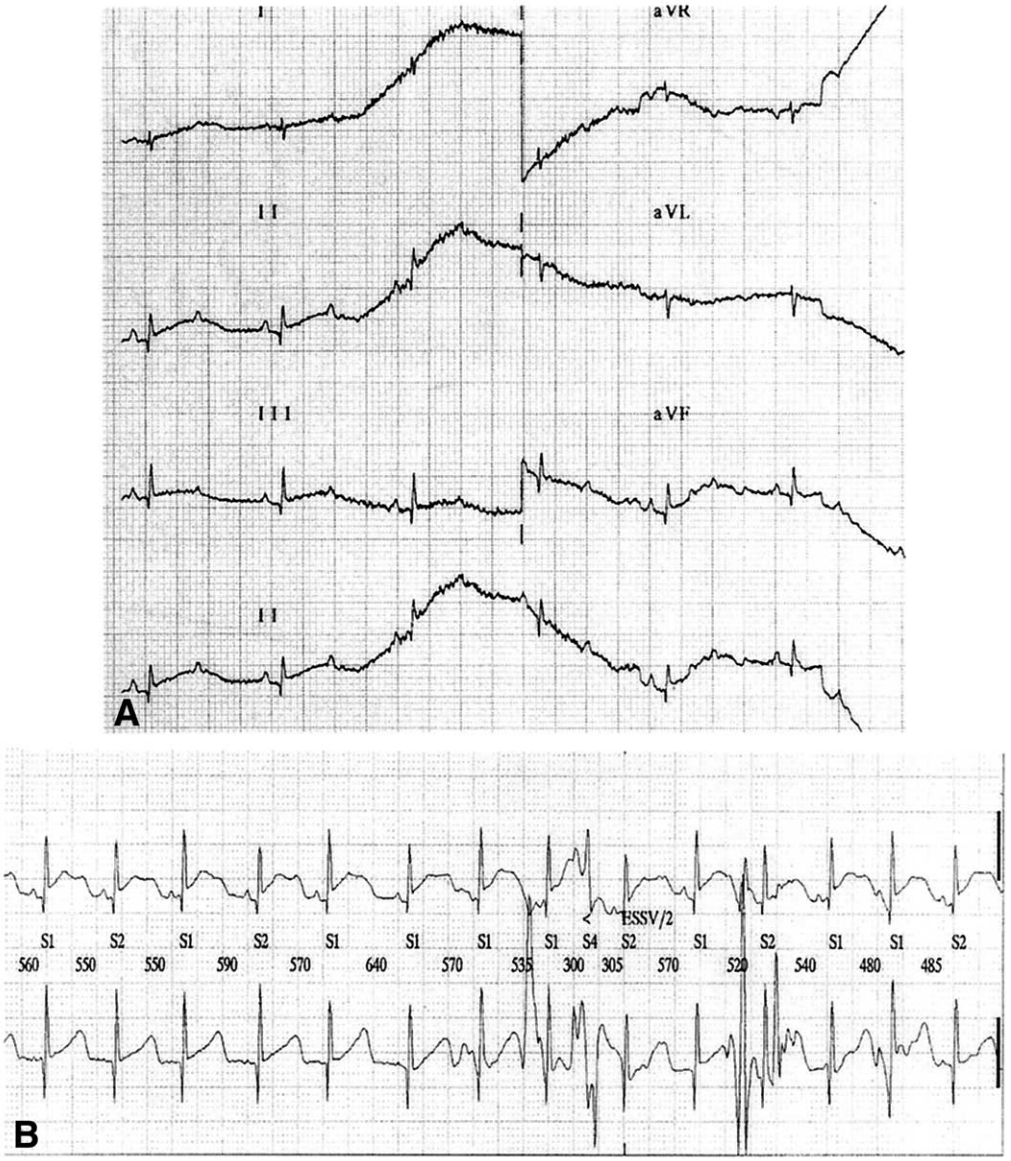

Figure 1. Electrocardiographic **(A)** and Holter **(B)** recordings of a one-day-old neonate with bradycardia attributable to 2:1 atrioventricular block (AVB). The Holter recording showed 1:1 sinus rhythm periods, thus demonstrating that the AVB was intermittent. Furthermore, the notched T-wave morphology pointed to a mutation in *HERG*, which was identified.

cardia attributable to 2:1 AVB has a severe prognosis, mainly during the first month of life.

As of today, little is known about the genotype of patients with LQTS and 2:1 AVB. Recent reports of LQTS with functional 2:1 AVB have been related to homozygous mutations in *HERG* (8–11) or *SCN5A* (14). Three infants with homozygous *HERG* mutations had a prolonged QTc, with functional 2:1 AVB with one sudden death in utero, whereas heterozygous carriers in the family had a normal phenotype (8–11). The child with a homozygous *SCN5A* mutation was not symptomatic during the first month of life and was older at diagnosis (14). In our series, we also found that neonates with AVB had mutations in *HERG*, but at the heterozygous state (n = 8) or combined with mutations in other LQTS genes (n = 1). However, any genetic defect associated with electrophysiologic anomalies producing major ventricular repolarization prolongation associated with a fast sinus rate could promote such a phenotype. In contrast, we did not have evidence of any AV conduction disorders in our LQT1 neonates, even in those with the longest QTc. This could be explained by the fact that in our population, neonates with mutations in *KCNQ1* have slower sinus rates than those with mutations in *HERG*. In the case of relative sinus bradycardia, the P wave occurs after the end of the ventricular refractory period, even when there is a major prolongation of the T wave, thus avoiding functional 2:1 AVB. The underlying molecular defect associated with sinus bradycardia remains to be explored. There is evidence

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that LQT1 patients have slower heart rates, particularly during effort. A diminished heart rate response to exercise has been evidenced in older LQT1 patients compared with LQT2 patients (15). It appears that 2:1 AVB is not related to mutations in *KCNQ1*, as opposed to mutations in *HERG* at the heterozygous or the homozygous state or in *SCN5A* at the homozygous state in an older child (14). Despite the role of *SCN5A* in conduction disorders in older patients, we have not yet identified isolated mutations in this gene in our neonate population with bradycardia.

Long QT syndrome with 2:1 AVB is rare, with an incidence of 4% reported in pediatric series and a high mortality rate (5). The death rate in our population was lower (3 [13%] of 23 patients), probably as a result of prenatal diagnosis and aggressive initial therapy combining BB and pacemaker implantation in 60% of the 2:1 AVB neonates. Among the three deaths, one occurred in the total absence of treatment and the two others under BB therapy, but in the context of sepsis in one case and with pacing failure in the other case. These patients were not given the a full therapeutic option and were the first of our series. Management of such patients has been improved since. We confirm that LQTS in neonates with 2:1 AVB is malignant, as attested by the high rate of cardiac arrest or hemodynamic failure (26%) and torsades de pointes (30%), compared with reported pediatric series of older patients of a mean age of 6.8 ± 5.6 years (9% cardiac arrest, 6% torsades de pointes) (16). In contrast, infants with isolated sinus bradycardia appear to have a more benign initial prognosis under initial BB therapy. However, one neonate with LQTS and torsades de pointes with neither AVB nor bradycardia died suddenly at nine weeks under BB therapy (17).

Conclusions. Atrioventricular conduction disorders in neonates with LQTS seem to be associated preferentially with a *HERG* mutation, either isolated or combined, as opposed to persistent sinus bradycardia, which seems to be associated with *KCNQ1* mutations. Early onset of LQTS with bradycardia attributable to 2:1 AVB has a poor prognosis, mainly during the first month of life, and requires pacemaker implantation combined with BB. These findings should be confirmed by larger collaborative studies.

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