Autonomic Function and QT Interval During Night-Time Sleep in Infant Long QT Syndrome

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Background: Sudden infant death syndrome mainly occurs during night-time sleep. Approximately 10% of cases are thought to involve infants with long QT syndrome (LQTS). Autonomic function and QT interval in night-time sleep in early infancy in LQTS infants, however, remain controversial.

Methods and Results: Holter electrocardiography was performed in 11 LQTS infants before medication in early infancy, and in 11 age-matched control infants. Control infants were re-evaluated in late infancy. The power spectral density was calculated and parasympathetic activity and sympathovagal balance were obtained. Electrocardiograms of a representative hour during night-time sleep, daytime sleep, and daytime activity, were chosen and QT/RR intervals were manually measured. LQTS infants had significantly lower parasympathetic activity and higher sympathovagal balance during night-time sleep than control infants in early infancy. These autonomic conditions in early infancy were significantly depressed compared with late infancy. Corrected QT interval (QTc) during night-time sleep (490 ± 20 ms) was significantly longer than that in daytime sleep (477 ± 21 ms, $P=0.04$) or daytime activity (458 ± 18 ms, $P=0.003$) in LQTS infants, and significantly longer than that during night-time sleep in controls.

Conclusions: A combination of the longest QTc and autonomic imbalance during night-time sleep in early infancy may be responsible for development of life-threatening arrhythmia in LQTS infants. Critical cases should be included in future studies.

Key Words: Autonomic function; QT interval; Sleep; Sudden infant death

Congenital long QT syndrome (LQTS) is a genetic disorder characterized by delayed repolarization and a long QT interval on 12-lead electrocardiography (ECG). The hallmark of LQTS is syncope or sudden death due to torsade de pointes.^{1–3} Sudden infant death syndrome (SIDS) is one of the major causes of death in infancy, with the highest prevalence between 2 and 4 months of age,^{4–6} and up to 83% of SIDS deaths occur during night-time sleep.^{7,8} SIDS is multi-factorial in origin,^{4–6} but prolongation of the QT interval in the first week of life is strongly associated with SIDS,⁹ and on genetic analysis approximately 10% of SIDS victims carry functionally significant mutations in LQTS genes.^{10,11}

The autonomic nervous system plays an important role in the modulation of cardiac electrophysiology and arrhythmogenesis.¹² Autonomic function matures in infancy, especially in early infancy.^{13,14} An abnormality in cardiac sympathetic innervation or in its development is thought to be associated with a prolonged QT interval.¹⁵ SIDS is most prevalent during early infancy, and heart rate variability (HRV), one of the most promising quantitative

markers of autonomic activity,¹⁶ has been assessed in pre-term and term infants, and in infants who later died of SIDS, during sleep in early infancy.^{13,14,17–19} In these studies, the association between autonomic function and QT interval was also examined,^{18,19} but many studies were performed only during daytime sleep^{13,14,18} or night-time sleep.^{17,19}

The aims of the present study were therefore to assess the circadian change in autonomic function using HRV, and to clarify the differences in QT interval between night-time sleep, daytime sleep, and daytime activity in LQTS infants before starting medication, and in age-matched control infants in early infancy. Autonomic function and QT interval were re-evaluated in late infancy in the same control infants to examine autonomic maturation from early to late infancy.

Methods

Participants

The participants consisted of 11 LQTS infants in early infancy (mean age, 11.8 ± 7.5 weeks) before β -blocker

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treatment and 11 age-matched control infants (Table 1). The control infants were re-evaluated in late infancy (mean age, 39.6±5.6 weeks). The LQTS infants were not assessed in late infancy, because all LQTS infants were taking β -blockers and the dose per day differed between them (Table 2).²⁰ The study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center.

Diagnosis of LQTS in Infancy

LQTS was diagnosed when infants had a corrected QT interval by Bazett's formula (QTc) ≥ 470 ms on resting ECG, and prolonged QTc was sustained during follow-up at 2 or 3 weeks.²⁰ Infants with QTc ≥ 500 ms on Holter ECG were treated with medication to prevent LQTS-related symptoms during infancy, and they were also diagnosed with LQTS (Table 2). No infants had ventricular tachycardias such as torsade de pointes, syncope, or cardiac arrest.

Genetic Testing

Genetic testing was performed after obtaining written informed consent. In the first genetic testing, screening for LQT1 (*KCNQ1*), -2 (*KCNH2*), -3 (*SCN5A*), -5 (*KCNE1*), -6 (*KCNE2*), and -7 (*KCNJ2*) was performed using polymerase chain reaction and direct DNA sequencing.²¹ When no pathogenic mutations were identified, in the first study, genes related to LQTS and catecholaminergic polymorphic ventricular tachycardia were retrospectively screened using a targeted gene sequencing method with the HaloPlex Target Enrichment System (Agilent Technology, San Diego, CA, USA) and the MiSeq system (Illumina, San Diego, CA, USA). Detected variants were confirmed using Sanger's method.²²

HRV

Two-channel 24-h Holter ECG monitoring was performed in all infants. HRV was analyzed on a Holter analysis system (SCM-8000, Ver 54-11, Fukuda Denshi, Tokyo, Japan). After manual checks of the QRS configuration, an R wave was inserted at the midpoint of the long period, when non-normal R wave was detected. The number of non-normal R waves was trivial in the present study. In LQTS infants, control infants in early infancy, and control infants in late infancy, the median of the non-normal R waves was 0.5 beats/day (range, 0–54 beats/day), 0.5 beats/day (range, 0–27 beats/day), and 0.5 beats/day (range, 0–9 beats/day), respectively. The power spectral density was computed as low-frequency (LF; 0.04–0.15 Hz)

Table 1. Participant Characteristics

	LQTS	Control	P-value
No. participants	11	11	
Sex (M/F)	6/5	5/6	0.67
Gestational age (weeks)	39.1±1.0	39.1±1.2	0.56
Birth weight (g)	2,991±496	2,974±355	0.90
Early infancy			
Age (weeks)	11.8±7.5	11.6±3.4	0.52
Weight (g)	5,414±1,332	5,623±729	0.85
Late infancy			
Age (weeks)	–	39.6±5.6	
Weight (g)	–	7,915±1,092	

Data given as mean±SD. LQTS, long QT syndrome.

Table 2. LQTS Infant Characteristics

ID no	Sex	First ECG [†]		Maximum QTc (rest) [‡]		Maximum QTc (Holter) [§]		Diagnostic events	Genes	Mutations	Medication	
		Age (weeks)	QTc	Age (weeks)	QTc	Age (weeks)	QTc				Propranolol (mg/kg/day)	Mexiletine (mg/kg/day)
1	F	12.4	0.520	12.4	0.520	12.4	0.496	Family (mother)	<i>KCNQ1</i>	c.502G>A, p.G168R	1.0	(–)
2	M	4.4	0.458	9.1	0.472	7.3	0.527	ECG screening [¶]		(Not identified)	0.7	3.6
3	M	5.3	0.483	5.3	0.483	5.3	0.534	ECG screening [¶]	<i>KCNH2</i>	c.3065delT, p.L1022Pfs+35X	0.9	3.0
4	F	3.9	0.485	15.9	0.491	47.9	0.501	Family (father)	<i>KCNQ1</i>	c.563delG, p.R190Gfs+47X	1.6	(–)
5	M	7.6	0.470	7.6	0.470	7.6	0.504	Family (mother)	<i>KCNH2</i>	c.65T>A, p.F22Y	0.3	6.0
6	M	23.6	0.432	30.9	0.462	23.6	0.536	By chance		(Not identified)	1.1	2.3
7	F	4.1	0.451	15.0	0.512	37.1	0.520	Family (father)	<i>KCNQ1</i>	c.1663C>T, p.R555C	1.8	(–)
8	F	4.1	0.469	7.3	0.498	7.3	0.510	ECG screening ^{††}		(Not identified)	1.9	4.9
9	F	4.6	0.450	10.9	0.510	13.4	0.514	ECG screening ^{††}		(Not identified)	1.6	(–)
10	M	4.6	0.456	25.6	0.489	28.4	0.504	ECG screening ^{††}		(Not identified)	1.9	(–)
11	M	8.0	0.486	10.9	0.488	8.0	0.518	Family (mother)	<i>KCNH2</i>	c. 503C>T, p. P168L	2.1	(–)

[†]At first visit to hospital or at ECG screening; [‡]on resting ECG at outpatient clinic; [§]on Holter ECG. [¶]ECG screening of 1-month-old infants to identify prolonged QT interval between 2010 and 2011;²⁰ ^{††}ECG screening of 1-month-old infants to identify prolonged QT interval between 2014 and 2016 (Yoshinaga M; unpublished data, 2018). ECG, electrocardiography; LQTS, long QT syndrome; QTc, Bazett's corrected QT.

Figure 1. Selection of representative hour for night-time sleep, daytime sleep, and for daytime activity, in a representative case (long QT syndrome patient 8; 7 weeks of age). ECG, electrocardiogram.

and high-frequency (HF; 0.15–0.40 Hz) components in 60-min segments with a 1024-point fast Fourier transform algorithm and a frequency resolution of 0.008 Hz. The logarithm of these component values was used. The $\text{Ln}(\text{HF})$ component and the $\{\text{Ln}(\text{LF})/\text{Ln}(\text{HF})\}$ ratio were used as indices of parasympathetic activity^{23,24} and the sympathovagal balance of the heart, respectively.^{23,24} To investigate the circadian variability of HRV, spectral data variables were averaged for each hour throughout the day.

QT/RR Interval Measurement

QT/RR intervals were measured at three selected periods: during night-time sleep; daytime sleep; and during daytime activity. In the present study, night-time and daytime were defined as 23:00–06:00 hours and as 07:00–18:00 hours, respectively. An hour during which the total beats per hour was lowest during the night-time and daytime was chosen for the night-time sleep and daytime sleep, respectively, and an hour during which the total beats per hour was highest during daytime was chosen for the daytime activity period (Figure 1).

Three ECG at maximum, average, and minimum heart rates were printed out at the representative hour during night-time sleep, daytime sleep, and daytime activity. For each ECG, three consecutive QT/RR intervals were manually measured using the tangent method by one of the authors (M.Y.). Bazett's formula was used to calculate QTc in the present study, because this correction had a more significant association with autonomic function than Fridericia's formula in each period (data not shown).

QTc and Autonomic Activity

To determine the association between QTc and autonomic activity, a 5-min HRV segment was obtained with a 256-point fast Fourier transform algorithm, setting the QT/RR measurement beats at the midpoint of each 5-min segment.

Statistical Analysis

Differences in the means were examined using Mann-Whitney U-test or Wilcoxon signed-ranks test. Differences in QTc and heart rate between night-time sleep, daytime sleep, and daytime activity were analyzed using Friedman's

ANOVA and the Dunn-Bonferroni tests. Spearman's rank test was used to evaluate the correlation coefficients. Statistical analysis was performed using IBM SPSS Statistics 23 (IBM Japan, Tokyo, Japan). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Participant Characteristics

Gestational age, birth weight, and weight in early infancy were not different between the LQTS and control infants (Table 1). Mutations were identified in 6 of 11 LQTS infants (*KCNQ1* in 3 and *KCNH2* in 3; Table 2). The mutation in LQTS infant 5 was finally determined on targeted gene screening. Diagnostic events were identified in family studies in five infants and ECG screening programs in five, and by chance in one. ECG screening to identify prolonged QT interval in 1-month-old infants was performed from 2010 to 2011²⁰ and from 2014 to 2016.

Circadian Changes in Autonomic Activity in Infancy

LQTS infants had a significantly lower $\text{Ln}(\text{HF})$ component at 23:00 hours, 02:00 hours, 03:00 hours, and 06:00 hours than age-matched control infants (Figure 2A). Conversely, LQTS infants had a higher $\text{Ln}(\text{LF})/\text{Ln}(\text{HR})$ ratio than control infants during night-time at 00:00 hours, 02:00 hours, and at 04:00 hours (Figure 2B). The power of the $\text{Ln}(\text{HF})$ component in early infancy in both LQTS infants and control infants, however, was significantly lowered from 23:00 to 03:00 hours, from 05:00 to 07:00 hours, and at 11:00, 12:00, and 15:00 hours compared with that in late infancy in control infants. Conversely, the $\text{Ln}(\text{LF})/\text{Ln}(\text{HF})$ ratio in early infancy was significantly higher than in late infancy at 23:00 hours, 02:00 hours, and 03:00 hours; from 05:00 to 08:00 hours; and at 11:00, 12:00, and 15:00 hours.

With respect to the autonomic activity according to LQTS genotype, there was no difference in $\text{Ln}(\text{HF})$ components or in $\{\text{Ln}(\text{LF})/\text{Ln}(\text{HF})\}$ ratio at each hour between infants with the LQT1 and LQT2 genotypes.

QTc

Mean QTc in LQTS infants was longer at the maximum

Table 3. QTc vs. HR, Time of Day and Activity Status

		QTc (ms)			Friedman test	P-value		
		Maximum HR (A)	Average HR (B)	Minimum HR (C)		A vs. B	A vs. C	B vs. C
LQTS infants								
Night-time sleep	490±20	467±22	431±29	<0.001	0.17	<0.001	0.03	
Daytime sleep	477±21	459±25	440±24	0.002	0.17	0.001	0.33	
Daytime activity	458±18	447±19	449±23	0.09†	NS†	NS†	NS†	
Control infants in early infancy								
Night-time sleep	437±11	415±19	370±19	<0.001	0.17	<0.001	0.03	
Daytime sleep	435±9	414±14	380±17	<0.001	0.60	<0.001	0.01	
Daytime activity	409±14	410±22	381±19	0.003	1.00	0.004	0.03	
Control infants in late infancy								
Night-time sleep	433±23	397±15	359±24	<0.001	0.17	<0.001	0.03	
Daytime sleep	423±16	399±23	364±27	<0.001	0.10	<0.001	0.10	
Daytime activity	411±24	395±22	373±19	0.001	0.10	0.001	0.41	

Data given as mean±SD. †Multiple comparison test not performed. NS, not significant (Friedman's ANOVA). Other abbreviations as in Table 2.

heart rate than at the average and at the minimum heart rates during night-time and daytime sleep (Table 3). In control infants, mean QTc at maximum heart rate was longer than at minimum heart rate during night-time and daytime sleep and daytime activity. Heart rate during these three periods is listed in Table S1.

At maximum heart rate, QTc in LQTS infants during

night-time sleep was significantly longer than that in controls during night-time sleep (Figure 3A). In LQTS infants, QTc during night-time sleep was significantly longer than that during daytime sleep and daytime activity (Figure 3A). In early infancy in controls, QTc during sleep was longer than that during daytime activity. In late infancy in controls, a significant difference was still present between

Figure 3. Bazett's corrected QT (QTc) at (A) maximum, (B) average, and (C) minimum heart rate in infants according to long QT syndrome (LQTS) status, time of day, and stage of infancy. Data given as mean and SEM.

night-time sleep and daytime activity.

At average heart rate in LQTS infants, QTc during night-time sleep was longer than that during daytime activity (Figure 3B). No significant difference was seen in QTc between the three periods in controls. At the minimum heart rate, no significant difference was seen between the three periods in both LQTS infants and in control infants (Figure 3C).

With respect to QTc according to LQTS genotype, QTc at average heart rate during midnight sleep in LQT2 infants was significantly longer than that in LQT1 infants (497 ± 19 vs. 477 ± 17 ms, respectively; $P=0.0495$).

QTc and Autonomic Activity

There was no significant association between QTc and autonomic activity in early infancy when assessed separately in LQTS or in control infants (Table S2). The associations were then re-assessed after combining the data of the LQTS infants and control infants in early infancy. During night-time sleep, QTc had a significantly negative association with $\ln(\text{HF})$ at the maximum, average, and minimum

heart rate, and a significantly positive association with sympathovagal imbalance at the minimum heart rate (Table 4; Figure 4).

Discussion

LQTS infants had significantly lower parasympathetic activity and higher sympathovagal balance during several night-time hours than control infants in early infancy, but autonomic function in both LQTS infants and control infants in early infancy showed significantly decreased parasympathetic and increased sympathovagal conditions compared with that in late infancy in control infants. Under the conditions of this autonomic dysfunction, LQTS infants had significantly longer QTc at maximum heart rate during night-time sleep than during daytime sleep or daytime activity in early infancy.

In studies of infantile autonomic activity, both term and preterm control infants had increased parasympathetic activity from early infancy to late infancy during daytime sleep^{13,14} or night-time sleep.¹⁷ In the present study of the

Table 4. QTc and HRV in Early Infancy vs. LQTS Status

	Night-time sleep		Daytime sleep		Daytime activity	
	Ln(HF)	Ln(LF)/Ln(HF)	Ln(HF)	Ln(LF)/Ln(HF)	Ln(HF)	Ln(LF)/Ln(HF)
QTc at maximum HR						
Coefficient	-0.447	0.379	-0.018	0.294	-0.100	-0.089
P-value	0.04	0.08	0.94	0.19	0.66	0.70
QTc at average HR						
Coefficient	-0.451	0.377	-0.390	0.470	-0.130	-0.023
P-value	0.04	0.08	0.07	0.03	0.56	0.92
QTc at minimum HR						
Coefficient	-0.586	0.512	-0.272	0.346	-0.142	-0.034
P-value	0.004	0.02	0.22	0.12	0.53	0.88

HF, high frequency; HR, heart rate; HRV, heart rate variability; LF, low frequency. Other abbreviations as in Table 2.

Figure 4. Bazett's corrected QT (QTc) at average heart rate vs. the natural logarithm of the high-frequency component (Ln(HF)) during night-time sleep according to genotype in long QT syndrome (LQTS) infants and control infants in early infancy.

circadian changes in autonomic activity, Ln(HF) power was augmented and Ln(LF)/Ln(HF) ratio was decreased throughout the day, and especially during night-time sleep, from early to late infancy in control infants. This indicates that low parasympathetic activity and a high sympathovagal balance are present during night-time sleep in early infancy. The Ln(HF) power during night-time sleep was negatively associated with QTc, when the data of LQTS and control infants were combined. Considering that sympathetic stimulation precipitates ventricular tachyarrhythmias and sudden cardiac death in patients with LQTS,¹² the presence of autonomic immaturity during night-time sleep in early infancy is thought to be a high risk factor for life-threatening arrhythmias in LQTS infants.

In the 1970s, Schwartz proposed a hypothesis that an abnormality in cardiac sympathetic innervation or in its development was associated with QT prolongation and was associated with the development of SIDS.¹⁵ This hypothesis prompted many investigators to measure the QT interval during sleep in healthy controls and in patients with disease conditions. Additionally, during rapid eye movement (REM) sleep, conditions of intermittent bursts of sympathetic activity are present on a background of powerful bursts of parasympathetic activity.^{25–27} Many studies involving adults supported these findings. The QT interval during night-time sleep is longer than that during

the daytime or in the awake state,^{28–30} and QTc during REM sleep was longer than that during non-REM sleep, if present.^{31,32}

In the pediatric field, however, the effect of sleep on QT interval was contradictory. Haddad et al measured computer-assisted QT interval in daytime sleep 2–3 h after midmorning feed, and reported that QTc in REM sleep was shorter than that during non-REM sleep in control infants,^{33,34} and in infants who had an aborted SIDS episode in early infancy.³⁴ Montague et al determined computer-assisted QTc at five random times throughout the 24-h Holter monitoring period and reported that maximum QTc at these five time points was significantly shorter in infants at risk for SIDS than in age- and sex-matched control infants.³⁵ Conversely, Franco et al reported that QTc in infants who later died of SIDS was significantly longer than that in age-matched control infants in the REM, non-REM sleep, and total sleep period,¹⁹ but that QTc was not different between REM and non-REM sleep in these future SIDS victims.¹⁹ There are some possible explanations for these discrepancies. Computer-assisted averaged ECG configurations, used in some studies,^{33–35} may not be applicable for infants and children because sinus arrhythmia is frequent and beat-to-beat QT/RR intervals are largely changeable in these age groups. In the study that used manual QT measurement, one set of three

consecutive beats was chosen for REM and non-REM analysis;¹⁹ this might result in loss of QTc during the intermittent burst of sympathetic activity (at maximum heart rate) and at the powerful burst of parasympathetic activity (at minimum heart rate).

In the present study, therefore, three sets of QT/RR intervals were selected and manually measured at the maximum, average, and minimum heart rates during night-time sleep, daytime sleep and in daytime activity. QTc at the maximum heart rate in night-time sleep may correspond to the condition of intermittent bursts of sympathetic activity on a background of parasympathetic activity. At the maximum heart rate, LQTS infants had a significantly longer QTc during night-time sleep than during daytime sleep or daytime activity. In early infancy in the controls, QTc during night-time and daytime sleep was significantly longer than that during daytime activity. This indicates that night-time sleep is associated with a risk for longer QTc in early infancy, especially in LQTS infants.

No infants with *SCN5A* mutations were included in the present study. In a study of postmortem genetic screening in victims of SIDS, the most prevalent gene was *SCN5A*.^{10,11} Arnestad et al reported on 19 SIDS victims with pathogenic mutations associated with LQTS in Norway: five, five, and 13 patients had *KCNQ1*, *KCNH2*, and *SCN5A* mutations, respectively.¹⁰ Otagiri et al reported on four SIDS victims in Japan, consisting of one with *KCNQ1*, one with *KCNH2*, two with *SCN5A*, and one with digenic *KCNH2* and *SCN5A* mutation.¹¹ Conversely, Horigome et al reported on 58 infants with congenital LQTS in Japan diagnosed in the fetal, neonatal, and infantile periods, including 11 with *KCNQ1*, 11 with *KCNH2*, and 6 with *SCN5A* mutations.³⁶ They also reported that one patient each from these three genotype groups developed aborted cardiac arrest. This suggests that the most prevalent genotypes of congenital LQTS diagnosed in the infantile period are *KCNQ1* and/or *KCNH2* when we combine the SIDS victims and the patients diagnosed in the infantile period. No data that can explain the absence of patients with *SCN5A* mutations were available in the present study; this might have occurred by chance because of the small number of patients included. Infants with *SCN5A* mutations, however, should be included in a future study.

This study also had some other limitations. First, the number of LQTS infants was small and the present study did not include any infants who later died of SIDS or who were at risk for SIDS, although several previous studies have.^{19,33,35} This means that the present study was not able to investigate the direct association between LQTS and SIDS. To determine accurate autonomic activity in LQTS infants, it is essential to assess the function without the effect of β -blocker. It is impossible to examine 24-Holter ECG in critical LQTS infants without medication. In the present study, we were able to perform 24-Holter ECG partly because ECG screening programs were present at 1-month medical check-up; accumulation of data, however, including critical cases before treatment, is warranted. Second, we did not determine the sleep stage, especially the REM stage. Further studies including the sleep stages are needed. Third, diagnostic criteria for QT prolongation in Holter ECG data are currently unavailable. With regard to computer-assisted QT measurements on Holter ECG in adults, an early study in 1996 showed that mean QTc in 21 adults was 443 ± 15 ms, and that 6 of these 21 adults had maximum QTc ≥ 500 ms;²⁸ in a recent study in 2016,

however, computer-assisted QTc was 400 ± 16 ms in 101 men and 416 ± 16 ms in 99 women,³⁷ suggesting that QTc ≥ 500 ms in control adults is a rarity.³⁷ In the present study, maximum QTc during night-time sleep in control infants was 456 ms. We then used QTc > 500 ms for QT prolongation in Holter ECG data, which, on resting ECG, is a high risk factor in patients with LQTS.³⁸ Finally, in future studies, LQTS infants should be classified by genotype to improve the risk stratification for targeted management according to genotype or mutation type.³⁹

Conclusions

A combination of two major risk factors may be responsible for development of life-threatening arrhythmia in LQTS infants: longest QTc and autonomic imbalance; and undeveloped parasympathetic activity and accentuated sympathovagal balance, during night-time sleep in early infancy. To prevent sudden infant death from QT prolongation, screening of infants with prolonged QT interval in early infancy is essential because β -blocker therapy is known to shorten QT interval and to decrease LQTS-related symptoms, although strategies to screen infants with QT prolongation are still controversial.^{40,41}

Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Table S1. HR vs. time of day, sleep and LQTS status

Table S2. QTc and HRV correlations in early infancy vs. LQTS status

Please find supplementary file(s);
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