

aborted cardiac arrest (ACA) (5 cases), AVB (5 cases), VT/TdP (5 cases), and other miscellaneous abnormalities.

The ECG on diagnosis, or immediately after birth for fetal cases, showed that the HR and QTc interval (corrected using Bazett formula) ranged from 50 to 160 (102 ± 28) bpm, and from 360 to 774 (563 ± 70) ms, respectively.

Genotype-Phenotype Correlation

Among 41 patients who underwent genetic testing, mutations were identified in 29 (71%) cases; including *KCNQ1* gene mutations (LQT1) in 11, *KCNH2* mutations (LQT2) in 11, *SCN5A* mutations (LQT3) in 6, and *CACNA1C* (LQT8) in 1. Twelve patients also underwent genotyping, but no mutation was found. Table 2 lists the demographic and clinical features of these subjects (references 16, 17, and 23 reported the same cases 2, 12, and 27 in Table 2) and of those with no known mutations.

The remaining 17 subjects (6 fetuses, 8 neonates, 3 infants) did not undergo genetic analysis due to lack of such analysis at that time, death soon after birth, or refusal by parents. Five had SCD/ACA (Table 3), including a 1-day-old neonate who had AVB and died at 57 days of age in 1984. This case was later assumed to be LQT8, based on characteristic phenotypes such as syndactyly. AVB and VT/TdP were observed in 7 and 5 cases, respectively, in this group.

Although HR and QTc values were not different among LQT1, LQT2, LQT3, and mutation-negative groups, the incidence of VT/TdP was higher in LQT2 and LQT3 compared with LQT1 (Table 4). The incidence of AVB tended to be higher in LQT3 compared with LQT1 but statistically insignificant. On the other hand, the presence of family history of LQTS was more frequent in LQT1 than the mutation-negative group. The incidence of sinus bradycardia was comparable among the 4 groups (Table 4).

Table 3 lists cases with SCD/ACA; only 4 genetically confirmed cases were included, and 4 were mutation-negative, although the remaining 6 cases did not undergo genotyping. These individuals showed bradycardia (97 ± 31 bpm; 10/14 showed HR < 110 bpm) and markedly prolonged QTc (617 ± 81 ms).

Treatment

With regard to the treatment of fetal VT/TdP, antiarrhythmic agents were administered transplacentally in 4 of 18 fetal cases (propranolol in 3 cases, lidocaine in 1, mexiletine in 1, flecainide in 1, and magnesium in 1), using the method described in detail in our previous report.¹⁷ None of the 4 cases was genetically confirmed prenatally. When 2 or 3 of the following findings of sinus bradycardia, VT, and AVB were observed in a structurally normal heart, LQTS was strongly suggested, and β -blockers, sodium channel blockers (lidocaine, mexiletine), and magnesium (Mg) were selected as typical antiarrhythmic agents, instead of amiodarone or sotalol, which may prolong the QT interval. These drugs were used in combination until VT/TdP was controlled and proved effective in all 4 cases. However, preterm delivery was conducted in 2 cases both at 33 weeks of gestation due to recurrent VT/TdP and depression of fetal physical activity in one and to fetal hydrops and distress in the other. In the remaining 14 cases, pharmacotherapy was initiated after

confirmation of the type of arrhythmias after birth. However, no fetal death was noted.

For 15 neonatal cases who presented with VT/TdP (including those who did not undergo genotyping), acute pharmacotherapy consisted of 2 or more of the following drugs: β -blockers, mexiletine, lidocaine, Mg, phenytoin, and others, except for 2 cases who were treated with phenytoin alone and 1 with mexiletine alone. Most of these cases were judged to respond the combination therapy. In 5 neonates in whom LQT3 was strongly suggested based on a typical ECG finding called late-appearing T wave, mexiletine was first administered but proved insufficient, and β -blockers were also added in all 5.

For those with LQTS presenting in infancy, 6 cases received acute pharmacotherapy (2 or all of propranolol, mexiletine, and Mg). No additional agent was administered. Thus, in all age groups, the acute therapy for VT/TdP consisted of a single drug to which 1 or more drugs was then added until the arrhythmia was controlled, independent of the genotype. Actually, the genotype was not identified during the acute phase in most cases. Furthermore, genotyping was not conducted in those 17 cases who presented before 1999.

Maintenance therapy consisted mainly of β -blockers (or no therapy) for LQT1 and mostly of mexiletine/ β -blockers for LQT2 and LQT3 (Table 2). β -Blockers were added in 8 LQT2 cases after confirmation of the genotype. In all 6 LQT3 cases, mexiletine was maintained (combined with β -blockers) from acute through chronic phase after determination of the genotype.

Nine patients underwent pacemaker implantation (PMI), 5 with ventricular pacing mode (VVI) and 1 with atrial pacing mode (AAI), from age 1 day to 8 years due to severe bradycardia caused by AVB, inducing VT/TdP. In 6 cases, VT was completely suppressed after PMI. Only 2 patients had an implantable cardioverter-defibrillator (ICD) at ages 4 (LQT3) and 25 months (mutation negative), respectively, due to recurrent VT/TdP with satisfactory results.

Outcome

During the follow-up period of 8 days to 23.5 years (median, 4.25 years), 7 SCD and 7 ACA were registered (age at SCD or ACA range, 8 days to 10 years; median, 10.5 months); 6 did not have genetic testing, whereas 4 showed no mutation. Only 4 were genetically confirmed (Table 3). One case was later suspected to be LQT8, based on the phenotype including syndactyly. Among the 14 SCD/ACA cases, 12 had been under pharmacotherapy, 5 with both β -blockers and sodium channel blockers, and 2 had had PM or ICD. Four cases developed significant neurological deficits after cardiorespiratory resuscitation.

Discussion

The noteworthy finding of the present study was that 49 of 58 cases (84%) were diagnosed at the fetal or neonatal period, although this survey covered the entire infantile period. Remarkably, two thirds of the neonatal cases were diagnosed within 2 days of life; this period should be recognized as the most vulnerable period. The number of cases diagnosed after the neonatal period was only 9. Considering that the average age at appearance of symptoms in LQT2 and LQT3 is after

Table 2. Clinicogenetic Details

Case	LQT Type	Mutation	Age at Diagnosis/Sex	Clinical Presentation	FH	HR, bpm	QTc, ms
1	LQT1	Thr587Met	Fetus/M	FH, brady	+	109	561
2	LQT1	Ala341Val	Fetus/M	Brady	+	110	590
3	LQT1	Ala341Val	Neonate/M	FH	+	110	520
4	LQT1	Ile313Lys	Neonate/M	FH	+	102	589
5	LQT1	Ile313Lys	Neonate/M	FH	+	115	554
6	LQT1	276delSer	Neonate/M	Prolonged QT	+	115	570
7	LQT1	Asp611Tyr	Neonate/M	Brady	+	80	550
8	LQT1	Asp611Tyr	Neonate/F	FH	+	ND	ND
9	LQT1	Thr458Met	Neonate/M	FH	+	126	530
10	LQT1	Gly643Ser	Infant/M	ACA	-	109	554
11	LQT1	Gly269Ser	Infant/F	Cyanosis	-	113	586
					82%	109±12	560±24
12	LQT2	Gly628Ser	Fetus/M	VT/TdP, AVB	-	50	631
13	LQT2	del(7)(q32qter)	Fetus/F	TdP	-	111	492
14	LQT2	Ser243 + 112X	Fetus/F	FH	+	160	360
15	LQT2	Gly628Ala	Fetus/F	Syncope, VT/TdP, AVB	+	78	570
16	LQT2	Thr613Met	Fetus/M	VT/TdP, AVB	-	60	578
17	LQT2	Ala561Val	Neonate/M	Cyanosis, VT/TdP	-	86	520
18	LQT2	Gly628Ser	Neonate/M	TdP, brady	-	111	550
19	LQT2	Thr613Met	Neonate/M	convulsion, VT	-	140	599
20	LQT2	Gly572Ser	Neonate/F	TdP, AVB	-	91	520
21	LQT2	Ala614Val	Neonate/F	Syncope, VT	+	98	500
22	LQT2	Asn633Ser	Infant/F	VT/TdP, AVB	-	60	600
					27%	95±34	538±74
23	LQT3	Ala1186Thr	Fetus/M	AVB	+	78	679
24	LQT3	Asn1774Asp	Fetus/M	convulsion, VT/TdP, AVB	-	115	670
25	LQT3	Val176Met	Neonate/F	TdP, AVB	+	63	600
26	LQT3	Asn406Lys	Neonate/M	Syncope, TdP	+	129	598
27	LQT3	Arg1623Gln	Neonate/F	Heart failure	-	79	483
28	LQT3	Leu1772Val	Infant/M	ACA	-	138	520
					50%	100±31	592±79
29	LQT8	Gly406Arg	Neonate/M	AVB	-	141	581
30	Unidentified	-	Fetus/F	Brady	+	80	554
31	Unidentified	-	Fetus/M	Brady	-	100	510
32	Unidentified	-	Fetus/M	VT	-	85	590
33	Unidentified	-	Fetus/M	AVB	-	80	600
34	Unidentified	-	Neonate/F	Syncope	-	100	647
35	Unidentified	-	Neonate/F	Arrhythmia	-	126	586
36	Unidentified	-	Neonate/F	ACA	-	111	638
37	Unidentified	-	Neonate/M	Brady	-	93	550
38	Unidentified	-	Neonate/F	FH	+	120	520
39	Unidentified	-	Infant/F	ACA	-	160	470
40	Unidentified	-	Infant/F	ACA	-	100	774
41	Unidentified	-	Infant/F	PAC with block	-	60	460
					17%	104±32	575±86

(Continued)

Cases 2, 12, and 27 are reported in references 16, 17, and 23, respectively. ACA indicates aborted cardiac arrest; AVB, atrioventricular block; BB, β-blocker; brady, bradycardia; FH, family history; HR, heart rate; ICD, implantable cardioverter-defibrillator; lsp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; PAC, premature atrial contraction; Pheny, phenytoin; PM, pacemaker; SCD, sudden cardiac death.

Table 2. Continued

Sinus Brady	VT/TdP	AVB	Acute Therapy	Maintenance Therapy	PMI/ICD	Follow-Up	Outcome
+	-	+	-	-	-	0 mo	Alive
+	-	-	-	BB	-	9 y	Alive
+	-	-	-	BB	-	4 y, 1 mo	Alive
+	-	-	-	BB	-	11 y, 10 mo	Alive
+	-	-	-	BB	-	10 mo	Alive
+	-	-	-	-	-	11 mo	Alive
+	-	-	-	-	-	7 y, 3 mo	Alive
+	-	-	-	-	-	5 y, 8 mo	Alive
-	-	-	-	-	-	4 y, 5 mo	Alive
+	-	-	Lido, Mexil	Mexil	-	9 y, 1 mo	Alive
+	-	-	-	-	-	7 y, 8 mo	Alive
73%	0%	9%				Median 68 mo	
+	+	+	Lido, Mg, BB, Mexil, Pacing	BB, Mexil	PM	3 y	Alive
+	+	-	-	BB	-	1 y	Alive
-	-	-	-	BB	-	2 y, 2 mo	Alive
+	+	+	Lido, Mg, BB, Mexil, pacing	BB, Mexil	PM	8 y, 1 mo	Alive
+	+	+	Mg, Mexil	BB, Mexil	-	8 mo	Alive
+	+	-	Lido, Mg, Mexil	BB, Mexil	-	11 y, 4 mo	Alive
+	+	+	Mexil	BB, Mexil	-	7 mo	Alive
-	+	-	Mg, BB	BB	-	8 y	Alive
+	+	+	Pheny	BB, Mexil	-	18 y, 5 mo	Alive
+	+	-	Pheny, DC	Pheny, BB	-	23 y, 6 mo	Alive
+	+	+	-	BB, Mexil	PM	15 y, 4 mo	Alive
82%	91%	55%				Median 96 mo	
+	+	+	Mexil	Mexil	PM ICD	3 y, 4 mo	Alive
+	+	+	BB, Mexil, Mg	BB, Mexil, Flecainide	PM	11 y, 4 mo	Alive
+	+	+	Lido, Mg, BB, Mexil	BB, Mexil	-	1 y, 3 mo	Alive
+	+	-	Lido, BB	BB, Mexil	-	11 mo	Alive
+	+	+	BB, Mexil, Lido	BB, Mexil	PM	8 y	Alive
-	+	+	Mg, BB, Mexil	BB, Mexil	-	3 y, 2 mo	Alive
83%	100%	83%				Median 39 mo	
-	+	+	BB, Mexil, Nifed	BB, Mexil, Nifed	-	3 y, 2 mo	Alive
+	-	+	-	BB, Mexil	-	2 y, 5 mo	Alive
+	-	-	-	BB	-	6 y, 5 mo	Alive
+	+	-	Lido, Mg	Mexil	-	5 y, 5 mo	Alive
+	-	+	BB, Mexil, Mg	BB, Mexil	-	4 mo	Alive
+	-	-	Lido, Mg, lsp	Mexil	-	4 y, 3 mo	Died
+	+	-	BB, Mg	BB	-	9 y, 5 m	Alive
-	+	-	Lido, BB, pheny, Mexil	Mexil	-	11 y, 9 mo	Alive
+	-	-	-	-	-	9 y, 6 mo	Alive
-	-	-	-	-	-	6 mo	Alive
-	+	-	BB, Mexil	BB, Mexil	ICD	7 y, 2 mo	Alive
+	+	+	Mexil	Mexil	-	4 y3 mo	Alive
+	-	-	BB, Mexil	BB, Mexil	-	7 y, 5 mo	Alive
75%	42%	25%				Median 71 mo	

Table 3. Clinicogenetic Details of Cases With Sudden Cardiac Death or Aborted Cardiac Arrest

Case	Case No. in Table 2	Genotyping	Age at Diagnosis	Age at SCD or ACA	HR, bpm	QTc, ms	Maintenance Therapy Until SCD/ACA	Acute Therapy for SCD/ACA Event
1	23	LQT3 (Ala1186Thr)	Fetus (28 wk)	1 y, 10 mo (aborted)	78	679	Mexil	Mexil, DC
2	...	No gene test	Fetus (31 wk)	8 d	60	570	...	Lido, lsp, Pacing, DC
3	...	No gene test	Fetus (36 wk)	57 d	90	600	BB, Mexil	DC
4	29	LQT8 (Gly406Arg)	Neonate (0 d)	1 y, 5 mo (aborted)	141	581	BB, Nifed	Mexil, Mg
5	...	Negative result	Neonate (0 d)	4 y	100	647	Mexil	DC
6	...	Negative result	Neonate (0 d)	<1 mo (aborted)	111	638	Mexil	Lido, Mexil, BB, Pheny
7	17	LQT2 (Ala561Val)	Neonate (1 d)	10 y (aborted)	86	520	BB, Mexil	Lido, Mexil, Mg, DC
8	...	No gene test (possible LQT8)*	Neonate (1 d)	57 d	70	640	BB	...
9	...	No gene test	Neonate (4 d)	5 y, 4 mo	60	590	... (refused)	...
10	...	No gene test	Infant (1 mo)	2 y	130	640	BB, Mexil	Lido, Mg
11	...	No gene test	Infant (1 mo)	1 y, 10 mo	60	740	BB, Mexil, PM	Lido, Mexil, BB, Mg, Pacing
12	10	LQT1 (Gly643Ser)	Infant (1 mo)	1 mo (aborted)	109	554	Mexil	Lido
13	39	Negative result	Infant (2 mo)	4 mo (aborted)	160	470	BB, Mexil, ICD	(aborted by ICD)
14	40	Negative result	Infant (2 mo)	2 mo (aborted)	100	774	Mexil	Mexil
				median 10.5 mo	97±31	617±81		

ACA indicates aborted cardiac arrest; BB, β-blocker; ICD, implantable cardioverter-defibrillator; lsp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; Pheny, phenytoin; SCD, sudden cardiac death.

*LQT8 was retrospectively possible because phenotype included syndactyly.

school age,² we speculate a considerable number of patients are considered to go through infancy uneventfully.

Garson et al⁴ reported 287 patients with LQTS age <21 years; their mean±SD age at presentation was 6.8±5.6; and 9% presented with cardiac arrest, 26% with syncope, and 10% with seizures. Although 20% of their subjects were <1 month of age, they did not investigate that age group separately. In the present study, confined to the subjects age <1, clinical features were largely different; that is, the incidence of malignant arrhythmias and bradycardia was high^{6,7} whereas that of syncope and seizures was low.

Regarding genotype-phenotype correlations, Zareba et al¹⁸ investigated child and adult LQTS and reported that LQT1 was associated with the highest risk of first cardiac event among the 3 most typical genotypes (LQT1–3). By the age of 15, syncope, ACA, or SCD was noted in 53% of their patients with LQT1 compared with 29% of LQT2 and 6% of LQT3,

although cardiac events occurred in LQT3 were more lethal compared with those in LQT1 or LQT2. In contrast, the present study demonstrated that patients complicated by VT/TdP or AVB were almost exclusively those with LQT2 or LQT3 (and LQT8). LQT3 patients in the present study showed the most severe clinical course, similar to those in later-presenting LQT3. Further, patients with LQT1 mostly showed an uneventful clinical course apart from sinus bradycardia,⁶ and the reason for diagnosis was bradycardia or prolonged QT interval itself on ECG identified on family screening. Another remarkable feature in our young age group was that a considerable number of patients with malignant arrhythmias were mutation-negative as far as LQT1–3 genes were typically examined. This suggests that this age group includes individuals with rare known mutations that were not examined in the present study as well as those with currently unidentifiable mutations.

Table 4. Comparison of Parameters Among the Groups

Parameter	LQT1 (n=11)	LQT2 (n=11)	LQT3 (n=6)	Negative (n=12)	Global Test	Pairwise Comparison
HR, bpm	109±12 (n=10*)	95±34	100±31	104±32	NS	
QTc, ms	560±24 (n=10*)	538±74	592±79	575±86	NS	
Proportion with family history, %	82	27	50	17	P<0.05	LQT1–Negative, P<0.05
Proportion with sinus bradycardia, %	73	82	83	75	NS	
Proportion with VT/TdP, %	0	91	100	42	P<0.05	LQT1–LQT2, P<0.001 LQT1–LQT3, P<0.005
Proportion with AVB, %	9	55	83	25	P<0.05	(LQT1–LQT3, P=0.068)

Data are mean±SD or %. One-way ANOVA was used to compare mean values of HR and QTc. χ^2 test was used to test differences in proportions of subjects with family history, sinus bradycardia, VT/TdP, and AVB among the 4 groups. Pairwise comparisons were conducted using Bonferroni adjustment and Bonferroni inequality of P value. NS indicates not significant; Negative, gene mutation-negative group.

*No. of cases is 10 because data were not available in 1 case.

Notably, many patients in the present study showed sinus bradycardia, although HR was not significantly different among LQT1, LQT2, and LQT3. Sinus bradycardia has been considered a significant presentation of LQTS, especially in the fetal-neonatal period,^{3,19,20} and is often a clue to the diagnosis of LQTS. The present study verified that sinus bradycardia is common among all types of LQTS in this age group, especially in fetal-neonatal periods.

Another remarkable feature of the present study was the high incidence of AVB (55% in LQT2, 83% in LQT3), compared with 5% or less in child or adult LQTS.^{4,20} It is intriguing that mutations in our LQT2 patients were almost exclusively located at the pore region of HERG gene (amino acid residues 550 through 650),²¹ as mutations in that region are related to high risk for cardiac events.^{21,22} Lupoglazoff et al⁶ reported similar phenotype tendency for neonates with LQTS, that AVB is associated with LQT2 and sinus bradycardia with LQT1. Most of their LQT2 cases also had a mutation in the pore region of the HERG gene, although this was not mentioned in their report. AVB in neonates with an SCN5A mutation have also been reported in single case reports.^{8,11,23,24} Considering the implication of sodium channel dysfunction in many other hereditary arrhythmias,²⁵ the association between LQT3 and AVB is an important finding.

SCD/ACA was seen in 14 cases (24% of all subjects) (7 SCD, 7 ACA), even though 12 of them were under treatment with β -blockers, mexiletine, or both when the events occurred (Table 3). The direct trigger of SCD/ACA remains to be determined, but the mean QTc interval of those patients was apparently prolonged (617 ± 81 ms), and patients with no gene test (6 cases) were included as well, possibly making the selection of drugs inappropriate, such that only β -blockers were given to a possible LQT3 patient. Furthermore, 4 other cases had no known mutation on genotyping. It is possible that the cryptogenic mutations unidentifiable in the current era could be resistant to many drugs.

Therapy

Because individuals with LQT3 showed serious clinical disorders, they were treated aggressively with multiple antiarrhythmic drugs including mexiletine, β -blockers, lidocaine, Mg, and PM/ICD, and only 1 definite LQT3 patient showed ACA. For LQT2, malignant arrhythmias were a little more controllable with the same kind of pharmacotherapy than for LQT3. Again, only 1 definite LQT2 patient showed ACA. Thus, no death was ultimately observed in LQT2 and LQT3. This favorable clinical course might be derived from implicit strategy prevalent among pediatric cardiologists in our country that early-onset LQTS should be treated with the combination of β -blockers and mexiletine at the start of therapy because the genotype is not easy to confirm immediately. In other words, treatment strategies in Japan have been driven more by the clinical symptoms than by the genotype. Nevertheless, the response to the multiple antiarrhythmic pharmacotherapy and the long-term outcome presented in this study are encouraging.

It should be noted that the number of patients who underwent PM/ICD was small in the present cohort compared with other reports.^{5,6} It is known that TdP tends to follow a prolonged R-R interval in LQT2 and LQT3, in which

conduction disturbances or sinus node dysfunction are common features.^{25,26} Thus, PM/ICD should be considered without delay even when the patient who shows drug-resistant, bradycardia-induced VT/TdP is a small baby.²⁷

Study Limitations

Because of the retrospective nature of the present survey using questionnaires, the extent of clinical data that could be obtained varied among cases. Although approximate tendency in genotype-phenotype correlations for infants with LQT1, LQT2, and LQT3 was determined, most cases registered in the present study did not undergo genetic analysis for genes other than the 3 typical types. One case with LQT8 was registered in addition to LQT1–3, but no cases with the other types (LQT4–7) were found. Also, decision of treatment strategy depended on the in-charge physician in each case without the use of a uniform protocol for VT/TdP and/or AVB, making it difficult to evaluate the effects of pharmacotherapy and to determine the event rate beyond infancy for each genotype other than the last outcome, alive or death. Therefore, we should wait for accumulation of more cases for establishment of the genotype-specific strategy.

Conclusion

Our nationwide survey indicates that early-onset malignant LQTS are mostly those with LQT2 and LQT3 among the 3 major genes, and the most vulnerable age to life-threatening arrhythmias is from 0 to 2 days of age. A combination pharmacotherapy with a β -blocker and mexiletine sometimes combined with Mg and PM/ICD is recommended as the initial therapy. Prospective study of a large number of patients with LQTS diagnosed from fetal to infantile periods and further application of gene testing are needed to establish the most appropriate treatment strategies for those patients.

Acknowledgments

We are grateful to Dr Minako Hoshiai, University of Yamanashi; Dr Fukiko Ichida, University of Toyama; Dr Hiroki Kajino, Asahikawa Medical College; Dr Masaru Miura, Tokyo Metropolitan Kiyose Children's Hospital; Dr Tomoaki Murakami, Hokkaido University; Dr Kiyoshi Ogawa, Saitama Children's Medical Center; Dr Hirofumi Saiki, Hyogo Children's Hospital; Dr Jun-ichi Sato, Funabashi Municipal Medical Center; Dr Hiroshi Shimizu, Chugoku Rosai Hospital; Dr Kenji Suda, Kurume University School of Medicine; Dr Hiroshi Suzuki, Yamagata University School of Medicine; Dr Jun-ichi Takagi, University of Miyazaki; Dr Sho Takeda, Seirei Hamamatsu General Hospital; Dr Kiyohiro Takigiku, Nagano Children's Hospital; and Dr Hiroyuki Yamagishi, Keio University, for their contribution to the survey.

Disclosures

Drs Shimizu and Horie were supported by the Health Sciences Research Grants (H18-Research on Human Genome-002) and a Research Grant for Cardiovascular Diseases (21C-8) from the Ministry of Health, Labor, and Welfare of Japan. The other authors declare no conflicts of interest.

References

1. Moss AJ, Kass RS. Long QT syndrome: from channels to cardiac arrhythmias. *J Clin Invest*. 2005;115:2018–2024.
2. Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, Moncalvo C, Tulipani C, Veia A, Bottelli G, Nastoli J. Association of

- long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA*. 2004;292:1341-1344.
3. Hofbeck M, Ulmer H, Beinder E, Sieber E, Singer H. Prenatal findings in patients with prolonged QT interval in the neonatal period. *Heart*. 1997;77:198-204.
 4. Garson A Jr, Dick M II, Fournier A, Gillette PC, Hamilton R, Kugler JD, van Hare GF III, Vetter V, Vick GW III. The long QT syndrome in children: an international study of 287 patients. *Circulation*. 1993;87:1866-1872.
 5. Gorgels AP, Al Fadley F, Zaman L, Kantoch MJ, Al Halcees Z. The long QT syndrome with impaired atrioventricular conduction: a malignant variant in infants. *J Cardiovasc Electrophysiol*. 1998;9:1225-1232.
 6. Lupoglazoff JM, Denjoy I, Villain E, Fressart V, Simon F, Bozio A, Berthet M, Benammar N, Hainque B, Guicheney P. Long QT syndrome in neonates: conduction disorders associated with HERG mutations and sinus bradycardia with KCNQ1 mutations. *J Am Coll Cardiol*. 2004;43:826-830.
 7. Shim SH, Ito M, Maher T, Milunsky A. Gene sequencing in neonates and infants with the long QT syndrome. *Genet Test*. 2005;9:281-284.
 8. Chang CC, Acharfi S, Wu MH, Chiang FT, Wang JK, Sung TC, Chahine M. A novel SCN5A mutation manifests as a malignant form of long QT syndrome with perinatal onset of tachycardia/bradycardia. *Cardiovasc Res*. 2004;64:268-278.
 9. Johnson WH, Yang P, Yang T, Lau YR, Mostella BA, Wolff DJ, Roden DM, Benson DW. Clinical, genetic, and biophysical characterization of a homozygous HERG mutation causing severe neonatal long QT syndrome. *Pediatr Res*. 2003;53:744-748.
 10. Hoorntje T, Alders M, van Tintelen P, van der Lip K, Sreeram N, van der Wal A, Mannens M, Wilde A. Homozygous premature truncation of the HERG protein: the human HERG knockout. *Circulation*. 1999;100:1264-1267.
 11. Schulze-Bahr E, Fenge H, Eitzrodt D, Haverkamp W, Monnig G, Wedekind H, Breithardt G, Kehl HG. Long QT syndrome and life threatening arrhythmia in a newborn: molecular diagnosis and treatment response. *Heart*. 2004;90:13-16.
 12. Arnestad M, Crotti L, Rognum TO, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Wang DW, Rhodes TE, George AL Jr, Schwartz PJ. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation*. 2007;115:361-367.
 13. Otogiri T, Kijima K, Osawa M, Ishii K, Makita N, Matoba R, Umetsu K, Hayasaka K. Cardiac ion channel gene mutations in sudden infant death syndrome. *Pediatr Res*. 2008;64:482-487.
 14. Tester DJ, McCormack J, Ackerman MJ. Prenatal molecular genetic diagnosis of congenital long QT syndrome by strategic genotyping. *Am J Cardiol*. 2004;93:788-791.
 15. Cuneo BF, Ovadia M, Strasburger JF, Zhao H, Petropoulos T, Schneider J, Wakai RT. Prenatal diagnosis and in utero treatment of torsades de pointes associated with congenital long QT syndrome. *Am J Cardiol*. 2003;91:1395-1398.
 16. Hamada H, Horigome H, Asaka M, Shigemitsu S, Mitsui T, Kubo T, Kandori A, Tsukada K. Prenatal diagnosis of long QT syndrome using fetal magnetocardiography. *Prenat Diagn*. 1999;19:677-680.
 17. Horigome H, Iwashita H, Yoshinaga M, Shimizu W. Magnetocardiographic demonstration of torsade de pointes in a fetus with congenital long QT syndrome. *J Cardiovasc Electrophysiol*. 2008;19:334-335.
 18. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, Benhorin J, Locati EH, Towbin JA, Keating MT, Lehmann MH, Hall WJ. Influence of genotype on the clinical course of the long-QT syndrome: International Long-QT Syndrome Registry Research Group. *N Engl J Med*. 1998;339:960-965.
 19. Beinder E, Grancay T, Menéndez T, Singer H, Hofbeck M. Fetal sinus bradycardia and the long QT syndrome. *Am J Obstet Gynecol*. 2001;185:743-747.
 20. Trippel DL, Parsons MK, Gillette PC. Infants with long-QT syndrome and 2:1 atrioventricular block. *Am Heart J*. 1995;130:1130-1134.
 21. Moss AJ, Zareba W, Kaufman ES, Gartner E, Peterson DR, Benhorin J, Towbin JA, Keating MT, Priori SG, Schwartz PJ, Vincent GM, Robinson JL, Andrews ML, Feng C, Hall WJ, Medina A, Zhang L, Wang Z. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation*. 2002;105:794-799.
 22. Nagaoka I, Shimizu W, Itoh H, Yamamoto S, Sakaguchi T, Oka Y, Tsuji K, Ashihara T, Ito M, Yoshida H, Ohno S, Makiyama T, Miyamoto Y, Noda T, Kamakura S, Akao M, Horie M. Mutation site dependent variability of cardiac events in Japanese LQT2 form of congenital long-QT syndrome. *Circ J*. 2008;72:694-699.
 23. Miura M, Yamagishi H, Morikawa Y, Matsuoka R. Congenital long QT syndrome and 2:1 atrioventricular block with a mutation of the SCN5A gene. *Pediatr Cardiol*. 2003;24:70-72.
 24. Lupoglazoff JM, Cheav T, Baroudi G, Berthet M, Denjoy I, Cauchemez B, Extramiana F, Chahine M, Guicheney P. Homozygous SCN5A mutation in long-QT syndrome with functional two-to-one atrioventricular block. *Circ Res*. 2001;89:e16-e21.
 25. Benson DW, Wang DW, Dymont M, Knilans TK, Fish FA, Strieper MJ, Rhodes TH, George AL Jr. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest*. 2003;112:1019-1028.
 26. Hansen RS, Olesen SP, Grunnet M. Pharmacological activation of rapid delayed rectifier potassium current suppresses bradycardia-induced triggered activity in the isolated Guinea pig heart. *J Pharmacol Exp Ther*. 2007;321:996-1002.
 27. Ten Harkel AD, Witsenburg M, de Jong PL, Jordaens L, Wijman M, Wilde AA. Efficacy of an implantable cardioverter-defibrillator in a neonate with LQT3 associated arrhythmias. *Europace*. 2005;7:77-84.

CLINICAL PERSPECTIVE

The congenital long-QT syndrome (LQTS) diagnosed at perinatal life and through infancy is associated with high morbidity and mortality rates. However, data on the clinical presentation and genotype-phenotype correlation of this youngest age group of LQTS are limited. A nationwide survey was conducted in Japan, and 58 cases (18 fetuses, 31 neonates and 9 infants) were registered. Among them, the peak age at diagnosis was 0 to 2 days, and the 3 most frequent clinical presentations included sinus bradycardia, ventricular tachycardia/torsades de pointes, and atrioventricular block. The genotype was confirmed in 29 (71%) of 41 patients who underwent genotyping; the incidence resembled that of child LQTS. Patients who presented with early-onset ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively those with LQT2 and LQT3 among the 3 major genes, but a considerable number of genetically unidentified ones were included. Sudden cardiac death/aborted cardiac arrest were prevalent in the latter. LQT1 patients tended to show only sinus bradycardia or positive family history of LQTS. These results mean that many life-threatening episodes observed in early-onset LQTS should be treated immediately and aggressively even without knowledge of the genotype. On the other hand, the present study was encouraging in that the outcome of patients was favorable with multiple pharmaceutical agents, typically with β -blockers, mexiletine, and magnesium and with pacemaker implantation/implantable cardioverter-defibrillator, independent of the genotype. Further application of gene testing is needed to establish the most appropriate genotype-specific strategy for these patients.

