Seasonal and Circadian Distributions of Cardiac Events in Genotyped Patients With Congenital Long QT Syndrome

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**Background:** Although the incidence of ventricular tachyarrhythmias associated with structural heart disease is highest in winter and during the daytime, seasonal and circadian variations among cardiac events in patients with congenital long QT syndrome (LQTS) remain unknown. The present study aims to determine seasonal and circadian cardiac events in patients with a congenital LQTS genotype.

**Methods and Results:** The medical records of 196 consecutive patients with symptomatic LQTS (age, 32±19 years; female, n=133; LQT1, n=86; LQT2, n=95; LQT3, n=15) who were genotyped between 1979 and 2006 at 2 major Japanese institutions were retrospectively analyzed. The patients with LQT1, LQT2, and LQT3 developed 223,550 and 59 cardiac events during a mean follow-up of 26, 33, and 25 years, respectively. The numbers of cardiac events significantly peaked during the summer among those with LQT1 (P<0.001) and from summer to fall in those with LQT2 (P<0.001), but reached the nadir in winter among those with LQT3 (P=0.003). Cardiac events significantly peaked in the afternoon (12:00–17:59) and morning (06:00–11:59) among those with LQT1 (P<0.001) and LQT2 (P<0.001).

**Conclusions:** The frequency of cardiac events was specifically seasonal and circadian among patients with the 3 major genotypes of congenital LQTS. (Circ J 2012; 76: 2112–2118)

**Key Words:** Cardiac events; Circadian; Long QT syndrome; Seasonal

We analyzed the medical records of patients genotyped with congenital LQTS to determine the seasonal and circadian occurrence of cardiac events.

**Methods**

**Study Population**
The present study included 196 (age, 32±19 years; female, n=133) consecutive patients with symptomatic LQTS and detailed medical information who were genotyped at 2 major Japanese institutions (National Cerebral and Cardiovascular Center, Suita, and Shiga University of Medical Science, Ohtsu).
between 1979 and 2006. Eighty-six, 95, and 15 patients had LQT1, LQT2, and LQT3, respectively. The LQTS patients having compound mutations or other mutations except for LQT1, LQT2, and LQT3 were excluded from the analysis. Symptoms included presyncope, syncope, and cardiac arrest. Sudden dizziness, palpitations, and chest pain persisting for over 30 s without a complete loss of consciousness confirmed by electrocardiogram (ECG) recordings as being associated with ventricular tachyarrhythmias at least once were included as presyncope. Multiple events were defined as over 2 cardiac events per 24 h period. Written informed consent was obtained from each patient in this study to undergo genetic testing. The privacy of the patients was protected by the anonymization of all data.

### Data Collection

In general, the LQTS patients were first referred to our hospital or to a local outpatient clinic for evaluation and therapy, and followed up routinely every 1–3 months. After genotyping at our hospital, they attended our outpatient clinic every 1–6 months (mean, 2.2±1.1 months; median, 2 months). The follow-up period included all periods since the first presentation at our hospital or a local outpatient clinic. A detailed history was obtained at each visit and all patients were encouraged to attend the clinic whenever they experienced palpitations, chest pain, presyncope, or syncope. Patients with cardiac arrest were usually conveyed to our hospital. We obtained as complete a medical history as possible from patients and their relatives, and retrospectively analyzed these records in detail to determine the seasonal and circadian distribution of cardiac events. Some patients were followed up at other outpatient clinics even after genetic testing when they lived far from our institutions. Local physicians or pediatric cardiologists then provided detailed information taken directly from their own medical records, as well as from the patients and their families.

Seasons are defined in the present study according to the Japanese calendar as winter, December to February; spring, March to May; summer, June to August; and fall, September to November. The time of day was classified as night-time (00:00–05:59), morning (06:00–11:59), afternoon (12:00–17:59), and evening (18:00–23:59). Triggers of cardiac events were classified as exercise, emotion, and rest or sleep without arousal according to a previous report. 10

### Statistics

Quantitative data are presented as means±SD or medians/ range, and were compared using ANOVA or Kruskal-Wallis analysis. Categorical data are presented as absolute and percentage frequencies, and were analyzed using the χ² test. The difference in the frequency of cardiac events was analyzed using the goodness-of-fit test for multinomial distribution. A value of P<0.05 was considered significant.

### Results

#### Patient Characteristics

The baseline characteristics of the study population are shown in Table 1. Females comprised about 70% of the LQT1 and LQT2 groups but only 40% of the LQT3 group. The total numbers of cardiac events were 223, 550, and 59 in the LQT1, LQT2, and LQT3 groups during a mean follow-up of 26, 33, and 25 years, respectively. The numbers of events per genotype significantly differed (P<0.007), being 2.6, 5.8, and 3.9 in the LQT1, LQT2, and LQT3 groups, respectively. Table 2 shows details of the cardiac events that occurred in each LQTS type. The frequency of more severe symptoms of cardiac events, such as syncope, cardiac arrest, and sudden death, were higher in the LQT1 and LQT3 groups than in the LQT2 group, in which such extreme symptoms accounted for 60% of the total number of events. Symptoms such as presyncope were milder in the remaining 40% of the LQT2 group.

#### Seasonal and Circadian Distribution of Cardiac Events in LQT1

Among a total of 223 cardiac events, details about the season and time of occurrence for 42 (18.8%) and 55 (24.7%) events, respectively, were vague. Among 181 (81.2%) events with de-
Detailed seasonal information, most occurred during the summer (84/181, 46.4%) and the frequency was lowest during the winter (25/181, 13.8%) (Figure 1). Among 168 (75.3%) events with detailed time information, the frequency was highest during the afternoon (82/168, 48.8%), followed by the morning (50/168, 29.8%), and lowest during the night-time (2/168, 1.2%) (Figure 2). Among the 50 events that occurred during the morning, extremely few arose at the time of awakening. Only 5 (10%) occurred during first 2 h of the morning (6:00–7:59) (P<0.001), and the remaining 45 (90%) events occurred during the late morning (8:00–11:59). Both the seasonal incidence of cardiac events among 3-month periods and the circadian incidence among 6-h periods statistically differed (both, P<0.001).

Seasonal and Circadian Distribution of Cardiac Events in LQT2
Among a total of 550 cardiac events, details about the season and time of occurrence were vague for 42 (7.6%) and 108 (19.6%) events, respectively. Among 508 (92.4%) cardiac events with detailed seasonal information, the frequency was highest during the summer (211/508, 41.5%), followed by the fall (166/508, 32.7%), and lowest during the winter (55/508, 10.8%) (Figure 1). Among 442 (80.4%) cardiac events with detailed seasonal information, most occurred during the summer (84/181, 46.4%) and the frequency was lowest during the winter (25/181, 13.8%) (Figure 1). Among 168 (75.3%) events with detailed time information, the frequency was highest during the afternoon (82/168, 48.8%), followed by the morning (50/168, 29.8%), and lowest during the night-time (2/168, 1.2%) (Figure 2). Among the 50 events that occurred during the morning, extremely few arose at the time of awakening. Only 5 (10%) occurred during first 2 h of the morning (6:00–7:59) (P<0.001), and the remaining 45 (90%) events occurred during the late morning (8:00–11:59). Both the seasonal incidence of cardiac events among 3-month periods and the circadian incidence among 6-h periods statistically differed (both, P<0.001).
detailed time information, the frequency was highest during the morning (169/442, 38.2%), followed by the afternoon (102/442, 23.1%), and evening (96/442, 21.7%) (Figure 2), and lowest during the night-time (75/442, 17.0%) (Figure 2).

Cardiac events associated with the morning were concentrated within the first 2 h of awakening (89/169, 52.7%) between 6:00 and 7:59 (P<0.001). Both the seasonal incidence of cardiac events among the 3-month periods and the circadian incidence among the 6-h periods statistically differed (both, P<0.001).

**Seasonal and Circadian Distribution of Cardiac Events in LQT3**

Among a total of 59 cardiac events, details about the season and time of occurrence were vague for 3 (5.1%) and 20 (33.9%) events, respectively. Among 56 (94.9%) events with detailed seasonal information, the frequency was the highest during the fall (20/56, 35.7%), followed by summer (17/56, 30.4%), and spring (14/56, 25.0%), and lowest during the winter (5/56, 8.9%) (Figure 1). Among 39 (66.1%) events with detailed time information, the frequency of cardiac events was highest at midnight in LQT3 compared with LQT1 and LQT2 (Figure 2). The seasonal incidence of cardiac events among the 3-month periods statistically differed (P=0.003), whereas the circadian incidence among the 6-h periods did not (P=0.679).

**Triggers of Cardiac Events in LQTS**

Figure 3 shows triggers for cardiac events. Triggers were confirmed in 203 (91.0%), 390 (70.9%), and 40 (67.8%) events in LQT1, LQT2, and LQT3, respectively. Most cardiac events in the LQT1 group developed during exercise (144/203, 70.9%), although fewer events occurred during emotional stress (13/203, 6.4%) or rest (5/203, 2.5%). Among 144 cardiac events caused by exertion, 39 (27.1%) were associated with swimming, which accounted for 52% of the triggers of cardiac events during summer exertion. No typical trigger was identified among patients with LQT2, although relatively more cardiac events developed in this group during emotional stress (128/390, 32.8%), such as arousal or being startled by the sudden ringing of a telephone or a bell, and psychological stress including fear, anxiety, and anger, and fewer developed during rest or sleep without arousal (109/390, 27.9%) or exercise (78/390, 20.0%). In addition, the features of exercise as a trigger for LQT2 were unlike those of LQT1 insofar as they were considerably milder and included routine activities such as standing from a seated position, walking, and brushing teeth. In addition, events tended to occur at the start of such activities in the LQT2 group compared with during more intense exercise in the LQT1 group. Cardiac events were more frequent during rest or sleep without arousal in the LQT3 group (19/40, 47.5%) compared with exercise (5/40, 12.5%) and emotional stress (6/40, 15.0%).

**Seasonal Distribution of Multiple Events**

Multiple events occurred within 24 h in 13/86 (15.1%), 30/95 (31.6%), and 4/15 (26.7%) patients with LQT1, LQT2, and LQT3, respectively. Among a total of 13 multiple events in the patients with LQT1, 2 (15.4%), 5 (38.5%), 5 (38.5%), and 1 (7.7%) occurred during the spring, summer, fall, and winter, respectively. Among a total of 55 multiple events in the LQT2 group, 3 (5.5%), 27 (49.1%), 22 (40%), and 3 (5.5%) events occurred during these respective seasons. Among a total of 4 multiple events that occurred in the LQT3 group, 2 (50.0%) occurred during the spring, 1 (25.0%) occurred during the summer, and 1 (25.0%) occurred during the winter. The seasonal distribution was significant in both the LQT1 and LQT2 groups, but was difficult to analyze in the LQT3 group because relatively few total events occurred. Over 75% and about 90% of multiple events in LQT1 and LQT2 occurred between summer and fall.

**Discussion**

Although several investigators have examined the seasonal or
circadian distribution of cardiac events in patients with structural heart diseases such as old myocardial infarction,4–9 hypertrophic cardiomyopathy,10 idiopathic dilated cardiomyopathy,11 or non-structural heart disease such as Brugada syndrome,12 those associated with congenital LQT syndrome have remained unknown. We therefore examined circadian and seasonal variations in patients with LQT syndrome in multiple institutions. Our findings indicated specific seasonal and circadian distributions of cardiac events in patients with congenital LQTS that are quite different from those occurring in patients with structural heart disease. Figure 1 shows that the incidence of cardiac events significantly peaked during the summer in LQT1 and during the summer to autumn in LQT2. Although events in LQT3 did not significantly peak during any particular season, a significant nadir was reached during the winter. Cardiac events were generally associated with more severe symptoms such as syncope, cardiac arrest, and sudden death in the LQT1 and LQT3 groups, but with milder symptoms among the LQT2 group. Triggers for cardiac events among the 3 genotypes were generally similar to those reported by others.10,11–14 The incidence of events significantly peaked between the morning and afternoon (6:00–17:59) in LQT1, and during the morning (6:00–11:59) in LQT2 (Figure 2). More events occurred during the late morning in LQT1 (P<0.001), and around the time of awakening in LQT2 (P<0.001). Although a significant circadian difference was not found, the frequency of cardiac events was relatively higher during the night-time to early morning in LQT3 compared with other LQT syndromes (Figure 3).

Possible Mechanisms for Seasonal Distribution of Cardiac Events

Although the frequency of cardiac events including VT/VF in patients with structural heart disease significantly increases during the winter,4–7,10,11,17,18 the frequency was higher during summer to autumn in patients with LQT1 and LQT2 and lowest during the winter among those with LQT3. Several potential factors could explain the differences in seasonal distribution of cardiac events in patients with long QT syndrome compared with those having structural heart disease. The most likely reason for the highest frequency of cardiac events occurring in LQT1 during the summer is that participation in activities such as swimming and running is higher during the summer, and children might have more opportunities to play outside during the summer in Japan. Athletic and swimming meets are usually held during this season in schools. Sympathetic nerve activities and catecholamine levels are closely related to the occurrence of cardiac events in individuals with LQT1.19–21 Most cardiac events occurred during exercise in our patients with LQT1, which supports previous findings.10,13,22,23 The reason why patients with LQT2 had the highest frequency of cardiac events from summer to early autumn remains unknown. However, seasonal variations in serum potassium levels could be 1 factor, as these levels are significantly lower in summer than in winter.24 This could be a result of a loss of potassium through profuse sweating or increased water intake. A close correlation has been implied between hypokalemia and LQT2, in which the cell surface density of the voltage-gated K+ channel, HERG, is regulated by a biological factor and the extracellular K+ concentration, and the administration of oral potassium results in a greater reduction in resting corrected QT (QTc) interval.25–27

The frequency of cardiac events was lower in patients with LQT3 during the winter than during other seasons, which is similar to that of Brugada syndrome.12 LQT3 and Brugada syndromes are both associated with mutations in SCN5A, the gene that encodes the α subunit of the sodium channel. Mutations in SCN5A result in an increase (gain of function) and decrease (loss of function) in the late sodium current (INa) in patients with LQT3 and Brugada syndrome, respectively, and are reportedly found in 18–30% of clinically diagnosed Brugada syndrome. Some single mutations in the SCN5A gene cause multiple phenotypes such as Brugada syndrome, sick sinus syndrome, and conduction disease in addition to the LQT3 phenotype.22,26–28 In addition, recent evidence shows considerable clinical overlap, implying a new disease entity known as the overlap syndrome of cardiac sodium channelopathy.31,32 The seasonal distribution of “multiple” events was similar to those of isolated episodes.

Possible Mechanisms for Circadian Distribution of Cardiac Events

One factor that might explain the varied circadian distribution of cardiac events is the effect of autonomic nervous activity. Sympathetic nerve activity is higher during the daytime and upon awakening.33–37 Cardiac events in patients with LQT1 are closely related to sympathetic nerve activities and plasma catecholamine levels, which are also higher during the daytime. In addition, daytime provides more opportunities for physical stress, because more exercise is accomplished during the daytime than during the night-time. Thus, the circadian profiles of cardiac events are similar between LQT1 and structural heart disease.

The frequency of cardiac events was significantly higher among patients with LQT2 during the early morning, when the alarm clock rings, or when they awakened, stood upright, walked, or performed daily rituals, such as face washing or brushing teeth. The response to epinephrine test in patients with LQTS reported by Noda et al might explain this circadian profile in patients with LQT2 in whom the QTc duration is transiently prolonged just after starting intravenous epinephrine and returns to the baseline level at the steady state. This suggests that cardiac events tend to occur immediately after an initial increase in sympathetic nerve activities or catecholamine levels, and that cardiac responses to epinephrine and or sympathetic nerve activity might be intensified at the time of awakening.

The circadian distribution of cardiac events in patients with LQT3 is difficult to conclude because of the low incidence. However, the tendency is quite similar to that of Brugada syndrome, in which cardiac events occur during the night and while asleep. Increased vagal activity apparently plays a significant role in the genesis of VF in patients with Brugada syndrome. The hereditary association in the seasonal distribution of “multiple” events was similar to those of patients with LQT3 and Brugada syndromes. Darwin et al recently uncovered molecular evidence that links circadian rhythms to vulnerability in ventricular arrhythmias in mice, in which cardiac ion-channel expression and QT-interval duration (an index of myocardial repolarization) exhibit endogenous circadian rhythmicity under the control of the clock-dependent oscillator, kruppel-like factor 15 (Klf15).38 This factor transcriptionally controls rhythmic expression of Kv channel-interacting protein 2 (KChIP2), a critical subunit required for generating the transient outward potassium current. A deficiency or excess of Klf15 causes a loss of rhythmic QT variation, abnormal repolarization, and enhanced susceptibility to ventricular arrhythmias. These mechanisms might participate in the circadian variation of ventricular arrhythmias.
associated with each type of LQT syndrome. Although gene-specific differences might be associated with a discrepancy in the occurrence of cardiac events, further investigations are required.

**Clinical Implications**

The present results indicate a need for more specific medical therapy, although further assessments are required. For example, amounts of medication should be increased in summer and taken in the morning by patients with LQT1, increased over summer to autumn and taken before falling asleep by patients with LQT2, and increased before falling asleep for patients with LQT3.

**Study Limitations**

First, the timing and number of events might have been underestimated because they were based on patients' recall and medical records. Not all cardiac events were memorized like those recorded by an implantable cardioverter defibrillator. However, more extreme symptoms such as syncope and cardiac arrest or death were usually memorable and a history was taken from not only the patients but also their families. Thus, underestimation of these more disastrous events was considered to be low. In contrast, the frequency of events such as presyncope could be overestimated because they could arise as a result of causes other than ventricular tachyarrhythmias. However, we defined the symptoms of presyncope as sudden dizziness, palpitations, and chest pain persisting for over 30 s without a complete loss of consciousness that were confirmed by ECG recordings as being associated with ventricular tachyarrhythmias at least once, and we attempted to minimize false-positive cases. Second, the influence of drug therapy was not considered in this study, so the precise effect of time-of-day-dependent exposure to β-blockers on the distribution of events was not analyzed. However, patients usually take medications in the morning and we did not change the medication according to the season. Third, some patients who had experienced a large number of events might have distorted the results. However, the tendencies of the seasonal and circadian distribution of cardiac events were similar, even when patients with a large number of cardiac events (≥10) were excluded. In addition, the tendency remained similar regardless of the severity of cardiac events (presyncope, syncope, cardiac arrest, and death). Finally, this was a retrospective study, and the population size and the number of events was small, especially among patients with LQT3. In addition, unavoidable bias was conferred by excluding patients with LQTS whose first manifestation of illness was sudden death. Therefore, further studies of a large number of patients (with an implantable cardioverter defibrillator if possible) are required to validate the present findings and to define the underlying mechanisms.

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**Disclosures**

This manuscript represents original work that has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract. All co-authors have read and approved the submission of the manuscript. There are no financial or other relationships that could lead to a conflict of interest (Conflict of Interest: none declared).

**References**

17. Klener RA, Poole WK, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220 000 cases. Circulation 1999; 100: 1630 – 1634.
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