Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome

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OBJECTIVES The aim of this study was to elucidate the genetic basis for long QT syndrome (LQTS) in patients with a personal or family history of postpartum cardiac events.

BACKGROUND The postpartum period is a time of increased arrhythmogenic susceptibility in women with LQTS.

METHODS Between August 1997 and May 2003, 388 unrelated patients (260 females, average age at diagnosis, 23 years, and average QTc, 482 ms) were referred to Mayo Clinic’s Sudden Death Genomics Laboratory for LQTS genetic testing. Comprehensive mutational analysis of the 5 LQTS-causing channel genes was performed. The postpartum period was defined as the 20 weeks after delivery. Cardiac events included sudden cardiac death, aborted cardiac arrest, and syncpe. The presence of a personal and/or family history of cardiac events during postpartum period was determined by review of the medical records and/or phone interviews and was blinded to the status of genetic testing.

RESULTS Fourteen patients (3.6% of cohort) had personal (n = 4) and/or family history (n = 11) of cardiac events during the defined postpartum period. Thirteen of 14 patients (93%) possessed an LQT2 mutation and 1 had an LQT1 mutation. Postpartum cardiac events were found more commonly in patients with LQT2 (13 of 80, 16%) than in patients with LQT1 (1 of 103, 1%, P < 0.0001).

CONCLUSIONS There is a relatively gene-specific molecular basis underlying cardiac events during the postpartum period in LQTS. Along with previous gene-specific associations involving swimming and LQT1 as well as auditory triggers and LQT2, this association between postpartum cardiac events and LQT2 can facilitate strategic genotyping.

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KEYWORDS Long QT syndrome; Postpartum period; Sudden death; Genetic testing

The congenital long QT syndrome (LQTS) comprises the first genetically defined type of arrhythmia to be understood at the molecular level as a primary cardiac channelopathy.1–3 To date, 6 LQTS genes have been identified: KCNQ1 (KVLQT1, LQT1), KCNH2 (HERG, LQT2), SCN5A (LQT3), ANKB (Ankyrin-B, LQT4), KCNE1 (minK, LQT5), and KCNE2 (MiRP1, LQT6).4–9 There are relatively gene-specific triggers for cardiac events in LQTS. Patients with LQT1 usually have cardiac events during exercise (62%), whereas LQT2 and LQT3 patients are more likely to have events during rest/sleep (29% and 39%);10 Moreover, swimming appears to trigger events in nearly 15% of children and young adults with symptomatic LQTS, and swimming-
triggered cardiac events almost universally denote the presence of LQT1.11–13 In contrast, the majority of cardiac events triggered by auditory stimuli such as the doorbell and alarm clock occur in patients with LQT2.14 Rashba and colleagues15 reported that the 40 weeks after the birth of a baby are associated with increased risk for cardiac events in women with LQTS, but the genetic underpinnings for such postpartum-triggered cardiac events were unknown. The objective of this study was to determine the genetic basis for LQTS in patients with a personal or family history of cardiac events occurring postpartum.

Methods

Study population

Between August 1997 and May 2003, 388 unrelated patients were referred to Mayo Clinic’s Sudden Death Genomics Laboratory for LQTS genetic testing because of a clinical suspicion of LQTS. The study was approved by Mayo Foundation’s Institutional Review Board. The presence of a personal and/or family history of cardiac events occurring postpartum was determined by review of the medical records and/or phone interviews and was blinded to the status of genetic testing. In an effort to focus on the time period where postpartum-associated physiological alterations are likely present and to minimize ascertainment/recall bias, the postpartum period was defined as the first 20 weeks after delivery.

The standard obstetrical/gynecologic definition of the postpartum period is 4 to 8 weeks, whereas the legal definition for maternal mortality data is the first year after delivery. Cardiac events included sudden cardiac death (SCD), aborted cardiac arrest, and syncope. Comprehensive mutational analysis of the 5 LQTS-causing channel genes: KCNQ1/KVLQT1 (LQT1), KCNH2/HERG (LQT2), SCN5A (LQT3), KCNE1/mink (LQT5), and KCNE2/MiRP1 (LQT6) was performed using exon-targeted amplification by polymerase chain reaction, denaturing high performance liquid chromatography, and automated DNA sequencing.16

Statistical analysis

All continuous variables were reported as the mean ± SD. A 2-tailed Fisher exact test was used to compare the prevalence of the cardiac events during postpartum in each gene mutation. A P value < .05 was considered to be statistically significant.

Results

Among this cohort of 388 unrelated patients (260 females, average age at diagnosis, 23 years, and average QTc, 482 ms), referred for mutational analysis of the LQTS-causing channel genes because of a clinical diagnosis of suspected LQTS, 14 patients (3.6%) had a personal and/or family history of at least one cardiac event during the defined postpartum period (Table 1). Four of these 14 index cases experienced postpartum cardiac events including: appropriate implantable cardioverter defibrillator therapy to terminate ventricular fibrillation during sleep at 4 and 20 weeks postpartum (case 12, Table 1), aborted cardiac arrest result-

<table>
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<tr>
<th>Case No.</th>
<th>Relationship to case</th>
<th>No. of cardiac events</th>
<th>Type of cardiac event</th>
<th>Time from delivery (weeks)</th>
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Family member = number in () indicates relatedness to the index case, (1) denotes a first-degree relative, either mother or sister; (2) indicates a second-degree relative, either aunt or niece; LQTS = long QT syndrome; SCD = sudden cardiac death.

* Denotes a novel LQTS-causing mutation.
† This patient received an appropriate shock by an implantable cardioverter defibrillator due to ventricular fibrillation.
‡ This patient also had a second-degree relative (maternal aunt) with postpartum sudden cardiac death.
§ Cardiac events occurred 1 hour after delivery.
ing in profound neurological injury at 16 weeks postpartum (case 1, Table 1), and syncpe at 8 weeks postpartum in 2 patients (cases 9 and 10). Eleven of 14 probands had a positive family history of a postpartum-triggered cardiac event: SCD in 7 including 5 first-degree relatives (either mother or sister), aborted cardiac arrest in 2, and syncpe in 2. The average time from delivery to a cardiac event was 10.5 ± 5.2 weeks (range 1 hour to 20 weeks, median 8 weeks, and mode 8 weeks).

Thirteen of the 14 postpartum-positive probands (93%) harbored mutations in KCNH2 (LQT2) including 8 novel mutations and 5 previously published mutations. One individual (7%) had a novel pore mutation in KCNQ1 (LQT1). Four of the 13 KCNH2 mutations localized to either the channel pore or transmembrane spanning domains while 9 resided in the cytoplasmic N- or C-terminal regions (non-pore regions, Table 1, Figure 1). The severity of cardiac events (aborted cardiac arrest or SCD vs. syncpe) was not significantly different between non-pore and pore mutations in the KCNH2-encoded HERG potassium channel (data not shown). None of the mutations identified were observed in over 1,400 reference alleles.17

Overall, 13 of the 80 index cases (16%) genotyped for LQT2 had a positive history of a cardiac event postpartum compared with 1 of 103 index cases with LQT1 and none of the remaining genotype positive individuals. Thus, the gene specificity of cardiac events during postpartum period in probands or family members was significantly greater in patients with LQT2 genotype than LQT1 genotype (16% vs. <1%, P = .0001) in this study cohort (Figure 2). Within this cohort of 388 unrelated patients, there was no personal or family history of a postpartum-triggered event among the 16 index cases with LQT3 or the single case of LQT5. There were no cases of LQT6.

Discussion

Although bringing in a new life is typically associated with great anticipation and excitement, new mothers with LQTS also enter into a period of increased vulnerability for a life-threatening arrhythmia during this postpartum period.15 Among this cohort of 388 unrelated patients referred for LQTS genetic testing, nearly 4% had a positive personal and/or family history of a postpartum cardiac event. Of the 260 females referred for LQTS genetic testing, 4 (1.5%) have had and survived a postpartum cardiac event. Over 90% of this postpartum-positive subset was found to harbor mutations in KCNH2 responsible for LQT2. Because of the small numbers of LQT3 (n = 16), LQT5 (n = 1), and LQT6 (n = 0) genotypes represented in this substantial unrelated patient cohort, one cannot conclude from this study that perhaps women with such a genotype are somehow protected against cardiac events during the postpartum period.

KCNH2 (HERG; chromosome 7q35-36) encodes the alpha subunit underlying delayed rectifier potassium channels (I_{Kr}) in the heart that mediate phase 3 repolarization.18,19 Mutations of the HERG channel result in decreased I_{Kr} which is the electrophysiologic phenotype in LQT2 patients.20 Previously, Moss and colleagues21 reported that patients with mutations in the channel pore of HERG had a more severe phenotype than those harboring non-pore mutations. In our study, the majority of postpartum-positive LQT2 patients had non-pore mutations despite their severe phenotype underscoring the profound heterogeneity in the clinical expression of LQTS.

<table>
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<tr>
<td>---</td>
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Figure 2 Gene-specificity of postpartum-triggered cardiac events. Thirteen of 80 unrelated patients (16%) with LQT2 had personal and/or a family history of cardiac events during the postpartum period, which was significantly greater than 1 of 103 patients (<1%) with LQT1 (P = .0001).
Precisely why the postpartum period is preferentially arrhythmogenic to those with an underlying LQT2 substrate is unknown. Previously, Rashba and colleagues reported on pregnant women with LQTS and found that the 40 weeks after delivery of a baby posed a far greater risk for cardiac events than either the 40 weeks of pregnancy or the 40 weeks before conception. However, the pathogenetic mechanism underlying this association was unknown.

The psychological stress, changes in sex hormone levels, lactation, alteration of sleep pattern, alteration of life style related to taking care of baby, and abrupt, intense new auditory stimuli (i.e., a crying baby) that are present postpartum may provide arrhythmogenic trigger(s) to women with LQT2. Generally, females have faster resting heart rates and longer QTc than males and a higher risk for syncope and sudden death in LQTS. Estrogen and progesterone may be arrhythmogenic and may play a critical role in cardiac repolarization. Changes involving the sex hormones of estrogen, progesterone, and prolactin during pregnancy and postpartum period could potentially increase the risk of cardiac events. However, levels of estrogen and progesterone are extremely low postpartum and would not likely mediate this LQT2 predilection for postpartum cardiac events. With respect to prolactin, Altemus and colleagues demonstrated that lactating women had increased vagal contribution to heart rate regulation, and postpartum women who were not lactating had evidence of elevated sympathetic and decreased parasympathetic nervous system activity.

Lanfranchi and colleagues demonstrated a divergent sex-related effect on the RR interval during rapid eye movement (REM) sleep with women having an accentuated QTc during REM compared with men. Sleep disturbance was greatest during the first postpartum month, particularly for first-time mothers, and there was improvement in sleep characteristics by the third month postpartum. These findings, perhaps, explain why most cardiac events occurred around 8 weeks postpartum in our study. Finally, auditory stimuli such as an alarm clock triggers cardiac events preferentially in patients with LQT2. Akin to an alarm clock, we speculate that perhaps a babies cry startling a LQT2 woman during REM sleep may be arrhythmogenic. This speculation is buttressed by observations by Shimizu and Antzelevitch whereby beta-adrenergic stimulation transiently increased action potential duration, transmural dispersion, and the incidence of torsades de pointes in a pharmacologic in vitro model of LQT2.

Study limitations

First, although we extensively reviewed all sources of data including phone interviews and medical records, it is possible that the ~4% prevalence of cardiac events occurring postpartum is an underestimate. Importantly, the genetic testing was performed independent of a subject’s postpartum phenotype, minimizing the potential for bias. Second, because of the unavailability of appropriately archived tissue, a molecular autopsy was not performed on each decedent who experienced SCD postpartum to confirm the presence of the same pathogenic LQTS-causing mutation established in the living proband in our cohort. However, the LQTS-causing mutation has been confirmed in 6 of 10 positive family history only cases (cases 2, 5, 6, 8, 13, and 14) by molecular autopsy or determination of its obligate presence through the subsequent voluntary participation of relatives to the index case. Although it seems quite reasonable to assume that the decedent shared the same mutation in the remaining cases, we cannot exclude the possibility of a non-LQTS sudden death such as pulmonary thromboembolism or the possibility that other LQTS-causing mutations or channel polymorphisms may have been additionally present in the decedent.

Conclusions

Approximately 4% of this LQTS cohort had a positive history of a cardiac event during the postpartum period, most commonly during the first 2 months after delivery. Mutations in KCNH2 (LQT2) were present in the majority of families experiencing postpartum sudden death, aborted cardiac arrest, or syncope. Along with swimming and LQT1 and auditory triggers and LQT2, this association between postpartum cardiac events and LQT2 can facilitate strategic genotyping. The precise triggers that render a woman with LQT2 susceptible to a life-threatening arrhythmia after giving birth warrant further investigation.

Acknowledgments

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References


