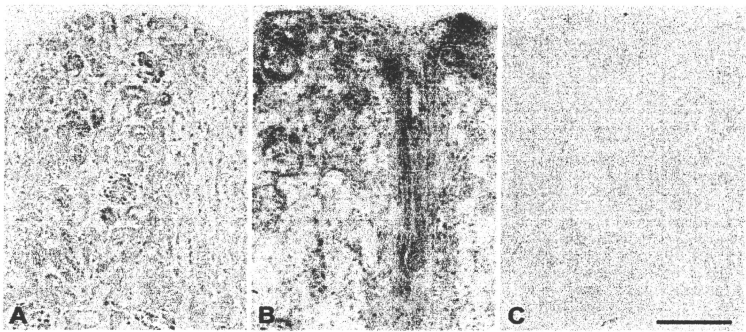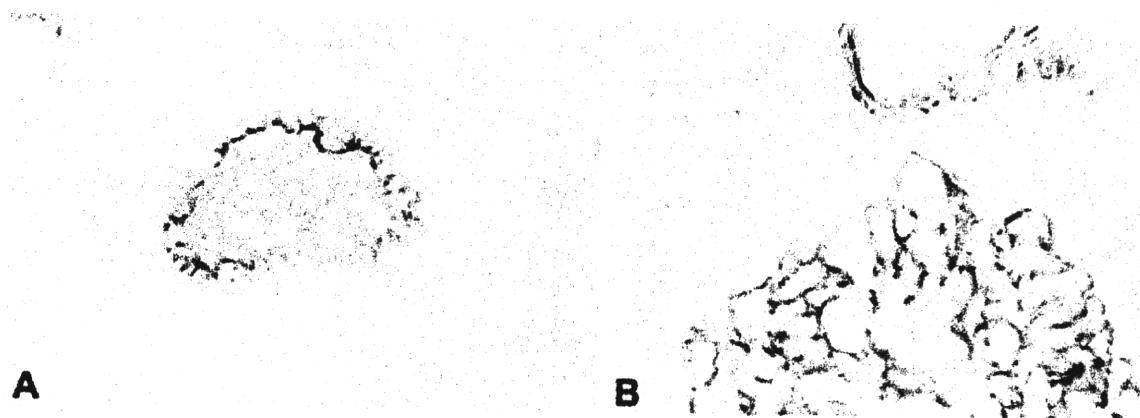Supplementary Figure 2

Supplementary Figure 3

A

B

Supplementary Figure 4

Determinants of Blood Rheology in Healthy Adults and Children Using the Microchannel Array Flow Analyzer

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Purpose: The reference values of blood rheology in healthy participants, especially children, are not available. The purpose of this study was to determine the blood passage time (BPT) as an index of blood rheology, in healthy children and adults, using the microchannel array flow analyzer, and to investigate the hematological factors that define BPT. *Methods:* Participants were 61 healthy children (35 boys, 26 girls; age 5-6 years) and 71 healthy adults (24 men, age 35.2 ± 14.1 years; 47 women, age 44.7 ± 14.1 years, mean ± standard deviation [SD]). Blood passage time and various hematological variables (blood cell count, serum lipids, and fibrinogen) were measured and compared among the

4 study groups. *Results:* Blood passage time values were significantly higher in adult men (48.8 ± 5.8 seconds) than in boys (41.9 ± 4.0 seconds), girls (43.7 ± 7.8 seconds), and adult women (42.4 ± 4.8 seconds). Stepwise regression analysis identified erythrocyte count and hemoglobin (Hb) as the significant and independent determinants of BPT ($P < .05$). *Conclusion:* Our study demonstrates that BPT is significantly longer in healthy adult men than in adult women and children, and that erythrocyte count and Hb are significant determinants of blood rheology.

Keywords: blood rheology; child; erythrocyte; viscosity

Introduction

Reduced blood rheology, or increased blood viscosity, correlates with thrombus formation through perturbation of blood coagulation and fibrinolysis

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system and is a risk factor for cardiovascular disease. Recently, Kikuchi et al[1,2] developed the microchannel array flow analyzer (MC-FAN) to measure blood rheology. The principal of the device is filtration, and the method has been applied for screening lifestyle-related disease, because it can easily detect abnormal blood rheology in patients with fatty liver disease,[3] hypercholesterolemia,[4] and metabolic syndrome.[5] In addition, Kamada et al[6] indicated that MC-FAN can be used for evaluation of thrombus formation.

Lifestyle-related diseases are believed to develop early in childhood,[7-10] and intervention from that period is required to prevent adulthood cardiovascular complications. We demonstrated that multiple cerebrovascular infarctions can develop even in children if blood rheology is markedly reduced in the presence of secondary erythrocytosis associated with cyanotic congenital heart defects.[11,12] In another study, we demonstrated that blood rheology is reduced even in young patients with cyanotic congenital heart disease, expressed as prolonged blood

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passage time (BPT), using MC-FAN.[13] Among the hematological parameters, the most significant factor that defines rheology was erythrocytosis. However, the reference values of blood rheology in children are not available. In this study, we measured BPT using MC-FAN in healthy children and compared the values with those of healthy adults. In the current study, we also investigated the hematological factors that define BPT.

Methods

Participants

We studied 61 healthy children (35 boys and 26 girls) and 71 healthy adults (24 men and 47 women). We excluded from the study those who were taking medications and those with hematological or lifestyle-related diseases. Before the commencement of the study, informed consent was obtained from the adult participants and from parents of the children. The study was approved in advance by the ethics committee for human research of University of Tsukuba.

Blood Sampling

Blood samples were collected from an antecubital vein between 9 AM and 10:30 AM after an overnight fast (except for water) and after at least a 15-minute rest immediately before sampling. The first sample was drawn into 2 polypropylene tubes (Venoject II; Terumo Co, Tokyo, Japan), 1 for serum collection and 1 containing 2.4 mg of ethylenediaminetetraacetic acid-2 kalium (EDTA-2K) for whole blood cell count. The latter sample was used for the measurement of erythrocyte count, hemoglobin (Hb) concentration, hematocrit (Hct), mean corpuscular volume (MCV), leukocyte count, and platelet (PLT) count using the Cell-Dyn (model 4000; Dianabot Inc, Tokyo, Japan). The second sample was gently introduced into a polypropylene tube containing 1/10 volume of 3.13% sodium citrate for measurement of plasma level of fibrinogen (Fbg). The serum sample was used for the measurement of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels using standard laboratory method. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald equation.[14]
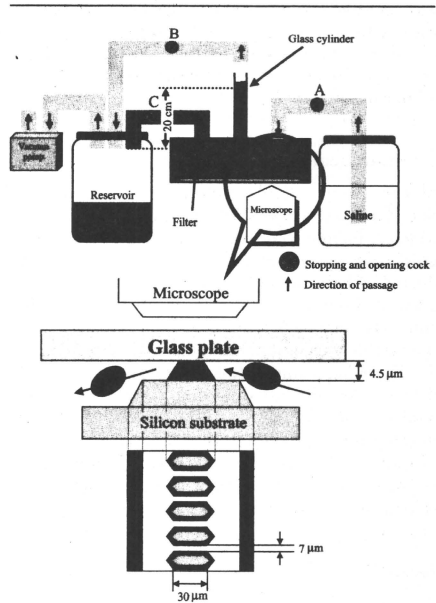

Figure 1. Schematic representation of the microchannel array flow analyzer (MC-FAN) and microchannel array (filters). The whole sample is introduced into a glass cylinder and is passed through a siliconized chip with 8736 slits (7 μm wide × 30 μm long) under negative pressure of 20 cm H_2O.

Measurement of BPT Using MC-FAN

Blood passage time was measured using MC-FAN system (Hitachi Haramachi Electronic Industrial Company, Ibaraki, Japan; Figure 1). The blood sample (1.9 mL) was stored in a polypropylene tube containing 2.4 mg of EDTA-2K and 0.1 mL of heparin sodium (Novo-Heparin 1000 units/mL; Mochida Pharmaceutical, Tokyo, Japan), and then 0.1 mL of the whole sample was introduced into a glass cylinder and passed through the siliconized chip with 8736 slits measuring 7 μm wide and 30 μm long under a negative pressure of 20 cm H_2O. The time for the blood sample of 0.1 mL to pass through the filters was measured as BPT. Calibration with saline (0.1 mL) was performed immediately before each new measurement. Reproducibility of BPT using MC-FAN was not verified in the current study as it

was repeatedly investigated in our previous studies with satisfactory results.[15,16] Furthermore, BPT has been confirmed to be proportional to blood viscosity.[17] Blood passage time was measured within 1 hour of sampling.

Statistical Analysis

All continuous variables were expressed as mean $\pm$ SD. Two-way analysis of variance (ANOVA), in which 2 factors were sex (men or boys, women or girls) and age categories (child, adult), was conducted with the interaction term of sex and age category. Multiple comparison of Tukey type was also conducted among the interaction levels to determine the significance of differences among variables.

The relationship between BPT and hematological variables was tested by simple linear regression model. Furthermore, stepwise linear regression model was carried out to assess independent predictors among the significant variables of simple linear regression analysis. A *P* value < .05 was considered statistically significant.

Results

Physical Characteristics of Participating Participants

Table 1 shows the anthropometric data of participating participants. There were significant differences in height, weight, body mass index (BMI), waist, systolic blood pressure (SBP), and diastolic blood pressure (DBP) based on age. Furthermore, there were significant differences in age, height, weight, and waist based on sex. Age, height, and weight showed significant interaction effects. Age, height, and weight showed significant interaction effects. Age, height, and weight showed significant difference based on interactions of sex and age category. For all 6 comparisons of every 2 variables among boys, girls, men, and women, 4 comparisons except boys-girls and men-women were significant for BMI, waist, SBP, and DBP.

Hematological Variables

Table 2 shows the comparison of hematological variables. There were significant differences based on age in Hct, Hb, MCV, leukocyte count, platelet count, total cholesterol (TC), HDL-C, and TG. There were also significant differences in erythrocyte

count, Hct, Hb, and LDL-C based on sex. Significant interaction was noted in erythrocyte count, Hct, Hb, TC, and HDL-C. For all 6 comparisons of every 2 variables among boys, girls, men, and women, there were mainly 3 types of difference patterns. The first pattern was significant differences in boys-women (A-D), girls-women (B-D), and men-women (C-D) for erythrocyte count, TC, and HDL-C. The second pattern was significant differences in boys-men (A-C), girls-men (B-D), and men-women (C-D) in Hct, Hb, and BPT. The third pattern was significant differences in boys-men (A-C), boys-women (A-D), girls-men (B-C), and girls-women (B-D) in MCV, leukocyte count, platelet count, and TG.

Blood Passage Time

Based on multiple comparison on the interaction term, BPT was significantly longer in adult men (48.8 $\pm$ 5.8 seconds) than in boys (41.9 $\pm$ 4.0 seconds), girls (43.7 $\pm$ 7.8 seconds), and adult women (42.4 $\pm$ 4.8 seconds). There was no difference in BPT values between boys and girls (Figure 2).

Relationship Between BPT and Hematological Variables

Table 3 shows the results of univariate analysis. Erythrocyte count, Hb, and Hct correlated significantly with BPT. Stepwise linear regression analysis of baseline characteristics identified erythrocyte count and Hb as significant independent determinants of BPT (Table 4).

Discussion

The current study demonstrated that BPT was significantly longer in healthy adult men than in the other groups, and there were no differences in BPT values by gender for children (Table 2, Figure 2). Among the anthropometric characteristics of the participants, BMI, SBP, and DBP also showed significant relationship among age categories but not sex categories. Waist showed similar significance pattern, except the presence of significance of sexes (Table 1).

Using the BPT values obtained in the current study, blood viscosity can be estimated with the following formula based on the fact that BPT correlates with blood viscosity ($R^2 = 0.973$, BPTs = 12.1 $\times$ viscosity [mPa·s at 1000 s^{-1}]), where BPT is the value

Table 1. Baseline Anthropometric Characteristics[a]

	Children		Adults		Between Age Categories (Child, Adult) P Value	Between Sexes P Value	Interaction (Age Category × Sex) P Value	Multiple Comparison on Interaction Terms (P < .05)
	Boys A	Girls B	Adult Men C	Adult Women D				
n	35	26	24	47	$P < .0001$ (for χ^2 test of independence between sex and age category)			
Age, years	5.77 (0.49), 35	5.46 (0.58), 26	35.2 (14.1), 24	44.7 (14.1), 47	<.0001	<.05	<.01	A-C,A-D, B-C,B-D,C-D
Height, cm	115.9 (5.4), 35	111.6 (6.6), 26	172.5 (5.3), 24	157.2 (5.0), 47	<.0001	<.0001	<.0001	A-B, A-C,A-D, B-C,B-D,C-D
Weight, kg	21.0 (3.9), 35	19.0 (2.6), 26	66.5 (6.4), 24	53.9 (5.5), 47	<.0001	<.0001	<.0001	A-C,A-D, B-C,B-D,C-D
Body mass index, kg/m²	15.6 (1.9), 35	15.2 (1.1), 26	22.0 (1.4), 24	21.8 (1.8), 47	<.0001	.348	.863	A-C,A-D, B-C,B-D
Waist, cm	52.9 (4.9), 35	51.0 (3.2), 26	81.3 (7.5), 10	76.4 (6.3), 22	<.0001	<.01	.216	A-C,A-D, B-C,B-D
Systolic blood pressure, mm Hg	94.4 (7.1), 35	93.1 (8.2), 26	120.3 (6.8), 17	116.7 (11.4), 40	<.0001	.162	.501	A-C,A-D, B-C,B-D
Diastolic blood pressure, mm Hg	53.9 (8.2), 35	53.3 (11.2), 26	78.2 (8.5), 17	74.0 (8.1), 40	<.0001	.165	.29	A-C,A-D, B-C,B-D

[a] Values are mean (SD), n.

Table 2. Hematological Variables of Participating Participants

	Children		Adults		Between Age Categories (Child, Adult) P Value	Between Sexes P Value	Interaction (Age Category × Sex) P Value	Multiple Comparison on Interaction Terms (P < .05)
	Boys A	Girls B	Adult Men C	Adult Women D				
Erythrocyte count, $10^4/\mu L$	476.5 (31.1), 11	471.3 (21.1), 9	488.9 (45.8), 24	430.9 (27.5), 47	.109	<.01	<.01	A-D, B-D,C-D
Hematocrit,%	39.4 (1.99), 11	38.4 (2.56), 9	45.3 (3.53), 24	39.6 (3.10), 47	<.0001	<.0001	<.01	A-C, B-C,C-D
Hemoglobin, g/dL	12.8 (0.84), 11	12.60 (0.77), 9	15.2 (1.30), 24	12.9 (1.15), 47	<.0001	<.0001	<.01	A-C, B-C,C-D
MCV, fL	82.8 (2.96), 11	81.4 (3.64), 9	92.7 (5.75), 24	92.1 (5.90), 47	<.0001	.423	.858	A-C,A-D, B-C,B-D
Leukocyte count, per μL	6709 (2255), 11	6689 (1621), 9	5096 (1314), 24	4630 (1137), 47	<.0001	.502	.538	A-C,A-D, B-C,B-D
Platelets, $10^4/\mu L$	31.0 (4.89), 11	31.0 (9.95), 9	21.5 (5.53), 24	24.1 (5.74), 47	<.0001	.425	.396	A-C,A-D, B-C,B-D
TC, mg/dL	170.1 (19.3), 35	177.7 (22.9), 26	179.1 (25.2), 24	202.6 (27.6), 47	<.01	<.01	.073	A-D, B-D,C-D
HDL-C, mg/dL	68.3 (11.9), 35	60.7 (10.63), 26	63.0 (16.3), 24	78.1 (16.8), 47	<.05	.149	<.0001	A-D, B-D,C-D
LDL-C, mg/dL	94.2 (14.1), 35	107.1 (15.5), 26	100.6 (23.4), 24	111.3 (20.1), 47	.139	<.0001	.672	A-B, A-D
Triglycerides, mg/dL	37.9 (25.3), 35	46.2 (16.0), 26	77.4 (30.7), 24	65.6 (26.0), 47	<.0001	.699	<.05	A-C, A-D, B-C, B-D
Fibrinogen, mg/dL	243.1 (52.4), 35	258.1 (58.2), 26	265.7 (97.6), 15	265.9 (458.8), 28	.227	.543	.557	—
BPT, seconds	41.9 (4.04), 35	43.7 (7.75), 26	48.8 (5.79), 24	42.4 (4.78), 47	<.01	<.05	<.0001	A-C, B-C,C-D

NOTES: BPT = Blood passage time; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Values are mean (SD), n; MCV, mean corpuscular volume; TC, total cholesterol.
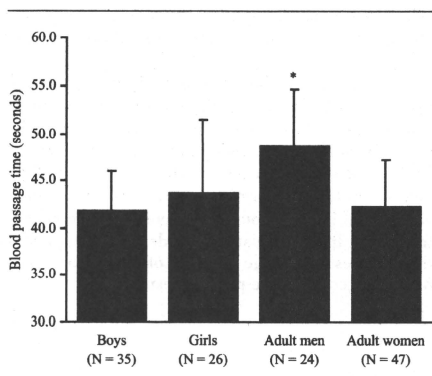
Figure 2. Blood passage time. Data are mean ± SD. *P < .05 versus the other 3 groups.

Table 3. Prognostic Factors of BPT by Simple Linear Regression

Variables	Coefficient	Standard Error (SE)	t Value	P Value
Age category	1.830	1.037	1.76	.080
Sex	−1.886	1.040	−1.81	.072
Erythrocyte count	0.071	0.014	4.88	<.0001
Hemoglobin	1.913	0.404	4.73	<.0001
Hematocrit	0.702	0.154	4.57	<.0001
MCV	−0.011	0.100	−0.11	.909
Platelet count	−0.130	0.098	−1.33	.186
Leukocyte count	0.0004	0.0004	1.02	.310
Total cholesterol	−0.005	0.019	−0.28	.778
HDL-C	−0.023	0.033	−0.70	.487
LDL-C	−0.016	0.027	−0.60	.553
Fibrinogen	0.007	0.010	0.70	.488

NOTES: BPT = Blood passage time; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MCV, mean corpuscular volume.

Table 4. Multiple Stepwise Linear Regression Analysis of Baseline Characteristics, Erythrocyte Count, Hb, and Hct

Variables	Coefficient	Standard Error (SE)	F Value	P Value
Erythrocyte count	0.044	0.019	5.20	<.05
Hb	1.079	0.538	4.02	<.05

NOTES: Hb = Hemoglobin; Hct = hematocrit.

measured using MC-FAN as in the current study, and blood viscosity is the value measured by a viscometer.[17] Thus, the estimated values of blood viscosity are as follow: 3.5 mPa·s for healthy boys, 3.6 mPa·s for girls, 4.0 mPa·s for adult men, and 3.5 mPa·s for adult women. These standard data would be useful for comparison of blood viscosity between those with at risk of cardiovascular disease and those without.

It has been reported that blood viscosity is significantly influenced by erythrocyte count, Hct, and Hb levels and increases exponentially with increases in Hct.[18,19] Our data demonstrated that adult men have the longest values of BPT (Figure 2). Stepwise regression analysis identified erythrocyte count and Hb as the significant predictors of BPT, that is, blood rheology, among blood components studied in the present investigation (Tables 3 and 4). Erythrocyte count was lower in adult women than in children, but Hb and Hct were not different between adult women and children. Blood passage time was also not different between adult women and children. This is probably derived from the difference in MCV values, that is, the volume of individual erythrocyte, which was larger in adult women than in children. The results of multiple comparison of interaction in our study showed that there was difference between age categories for MCV but not sex categories, and that only adult men showed difference for BPT, Hb, and Hct (Table 2). Previous studies reported that MCV is an index of erythrocyte deformability, and reduced MCV correlates with

reduced erythrocyte deformability, that is, reduced blood rheology.[20,21] Mean corpuscular volume is considered to have qualitative effects on blood rheology rather than quantitative effects like Hct.

This conclusion is compatible with the result that MCV was not identified as a significant independent determinant of BPT by stepwise regression analysis in the current study. However, further studies in a large number of participants are needed to clarify the effects of MCV on blood rheology.

Hyperlipidemia is considered to be associated with increased plasma viscosity. Lee et al[4] demonstrated that TC, LDL-C, and HDL-C influence BPT in patients with hypercholesterolemia, that is, even HDL-C correlates positively with BPT, which is in contrast to the present findings. In addition, it is possible that the increase in serum levels of TG and

LDL-C is related to decrease in blood rheology based on the qualitative effects of decreased erythrocyte deformability and increased erythrocyte aggregation.[22,23] However, this study suggests that the effect of serum lipids on blood rheology is negligible in healthy participants, and that factors defining blood rheology might depend partly on the age of the participant.

Plasma level of Fbg is also known to correlate with blood rheology as well as recognized as a risk factor for cardiovascular disease and coronary heart disease.[24] However, our results unexpectedly showed no difference in Fbg levels between children and adults (Table 2). Further studies are needed to determine how blood rheology is influenced by Fbg in healthy persons. In this regard, Katayama et al[13] and Wei et al[25] showed that the fibrinolytic parameter, tissue-type plasminogen activator (t-PA) antigen, correlates with blood rheology. Furthermore, erythrocyte, leukocyte, and platelets could have some effects on blood rheology at least under certain pathological conditions, though whether these variables influence blood rheology in healthy persons remains to be clarified. It is possible that various hematological parameters that influence blood rheology vary among diseases.

Blood passage time is a useful parameter for comprehensive screening of the risk of lifestyle-related diseases. Previous studies suggested that increased blood viscosity or prolonged BPT, that is, reduced blood rheology, is implicated in the pathogenesis and progression of cardiovascular diseases and mortality.[26-29] Blood passage time can be easily applied to this kind of screening. We also demonstrated that the measure can be applied for evaluation of abnormal blood rheology in erythrocytosis associated with cyanotic congenital heart disease,[13] although data of BPT in patients with anemia remain to be determined.

Study Limitations

This study provides standard values for blood rheology, which can be referred to in clinical settings. However, the number of participants in our study was small and all participants were Japanese, making it difficult to use the normal values for other races. Therefore, further studies of a large number of healthy children and adults and of patients with various disorders including obesity, hypertension, abnormal lipid profile, and diabetes are needed to

establish the standard values of BPT and for more application of MC-FAN to identify cardiovascular risks.

In conclusion, the current study demonstrated that BPT was longer in adult men than in adult women and children, and that erythrocyte count and Hb are significant and independent determinants of BPT in healthy participants. The values of BPT in healthy children determined in this study may provide useful information for screening of candidates for future lifestyle-related disorders; although further studies in a large number of participants are needed to confirm the present results.

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Original Article

Prevalence of childhood obesity from 1978 to 2007 in Japan

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Abstract   *Background*: There are few cross-sectional and longitudinal studies on identification of the age of onset of obesity. The purpose of the present study was therefore to investigate 30 years of cross-sectional and longitudinal changes in the prevalence of obesity from 1978 to 2007 in Japanese children and adolescents between 5 and 17 years of age, using population-based samples.

Methods: Subject data were obtained from the Annual Reports of the School Health Survey published by the Ministry of Education, Culture, Sports, Science and Technology, Japan. Obesity was defined as a body mass index (BMI) at or above the 95th percentile for age and gender based on the reference years from 1979 to 1981 in Japan. The BMI was calculated as weight in kg/(height in m)^2.

Results: Cross-sectional analysis of 5-, 8-, 11-, 14-, and 17-year-olds showed that the prevalence of obesity has gradually decreased since the early 2000s, with the highest prevalence in the late 1990s to early 2000s, except in 17 year-old boys. Longitudinal studies showed that the critical periods for developing obesity were in late infancy (between 5 and 6 years of age) and in the high school period in boys, and mainly in late infancy in girls.

Conclusions: Intervention to prevent obesity should be focused on late infancy in both genders and male adolescents in Japan.

Key words   obesity, population, prevention and control.

Obesity is considered a threat to public health, and the ongoing obesity epidemic represents a major public health concern worldwide.[1–3] In the Japanese adult population, the prevalence of obesity (body mass index [BMI] $\geq$ 25 kg/m^2) increased rapidly between 1984 and 2004 in men.[4] Men tend to develop obesity in their 40s or younger,[5] and tend to develop combined cardiovascular risks.[6] Obesity-associated risk factors arise in mildly to moderately obese conditions not only in adults but also in children in Japan,[7–10] indicating that primary prevention of obesity is important from childhood.

Analyzing the prevalence of obesity might identify periods of great vulnerability. There are few cross-sectional and longitudinal studies, however, on identification of the age of onset of obesity.[1,11] This information could be useful for determining when to prevent obesity.[1] Therefore, the aim of the present study was to investigate 30 years of cross-sectional and longitudinal changes in the prevalence of obesity from 1978 to 2007 in Japanese

children and adolescents between 5 and 17 years, using population-based samples.

Methods

Nationwide population-based data

The Ministry of Education, Culture, Sports, Science and Technology has performed the School Health Survey for height and weight since 1948. The data are collected by sampling with probability proportionate to size every year. The Ministry collects information each year from 72 380 kindergartners aged 5 years (from 1645 kindergartens), 270 720 elementary school children aged 6–11 years (from 2820 schools), 225 600 junior high school adolescents aged 12–14 years (from 1880 schools), and 126 900 high school adolescents aged 15–17 years (from 2820 schools).[12] These samples corresponded to 4.7% of all children and adolescents in Japan in 2007.[12]

Measurements of height and weight in Japan

In Japan, all children and adolescents in kindergartens and schools undergo a mandatory medical examination, performed by school doctors and nurses. Height and weight are measured by school nurses in early April each year. Height is measured to the nearest 0.1 cm without shoes and weight is measured to the nearest 0.1 kg in underwear.

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Collection and input of data for the present study

The frequency tables in the Annual Report of the School Health Survey[12] show frequency per thousand children for height (every 1 cm) and weight (every 1 kg) for each age and gender. Data are expressed to one decimal place.

The height and weight in the reports were input into a computer by personnel from a temporary-employment agency or secretaries of the National Hospital Organization Kagoshima Medical Center, and re-checked to ensure data were the same as the frequency tables. Financial support for the data input was provided by grants, as stated in the Acknowledgments section.

Definition of obesity

In the present study, obesity was defined as a BMI at or above the 95th percentile for age and gender based on the reference data in Japan. The BMI was calculated as weight in kg/(height in m)^2.

Reference data for the BMI percentile value for each age and gender

The prevalence of obesity (BMI ≥ 30.0) in adults is relatively low in Japan compared with that in Western populations, and thus a BMI ≥ 25 is usually used for the definition of obesity in Japanese adults.[13] Therefore, we used the Japanese data as a reference, and not the International data provided by Cole *et al.*[14] The percentile value of the BMI for each age and gender was determined from the frequency tables of height and weight from three successive years from 1979 to 81.[12] The prevalence of obesity in the reference years (1979–81) was 5% in all ages and genders. The cut-off points for obesity in the present study are shown in Table 1.

Cross-sectional surveillance of the prevalence of obesity

The prevalence of obesity was determined for 5-, 8-, 11-, and 17-year-old boys and girls between 1978 and 2007.

Longitudinal surveillance of the prevalence of obesity

We obtained data for the subjects between 5 and 17 years of age from 1978 for the present study. Subjects who were 5 years of age in 1978 were born in 1973, and we then made consecutive 4

year-interval cohorts, which were named as the 73–76, 77–80, 81–84, 85–88, 89–92, 93–96, and 97–00 birth cohorts.

Results

Prevalence of obesity in each age and gender in 2007

The prevalence of obesity in boys during the elementary school period (6–11 years of age in Japan) in 2007 was 4–5 points higher than that (5%) in the reference years (1979–81), while the prevalence in 5-year-old boys was 1.3 points higher than that in the reference years (Fig. 1). After a decrease in the prevalence of obesity during the junior high school period (12–14 years of age), the prevalence of obesity during the high school period (15–17 years of age) was approximately 6 points higher than that in the reference years.

A rapid increase in the prevalence of obesity was found in girls between 5 and 6 years of age, similar to that for boys (Fig. 1). The prevalence of obesity gradually decreased until the junior high school period, and then gradually increased during the high school period.

Cross-sectional surveillance of the prevalence of obesity

Changes in the prevalence of obesity for subjects who were 5, 8, 11, 14, and 17 years of age are shown in Figure 2. The increase in the prevalence of obesity was smallest in 5-year-old boys, and it then decreased after the mid-1990s (Fig. 2a). A rapid increase in the prevalence of obesity was present in 8-, 11-, and 14-year-old boys from the late 1980s to late 1990s; the prevalence of obesity of these ages then decreased after 2000. In contrast, the prevalence of obesity in 17-year-old boys had a prominent increase in 2002, and thereafter it increased to its highest point among these age groups in 2006.

The prevalence of obesity in 5-, 8-, 11-, and 14-year-old girls had a similar increase to that in boys from the late 1980s to late 1990s, and decreased after 2000 (Fig. 2b). The prevalence of
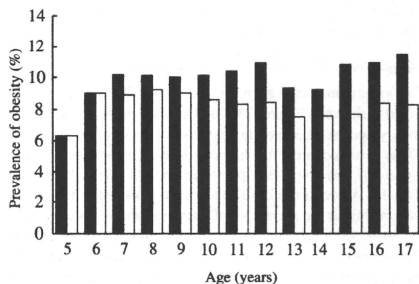
Table 1   Cut-off points for obesity

Age (years)	Male	Female
5	17.65	17.68
6	17.80	17.80
7	18.31	18.27
8	19.48	19.22
9	20.66	20.10
10	21.74	21.09
11	22.35	22.13
12	23.00	23.20
13	23.46	23.94
14	23.94	24.56
15	25.28	25.45
16	25.26	25.39
17	25.47	25.32

Fig. 1 Cross-sectional analyses of the prevalence of obesity in subjects between 5 and 17 years of age in (■) boys and (□) girls in 2007. A prominent increase in the prevalence of obesity occurred between 5 and 6 years of age in both genders. The prevalence of obesity increased again during high school in boys.
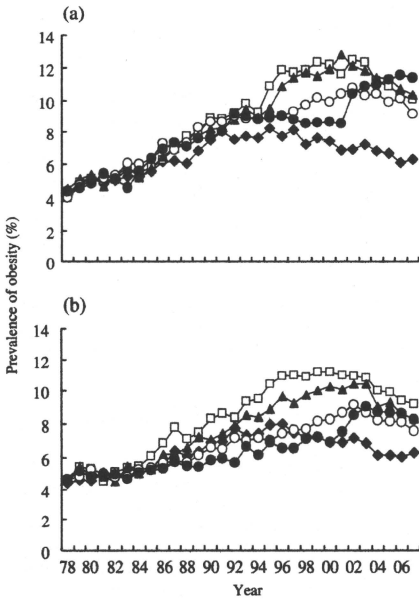
Fig. 2 Thirty year cross-sectional change in the prevalence of obesity in subjects (♦) 5, (□) 8, (▲) 11, (○) 14, and (●) 17 years of age from 1978 to 2007 in (a) boys and (b) girls. The prevalence of obesity gradually decreased from the early 2000s, with the highest prevalence occurring in the late 1990s–early 2000s, except for in 17 year-old boys.

obesity in 17-year-old girls increased in 2002, similar to that for boys, but it then decreased after this time.

Longitudinal surveillance of the prevalence of obesity

The longitudinal change in the prevalence of obesity in each cohort is shown in Figure 3. A sharp increase in the prevalence of obesity occurred between the ages of 5 and 6 in boys from the 1980s birth cohorts; the highest difference between 5- and 6-year-old boys was 3.7 points in the 93–96 birth cohorts (Fig. 3a). Among male birth cohorts, the more recent the cohort was, the higher the prevalence of obesity in almost all ages, until the 89–92 birth cohorts; the 89–92 birth cohort had the highest prevalence of obesity between the ages of 7 and 15 years. The prevalence of obesity in this cohort increased again at 15 years of age, after a decrease during the junior high school period. This tendency toward a higher prevalence of obesity was not present in the 93–96 and 97–00 birth cohorts.

A sharp increase in the prevalence of obesity also occurred between the ages of 5 and 6 in girls from the 1980s birth cohorts,

and the highest difference was 3.5 points in the 93–96 birth cohorts (Fig. 3b). Among female birth cohorts, the prevalence of obesity in the 89–92 birth cohort was highest at the ages of 7–13 years, which was similar to that for boys. The prevalence of obesity during junior high and high school decreased in all cohorts except for the 85–88 cohort.

Discussion

In the present study, cross-sectional analysis demonstrated that the prevalence of obesity gradually decreased from the early 2000s, with the highest prevalence occurring in the late 1990s–early 2000s, except for in 17-year-old girls. Longitudinal studies showed that the critical periods for developing obesity were in late infancy (between 5 and 6 years of age) and the high school period in boys, and mainly in late infancy in girls, indicating that interventions to prevent obesity should be focused on these groups.
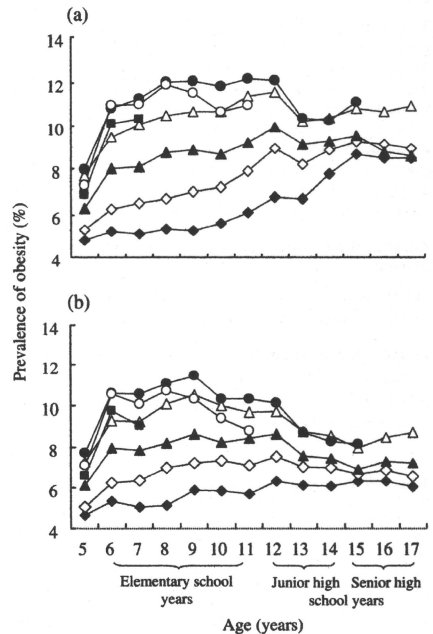

Fig. 3 Longitudinal changes in the prevalence of obesity in the 4 year-interval birth cohorts at each year of age in (a) boys and (b) girls. The (●) 89–92 birth cohort had the highest prevalence of obesity between the ages of 7 and 15 years in boys and between the ages of 7 and 13 years in girls. Birth cohorts: (♦) 73–76; (◇) 77–80; (▲) 81–84; (△) 85–88; (●) 89–92; (○) 93–96; (■) 97–00.

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Cross-sectional analysis showed that the prevalence of obesity gradually decreased, with the highest prevalence in the late 1990s–early 2000s in Japan. Obesity is a complex, multi-factorial disease that develops due to the interaction of genetic, metabolic, social, behavioral, and cultural factors.[1] In Japan, along with westernization of lifestyle after World War II and large economic growth between the late 1980s and early 1990s, obesity has become a major concern in both adult and pediatric populations.[5–9] In contrast, the Ministry of Health, Labor and Welfare devised a health promotion plan in 1988, called the "Active 80 Health Plan" to offer medical checks, nutrition and exercise counseling in each city and town, especially to promote physical activity.[15] The ministry published *Health Japan 21* in 2001, a 10 year national plan for health promotion and disease prevention and indicated several goals to be achieved before 2010.[15] The data presented here suggest that Japan has begun to reduce the problem of obesity in part, although the situation has not improved in infants, adolescents (the present study) or the adult population.[4,5,16]

The prevalence of obesity between 5 and 17 years of age in 2007 (Fig. 1) and longitudinal analysis of the prevalence of obesity (Fig. 3) show that the critical periods for developing obesity are in late infancy (between 5 and 6 years) in both genders. Infancy is a critical period for the development of obesity,[17] but the ages at risk for developing obesity during infancy are different between studies. A longitudinal study of subjects between the ages of 5 and 18 years in Indianapolis, USA, from 1985 to 2001 showed that the first peak for developing obesity was present between 5- and 7-year-old boys and girls, especially in black subjects.[11] Another longitudinal study of subjects between the ages of 2 and 15 years in Nuuk, Greenland, from 1973 to 1992 showed that a sharp increase was present between 2- and 4-year-old boys and girls in all birth cohorts during the study periods, and that an increase was not present around 5 years of age.[1] These results suggest that the period of adiposity rebound during infancy differs with ethnicity and country.

The prevalence of obesity tended to decrease during junior high school, which might be due to an increase in activity levels because almost all students participate in extracurricular activities at this age in Japan. In contrast, there was a prominent increase in the prevalence of obesity in 15-year-old boys of all birth cohorts (Fig. 3) and in 17-year-old boys (Fig. 2). Entrance examinations for school entry is mandatory for all students, with the exception of a small number of private schools, and a strong wish to enter famous high schools and universities or colleges is present in Japan; we suspect that more study and less physical activity may explain the increase in the prevalence of obesity in 15-year-olds, and the effect of this secular trend has recently increased in 17-year-old boys. The exact reason for the gender difference is not clear from the present study, but the same phenomenon is also present in the Japanese adult population. The prevalence of obesity increased between 1984 and 2004 in men, but not in women, and men develop obesity in their 40s or younger.[5,6]

In the present study obesity was more prevalent in boys than in girls after 7 years of age (Fig. 1). One reason for this finding

may be due to the difference in energy intake between genders. The total energy intake and intake of protein and fat were similar in subjects 1–6 years of age, and those in boys were higher than those in girls after 7 years of age in 2004.[18]

There were some limitations in the present study. First, the present study lacked data for changes in physical activities that are closely associated with the development of obesity, as mentioned in the previous section. Westernization of lifestyle and/or economic growth may affect the lifestyles of people in Japan as a whole. The association between prevalence of obesity and physical activity should also be further investigated to clarify gender difference, especially during the junior and senior high school periods. Second, we did not use the international cut-offs for obesity provided by Cole *et al.*[14] In Asian countries,[19] especially Japan,[9] obesity-associated disorders arise in mildly to moderately obese children[9] and adolescents.[19] Therefore, we used the Japanese data as a reference, and not the international cut-offs. The second reason for using our own cut-offs was that we intended to use the same prevalence of obesity (5%) in all age groups of both genders in the reference years.

Obesity is associated with the worsening of individual cardiovascular risks and/or the clustering of cardiovascular risks in children and adolescents worldwide.[20–23] The present and these studies indicate that prevention and control of childhood obesity are needed from early stages of childhood, as early as infancy.

In conclusion, cross-sectional analysis showed that the prevalence of obesity gradually decreased from the early 2000s, with the highest prevalence occurring in the late 1990s–early 2000s, except for 17-year-old boys. Longitudinal studies showed that the critical periods for developing obesity were in late infancy in both genders and the high school period in boys. Interventions to prevent obesity should be focused on late infancy in both genders and in adolescence for boys in Japan.

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Original Articles

Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life
A Nationwide Questionnaire Survey in Japan

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Background—Data on the clinical presentation and genotype-phenotype correlation of patients with congenital long-QT syndrome (LQTS) diagnosed at perinatal through infantile period are limited. A nationwide survey was conducted to characterize how LQTS detected during those periods is different from that in childhood or adolescence.

Methods and Results—Using questionnaires, 58 cases were registered from 33 institutions. Diagnosis (or suspicion) of LQTS was made during fetal life (n=18), the neonatal period (n=31, 18 of them at 0 to 2 days of life), and beyond the neonatal period (n=9). Clinical presentation of LQTS included sinus bradycardia (n=37), ventricular tachycardia/torsades de pointes (n=27), atrioventricular block (n=23), family history of LQTS (n=21), sudden cardiac death/aborted cardiac arrest (n=14), convulsion (n=5), syncope (n=5), and others. Genetic testing was available in 41 (71%) cases, and the genotype was confirmed in 29 (71%) cases, consisting of LQT1 (n=11), LQT2 (n=11), LQT3 (n=6), and LQT8 (n=1). Ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively observed in patients with LQT2, LQT3, and LQT8, as well as in those with no known mutation. In LQT1 patients, clues to diagnosis were mostly sinus bradycardia or family history of LQTS. Sudden cardiac death/aborted cardiac arrest (n=14) was noted in 4 cases with no known mutations as well as in 4 genotyped cases, although the remaining 6 did not undergo genotyping. Their subsequent clinical course after aborted cardiac arrest was favorable with administration of β-blockers and mexiletine and with pacemaker implantation/implantable cardioverter-defibrillator.

Conclusions—Patients with LQTS who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3, or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias, with only 7 deaths recorded. (*Circ Arrhythm Electrophysiol*. 2010;3:10-17.)

Key Words: arrhythmia ∎ long-QT syndrome ∎ genes ∎ death (sudden)

Congenital long-QT syndrome (LQTS) is an inherited disorder characterized by polymorphic ventricular tachycardia (VT), or torsades de pointes (TdP), syncope, and sudden cardiac death.[1] LQTS is often diagnosed in children from school age to young adulthood[2] and sometimes during fetal, neonatal, and infantile life.[3–5] Previous case reports

Table 1.   Questionnaire Items

1. Patient: Serial No. in each institution, initials, birth year, and month, sex
2. Age at diagnosis or suspicion (including gestational age for a fetus)
3. Clinical symptoms: Fetal arrhythmias, fetal heart failure, syncope, convulsion, heart failure, aborted cardiac arrest, others
4. ECG findings and arrhythmias (heart rate, QTc on ECG at presentation, sinus bradycardia, VT/TdP, atrioventricular block, other arrhythmias)
5. Family history of LQTS or other arrhythmias or sudden cardiac death (which member, and their outcome?)
6. Genotype
7. Treatment (acute therapy and maintenance therapy)
   pharmacotherapy (which drug, dose, age at initiation, and duration)
   device therapy (pacemaker implantation/implantable cardioverter-defibrillator) and age at application
8. Duration of follow-up
9. Outcome (alive or death, and neurological sequels of cardiac arrest)

suggest that the latter cases are at higher risk of development of life-threatening arrhythmias necessitating emergency treatment[3–5] and show higher mortality rates than the former age groups.[3,5–11] For example, recent progress in molecular biology has clarified that LQTS partly contributes to sudden infant death syndrome (SIDS).[12,13] Unfortunately, prenatal diagnosis of LQTS has been extremely difficult to confirm except for a limited number of cases for which prenatal gene screening[14] or fetal magnetocardiography (fMCG)[15–17] was applied.

Clinical Perspective on p 17

Thus, the clinical presentation, the genotype-phenotype correlation, and the outcome of patients with fetal, neonatal, or infantile presentation of LQTS remain to be elucidated. The purposes of this study were first, to report the findings of a nationwide survey conducted to define the clinical characteristics and the genotype-phenotype correlation, and second, to report the outcome of patients with LQTS diagnosed before birth and in the first year of life.

Methods

Population

The study population included fetuses, neonates, and infants (<1 year of age) diagnosed with LQTS based on ECG findings including prolonged QTc >0.46 seconds (using Bazett formula), with or without VT/TdP, who had no structural heart disease, family history of LQTS, or had undergone genetic testing. Those with normal QTc duration and no gene mutation known to cause LQTS were excluded. Patient data were collected using questionnaires. The form was sent to those councilors of the Japanese Society of Pediatric Cardiology and Cardiac Surgery who responded to a preliminary survey that they had 1 or more cases of LQTS diagnosed during fetal, neonatal, and infantile life. The items obtained from the responders are presented in Table 1.

The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba, and informed consent was obtained from each patient (or parents, if the patient was younger than 15 years of age) by a coordinator in charge in each institution before the patient's data were registered.

Genetic Analysis and Genotype-Phenotype Correlation

Genetic analyses were performed in 4 established laboratories in Japan. DNA was isolated from blood samples in each patient. Screening for mutations of at least 3 major genes causing LQTS

(KCNQ1, KCNH2, SCN5A) was performed using polymerase chain reaction (PCR)/single-strand conformation polymorphism or denatured high-performance liquid chromatography analysis. For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (ABI 3700 and ABI 3130xl, Applied Biosystems, Foster City, Calif). For those subjects in whom genotype was confirmed and those who underwent genetic analysis but found to have no mutation, genotype-phenotype correlations (or mutation-negative phenotype correlations) with the aforementioned items (Table 1) were investigated.

Statistical Analysis

All statistical calculations were conducted using the R software. Quantitative variables (heart rate [HR] and QTc) are presented as mean±SD and categorized variables (presence of FH, sinus bradycardia, VT/TdP, and atrioventricular block [AVB]) as proportions (percentages). One-way ANOVA was applied for comparisons of continuous variables, followed by pairwise comparisons with Bonferroni adjustment of probability values among 4 groups (LQT1, LQT2, LQT3, and mutation-negative groups). The equality of proportions for categorical variables among the 4 groups was examined by the χ^2 test (global test). When there was a significant difference in proportions, we performed pairwise comparisons between pairs of proportions with correction for multiple testing using Bonferroni inequality of probability values. Tests were 2-sided, and a probability value <0.05 was considered significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Population

A total of 58 cases (all Japanese; males 30, females 28) were registered from 33 institutions. Forty-one were born during the last 10 years (between 1999 and 2008), 14 between 1989 and 1998, 1 in 1986, and 2 in 1984. LQTS was diagnosed or suspected during fetal life at 18 to 40 weeks of gestation in 18 individuals, during neonatal life at 0 to 28 days in 31, and in infancy (<1 year) at 1 to 9 months in 9.

Clinical Features

For 18 fetuses with LQTS, clinical presentation (or clues to diagnosis or suspicion of LQTS) included bradycardia (15 cases), AVB (8 cases), VT/TdP (7 cases), and family history of LQTS (6 cases), including 1 family with a previous intrauterine death (items overlapped in some cases). Two fetuses were confirmed to be LQTS by fMCG, with QTc values of 570 and 680 on fMCG, and 590 and 700 on ECG soon after birth, respectively (these 2 cases have been reported previously).[16,17] No fetal death was noted in this group.

For 31 neonates with LQTS, the most frequent feature was sinus bradycardia (17 cases), followed by VT/TdP (15 cases), positive family history of LQTS (15 cases), including 1 with previous intrauterine death and 1 with infantile death, AVB (10 cases), syncope (5 cases), convulsion (5 cases), and others (items overlapped in some cases). Among the 31 neonatal cases, 18 (70%) were diagnosed within 2 days of life, and 8 of them had some significant fetal presentation (4 bradycardia or bradyarrhythmias, 4 tachyarrhythmias, and 1 hydrops), retrospectively.

As described above, the number of patients with LQTS diagnosed during infancy beyond the neonatal period was only 9. The clinical presentation of these patients included sinus bradycardia (5 cases), sudden cardiac death (SCD)/

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 by 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; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; PAC, premature atrial contraction; Pheny, phenytoin; PM, pacemaker; SCD, sudden cardiac death.