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Longitudinal change of cardiac electrical and autonomic function and potential risk factors in children with dravet syndrome

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ABSTRACT

Purpose: This study aimed to investigate cardiac electrical and autonomic function, the longitudinal changes, and the associated risk factors in children with Dravet syndrome (DS).

Methods: Twenty-four children with DS (11 boys, 13 girls; mean age, 7.2 ± 2.9 years) and 21 control subjects (9 boys, 12 girls; mean age, 8.2 ± 3.0 years) were enrolled in this study. P dispersion, QTc and QTc dispersion, and heart rate variability (HRV) were evaluated using standard electrocardiography and 24-hr Holter monitoring at the initial and follow-up study of the 6–12 months intervals.

Results: The DS group had significantly higher P dispersion ($p = 0.017$), QT and QTc dispersion values ($p < 0.001$ for two parameters) than the control group. Most HRV parameters, such as SDNN ($p < 0.001$), SDANN5 ($p < 0.001$), SDANN-index ($p = 0.001$), and RMSSD ($p = 0.006$) were all significantly lower in the DS group than in the control group. The mean values of initial QTc, QTc dispersion, and HRV parameters showed significantly increase (QTc and QTc dispersion) and decrease (HRV) in the follow-up study (mean duration: 1.2 ± 0.5 years) in 13 DS children. ± On multivariate regression analysis, epilepsy duration had an independently significant effect for the longitudinal change of QTc, QTc dispersion, and HRV.

Conclusions: DS children had significant different values of cardiac electrical and autonomic function compared with control group. Particularly, longer duration of epilepsy was significantly negative effect on the longitudinal change of cardiac autonomic function.

1. Introduction

Dravet syndrome (DS) is a severe epileptic encephalopathy that manifests in the first year of life in previously normal infants (Marini et al., 2007). Heterozygous mutations in the *SCN1 A* gene, encoding for neuronal sodium channel, are a major cause of DS and found in up to 75–80% of these patients (Marini et al., 2007). Sudden unexpected death in epilepsy (SUDEP) occurs more frequently in DS than in most other forms of severe epilepsy (Marini et al., 2007; Sakauchi et al., 2011). The underlying mechanisms of SUDEP remain debatable (Nashef et al., 2007), and suggested potential mechanisms include cardiac arrhythmia due to myocardial ischemia, arrhythmogenic drugs, electrolyte disturbances, spread of epileptic activity to the heart through the autonomic nervous system, and central or obstructive apnea (Stöllberger and Finsterer, 2004).

Because of the presence of epileptic syndromes caused by ion channel mutations, recent reports have speculated a pathogenic link between neuronal and cardiac channelopathies that could clarify the high incidence of SUDEP (Delogu et al., 2011; Nashef et al., 2007). Because the brain and heart share a similar ion channel setting, it could be reasonable to presume that neuronal ion channel mutations resulting in a central nervous system phenotype might also cause some pathologic function in myocardial cells related to a cardiac arrhythmogenic event, which might predispose patients to SUDEP. In a study by Delogu et al. (Delogu et al., 2011), DS patients had abnormal heart rate variability (HRV) suggesting a connection between cardiac autonomic

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dysfunction and SUDEP compared to both healthy children and patients with other forms of epilepsy, independent of antiepileptic therapy. Another study in children with DS reported that the decreased HRV and increased P wave and QT dispersion were important signs of autonomic dysfunction with increased adrenergic tone (Ergul et al., 2013). Recently, Myers et al suggest that autonomic dysfunction is associated with SUDEP risk in patients with epilepsy due to sodium channel mutations (Myers et al., 2018). However, few studies have evaluated the longitudinal change of cardiac electrical and autonomic functions and potential risk factors among children with DS.

Therefore, this study aimed to: (1) evaluate the electrocardiac characteristics and autonomic cardiac functions among children with DS compared to healthy children; (2) examine the longitudinal change of cardiac electrical and autonomic function, and (3) investigate the potential risk factors for cardiac autonomic dysfunction in children with DS using standard electrocardiography (ECG) and 24-hr Holter ECG monitoring.

2. Materials and methods

2.1. Patients

We included 24 patients diagnosed with DS (*SCN1 A* gene mutation demonstrated in all patients) at the Pediatric Neurology Department of Pusan National University Children's Hospital. Twenty-one sex- and age-matched healthy children were enrolled as the control group. The exclusion criteria were signs or symptoms of diseases known to influence cardiac electrical and autonomic functions including hypertension, renal disease, heart failure, diabetes, coronary artery, congenital or valvular heart diseases, cerebrovascular diseases, and use of antiarrhythmic (carbamazepine, phenytoin, or lamotrigine) or arrhythmic drugs (rufinamide, or lacosamide).

Information regarding demographic data, age at seizure onset, epilepsy duration, antiepileptic drugs (AEDs), and seizure frequency (per month) at the time of the electrocardiographic test was retrospectively collected from the patients' medical records. Most patients receiving AEDs were taking valproic acid, clobazam, topiramate, levetiracetam, and/or stripentol, and most children were on polytherapy of 3 or more AEDs. None were taking drugs like carbamazepine, phenytoin, lamotrigine, or lacosamide that could affect the ECG results. The baseline seizure frequency was calculated as the average value per month during the most recent 3 months of each patient's seizure diary.

2.2. Cardiac electrical and autonomic study

All patients and controls underwent a standard 12-lead ECG and a 24-hr ambulatory Holter ECG (DMS Cardioscan) as well as M-mode, 2D, and color Doppler echocardiography to exclude structural heart disease. None of the patients reported seizures during the 24-hr Holter recording period. Ventricular systolic and diastolic function was normal in all patients and controls. Digital recordings of all R-R intervals were edited automatically and a careful visual inspection was performed by two cardiologists who were blinded to the subjects' information.

All ECG strips were evaluated for rhythm, rate, QRS axis, PR, QRS, and QT and RR intervals as well as ventricular hypertrophy and arrhythmic abnormalities. The QT interval was measured on the standard 12-lead ECG, and the corrected QT interval (QTc) was calculated using the Fridericia formula ($QTcFri = QT/RR^{1/3}$). QT dispersion was calculated as the difference between the longest and the shortest QT interval; QTc dispersion was calculated in the same manner. P wave duration was measured over 3 consecutive cardiac cycles for each lead, and the average of these values was used in the analysis. P maximum and P minimum were defined as the longest and shortest durations among the 12 leads. P wave dispersion (P dispersion) was calculated as the difference between the maximum and minimum P wave durations (Babaoglu et al., 2011).

HRV was measured using 24-hr ambulatory 12-lead ECG Holter recordings in all subjects. The averaged values over 24 h were analyzed. The standard time domain measures of HRV were investigated for the analysis as follows: mean of normal RR intervals (NN), standard deviation for all NN intervals (SDNN), standard deviation of all RR intervals in successive 5-min segments of 24-hr ECG recording (SDANN5), mean of the standard deviation of all RR intervals for all 5-min segments (SDANN-index), and root-mean square differences between adjacent RR intervals (RMSSD) (Stein et al., 1994). Normal values of standard measures of HRV, which were obtained from studies in small numbers of subjects, are listed as 141 ± 39 ms for SDNN, 127 ± 35 ms for SDANN5, and 27 ± 12 ms for RMSSD (Stein et al., 1994). The above cardiac electrical and autonomic function was examined as the initial and follow-up study of 6–12 months' interval. The follow-up study was performed in 13 DS children. The difference or change between initial and follow-up study (D-RR, D–P dispersion, D-QT/QT dispersion, D-QTc/QTc dispersion, D-SDNN, D-SDANN5, D-SDANN-index, D-RMSSD) was investigated as the values of follow-up study minus those of initial test.

2.3. Standard protocol approvals, registrations, and patient consent

Ethical permission for this study was granted (number: 05-2015-110) by the Institutional Review Board of Pusan National University Yangsan Hospital and full informed written consent was obtained from each participant's family. The study complied with Helsinki Declaration standards.

2.4. Statistical analysis

The statistical analyses were performed using SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA) using raw scores. A two-tailed Chi-square test or Fisher's exact test was used to analyze categorical data, while Student's *t*-test was used to analyze normally distributed continuous variables. The Mann-Whitney *U* test was used to examine non-normally distributed continuous variables. For the comparison of initial vs follow-up electrocardiac tests in all patients, a paired *t*-test was used to evaluate the significant changes between the corresponding values. The relationship between two continuous variables was evaluated using Pearson's or Spearman's correlation as appropriate. Multivariate regression was used to identify factors that were independently associated with significant negative/positive change of the electrocardiac results. In all analyses, P values < 0.05 were considered statistically significant.

3. Results

3.1. Comparison of cardiac study findings of children with DS and controls

The demographic characteristics and initial electrocardiac results of the DS group (11 boys and 13 girls aged 2.5 − 11 years; mean age, 6.3 ± 2.9 years) and the controls (9 boys and 12 girls aged 4 − 12 years; mean age, 8.2 ± 3.0 years) are summarized in Table 1. No significant intergroup difference was found in age, sex, height, weight, or body mass index. Evaluation of the ECG revealed that RR interval, QT, and QTc intervals were similar between groups (Table 1). Children with DS had significantly higher values of P dispersion (58.0 ± 11.3 vs 46.2 ± 7.7 ms, $p = 0.017$), QT dispersion (119.6 ± 25.3 vs 76.1 ± 5.9 ms, $p < 0.001$) and QTc dispersion (118.0 ± 27.8 vs 77.1 ± 6.6 ms, $p < 0.001$) than the control group. Twenty-four-hour Holter ECG monitoring showed that nearly all HRV parameters, such as SDNN (89.9 ± 22.1 vs 126.3 ± 28.1 ms, $p < 0.001$), SDANN5 (74.1 ± 22.6 vs 112.3 ± 19.4 ms, $p < 0.001$), SDANN-index (40.6 ± 10.5 vs 63.3 ± 16.4 ms, $p = 0.001$), and RMSSD (35.1 ± 10.1 vs 48.9 ± 21.8 ms, $p = 0.006$) were all significantly lower in the DS group than in the control group (Table 1).

Table 1
Comparison of demographic profiles and cardiac electrical and autonomic test between patients and healthy controls.

	Total (N = 45)	DS (N = 24)	Control (N = 21)	*p* value
Male	20 (44.4%)	11 (45.8%)	9 (42.90%)	0.921
Age (years)	7.3 ± 3.0	6.3 ± 2.9	8.2 ± 3.0	0.223
Height (cm)	132.2 ± 19.8	128.1 ± 14.8	136.1 ± 21.4	0.074
Weight (kg)	29.4 ± 13.5	25.1 ± 6.5	31.7 ± 15.8	0.066
BMI (kg/m^2)	16.2 ± 30.0	15.9 ± 1.9	17.9 ± 2.3	0.095
Electrocardiac function				
RR interval (ms)	616.3 ± 48.1	623.5 ± 55.2	609.9 ± 28.2	0.151
P dispersion (ms)	51.7 ± 9.3	58.0 ± 11.3	46.2 ± 7.7	0.017*
QT (ms)	313.6 ± 24.7	320.7 ± 20.3	305.1 ± 26.3	0.075
QT dispersion (ms)	95.2 ± 32.3	119.9 ± 25.3	76.6 ± 5.9	< 0.001*
QTc (ms)	417.1 ± 20.9	421.7 ± 22.9	413.2 ± 15.5	0.226
QTc dispersion (ms)	95.9 ± 31.3	118.0 ± 27.8	77.1 ± 6.6	< 0.001*
NN (ms)	613.2 ± 66.1	607.8 ± 54.8	622.9 ± 42.4	0.077
SDNN (ms)	109.2 ± 30.7	89.9 ± 22.1	126.3 ± 28.1	< 0.001*
SDANN5 (ms)	93.1 ± 28.2	74.1 ± 22.6	112.3 ± 19.4	< 0.001*
SDANN-index (ms)	53.7 ± 19.3	40.6 ± 10.5	63.3 ± 16.4	0.001*
RMSSD (ms)	41.6 ± 17.7	35.1 ± 10.1	48.9 ± 21.8	0.006*

DS: Dravet syndrome; BMI: body mass index (kg/m^2); NN: mean of RR intervals; SDNN: standard deviation for all NN intervals; SDANN5: standard deviation of all RR intervals in successive 5-min segments; SDANN-index: mean of standard deviation of all RR intervals for all 5-min segments; RMSSD: root-mean square differences between adjacent RR intervals.

* $p < 0.05$: statistically significant.

3.2. Results and risk factors of the initial cardiac electrical tests in DS children

The initial cardiac electrical results and clinical characteristics of the children with DS were investigated and compared according to the epilepsy duration (Table 2). Mean epilepsy duration was 5.6 ± 4.2 years, and 14 (58.3%) showed the epilepsy duration of ≥ 5 years. They had significantly higher values of QT dispersion (130.9 ± 31.5 vs 102.2 ± 29.7 ms, $p = 0.021$), QTc (438.130.9 ± 31.5 vs 399.2 ± 55.4 ms, $p < 0.001$), and QTc dispersion (134.1 ± 25.5 vs 96.7 ± 15.7 ms, $p < 0.001$) than those of patients with shorter epilepsy duration (< 5 years). Most of HRV parameters including SDNN (78.5 ± 22.0 vs 105.1 ± 14.2 ms, $p < 0.001$), SDANN5 (61.0 ± 20.5 vs 91.5 ± 13.9 ms, $p < 0.001$), SDANN-index (33.8 ± 6.0 vs 49.7 ± 8.1 ms, $p < 0.001$), and RMSSD (27.5 ± 4.7 vs 45.2 ± 4.9 ms, $p < 0.001$) were significantly lower in the patients with longer epilepsy duration (≥ 5 years) than in them with shorter duration (< 5 years) (Table 2).

On multivariate regression analysis, longer epilepsy duration of ≥ 5 years were significantly associated with higher QTc ($p = 0.021$) and QTc dispersion ($p = 0.019$), and lower SNDD ($p = 0.033$), SDANN5 ($p = 0.044$), SDANN-index ($p = 0.025$), and RMSSD ($p = 0.021$) (Table 3). A much higher number of AEDs was meaningfully associated with lower SDNN ($p = 0.036$). Higher seizure frequency was significantly associated with lower SDANN-index ($p = 0.017$). The remaining factors did not contribute significantly to the multivariate models.

Table 2
Clinical characteristics of Dravet syndrome children and difference of the cardiac electrical function according to the duration of epilepsy.

Duration of epilepsy	Total DS (N = 24)	≥ 5 years (N = 14)	< 5 years (N = 10)	*p* value
Male	11 (45.8%)	6 (43.8%)	5 (50.5%)	0.729
Age (years)	6.3 ± 2.9	8.4 ± 1.5	4.0 ± 0.7	< 0.001*
Age of seizure onset (years)	0.6 ± 0.1	0.5 ± 0.2	0.6 ± 0.1	0.517
Duration of epilepsy (years)	5.6 ± 4.2	7.8 ± 4.7	3.4 ± 2.1	< 0.001*
Number of AEDs	4.4 ± 1.1	4.9 ± 1.0	3.7 ± 0.8	0.011*
Seizure type				0.539
Focal	9 (37.5%)	5 (35.7%)	4 (40.0%)	
Generalized	15 (62.5%)	9 (64.3%)	6 (60.0%)	
Seizure frequency (monthly)	4.4 ± 2.6	5.2 ± 2.3	3.4 ± 2.6	0.069
Electrocardiac function				
RR interval (ms)	623.5 ± 55.2	639.2 ± 79.7	606.2 ± 82.2	0.059
P dispersion (ms)	58.0 ± 11.3	59.2 ± 9.9	56.2 ± 11.3	0.066
QT (ms)	320.7 ± 20.3	319.1 ± 32.0	322.9 ± 48.6	0.628
QT dispersion (ms)	119.9 ± 25.3	130.9 ± 31.5	102.2 ± 29.7	0.021*
QTc (ms)	421.7 ± 22.9	438.5 ± 41.7	399.2 ± 55.4	< 0.001*
QTc dispersion (ms)	118.0 ± 27.8	134.1 ± 25.5	96.7 ± 15.7	< 0.001*
NN (ms)	607.8 ± 54.8	589.8 ± 42.1	621.5 ± 45.7	0.062
SDNN (ms)	89.9 ± 22.1	78.5 ± 22.0	105.1 ± 14.2	< 0.001*
SDANN5 (ms)	74.1 ± 22.6	61.0 ± 20.5	91.5 ± 13.9	< 0.001*
SDANN-index (ms)	40.6 ± 10.5	33.8 ± 6.0	49.7 ± 8.1	< 0.001*
RMSSD (ms)	35.1 ± 10.1	27.5 ± 4.7	45.2 ± 4.9	< 0.001*

DS: Dravet syndrome; AEDs: antiepileptic drugs; NN: mean of RR intervals; SDNN: standard deviation for all NN intervals; SDANN5: standard deviation of all RR intervals in successive 5-min segments; SDANN-index: mean of standard deviation of all RR intervals for all 5-min segments; RMSSD: root-mean square differences between adjacent RR intervals.

* $p < 0.05$: statistically significant.

Table 3
Multivariate regression for potential risk factors affecting the values of initial cardiac electrical and autonomic test in children with Dravet syndrome.

	Variables	Estimate	Standardized	T value	Pr(> |t|)
QTc					
	Duration of ≥ 5 yrs	52.968	1.074	3.370	0.021*
	Number of AEDs	1.657	0.069	0.329	0.748
QTc dispersion					
	Duration of ≥ 5 yrs	53.466	0.857	2.234	0.019*
	Number of AEDs	15.414	0.510	2.037	0.064
SDNN					
	Duration of ≥ 5 yrs	−8.835	0.158	0.617	0.033*
	Number of AEDs	−6.383	−0.637	−3.411	0.036*
	Sz frequency (mo)	−2.949	−0.329	−1.532	0.154
SDANN5					
	Duration of ≥ 5 yrs	−6.132	0.008	0.024	0.044*
	Number of AEDs	−3.428	−0.453	−1.999	0.073
	Sz frequency (mo)	−3.740	−0.421	−1.603	0.140
SDANN-index					
	Duration of ≥ 5 yrs	−11.608	−0.502	−2.159	0.025*
	Number of AEDs	−0.792	−0.071	−0.416	0.685
	Sz frequency (mo)	−2.638	−0.552	−2.823	0.017*
RMSSD					
	Duration of ≥ 5 yrs	−13.982	−0.710	−2.140	0.021*
	Number of AEDs	−1.365	−0.143	−0.578	0.574
	Sz frequency (mo)	−0.389	−0.020	−0.094	0.927

AEDs: antiepileptic drugs; Sz: seizure.
* $p < 0.05$: statistically significant.

3.3. Longitudinal change of cardiac electrical and autonomic function between initial and follow-up studies and independent risk factors in DS children

Out of 24 DS children, 13 (54.2%) were performed the follow-up studies including a standard 12-lead ECG and a 24-hr ambulatory Holter ECG. The remaining 11 children were underwent the only initial examination. No significant difference was revealed in age (6.1 ± 2.5 vs 6.4 ± 3.1 years, $p = 0.617$), sex (boys, 46.2% vs 45.5%, $p = 0.745$), epilepsy duration (5.5 ± 2.7 vs 5.8 ± 3.2, $p = 0.818$), seizure frequency (3.9 ± 2.6 vs 4.9 ± 2.7 per month, $p = 0.299$), and number of AEDs (4.0 ± 1.1 vs 4.6 ± 1.9, $p = 0.195$) between the 13 patients with the follow-up tests and the other 11 children. The mean follow-up duration of the 13 children was 1.1 ± 0.4 years, and the mean epilepsy duration at the follow-up tests was 6.6 ± 3.1 years (not shown in Table). The mean values of the initial QTc and QTc dispersion were 419.5 ± 39.7 ms and 117.4 ± 22.9 ms, and those of the follow-up QTc and QTc dispersion were 432.5 ± 45.4 ms and 131.4 ± 32.2 ms, which achieved longitudinally significant increase (D-QTc = 12.9 ± 11.1, $p = 0.045$; D-QTc dispersion = 13.9 ± 8.8, $p = 0.014$) (Fig. 1A). Most of the follow-up HRV parameters showed longitudinally significant decreased values (D-SDNN = −6.7 ± 7.1, $p = 0.017$; D-SDANN5 = −4.9 ± 5.2, $p = 0.041$; D-SDNN-index = −3.3 ± 3.2, $p = 0.044$; D-RMSSD = −3.7 ± 4.1, $p = 0.035$) (Fig. 1B). The longitudinal data of the initial and follow-up studies of the 13 individual were presented in Fig. 2.

On multivariate regression analysis, we investigated the independent risk factors affecting the difference of values between the initial and follow-up cardiac electrical studies in 13 DS children through multivariate regression analysis (Table 4). Longer epilepsy duration (or more than 5 years) had a significant effect on longitudinal change with increase of D-QTc ($p = 0.015$) and D-QTc dispersion ($p = 0.011$) and decrease of HRV parameters (D-SDNN, $p < 0.001$; D-SDANN5, $p < 0.001$; D-SDANN-index, $p < 0.001$; D-RMSSD, $p = 0.025$). Age of seizure onset, number of AEDs, seizure type and seizure frequency did not contribute significantly to the multivariate models.

4. Discussion

Electrocardiac characteristics and autonomic cardiac functions in 24 children with DS were evaluated in this study using standard ECG and 24-hr Holter ECG monitoring. The most important results obtained

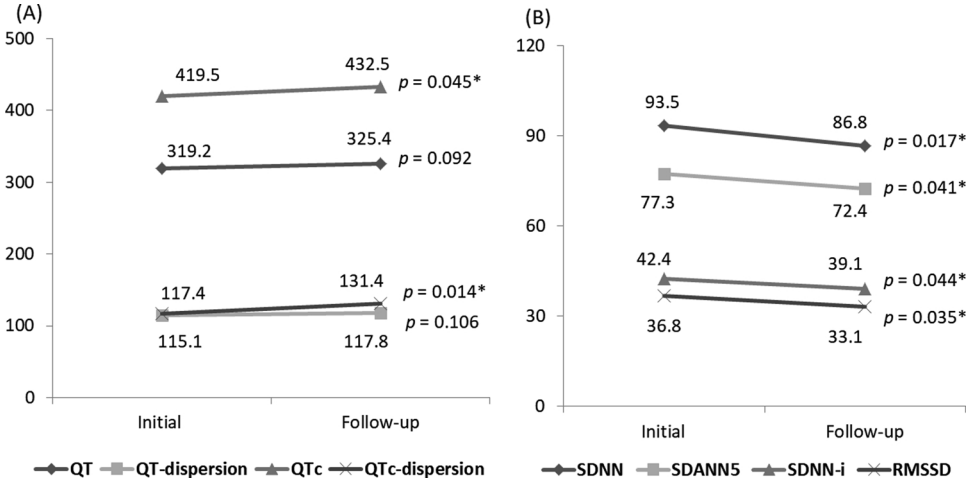

Fig. 1. The longitudinal change of the mean values between the initial and follow-up cardiac electrical and autonomic studies showed a significant increase of QTc and QTc dispersion (A), and a significant decrease of SDNN, SDANN5, SDNN-index, and RMSSD (B). (QTc dispersion, the difference between the longest and the shortest QTc interval; SDNN, standard deviation for all normal RR intervals; SDANN5, standard deviation of all RR intervals in successive 5-min segments of 24-hr ECG recording; SDANN-index, mean of the standard deviation of all RR intervals for all 5-min segments; RMSSD, root-mean square differences between adjacent RR intervals).

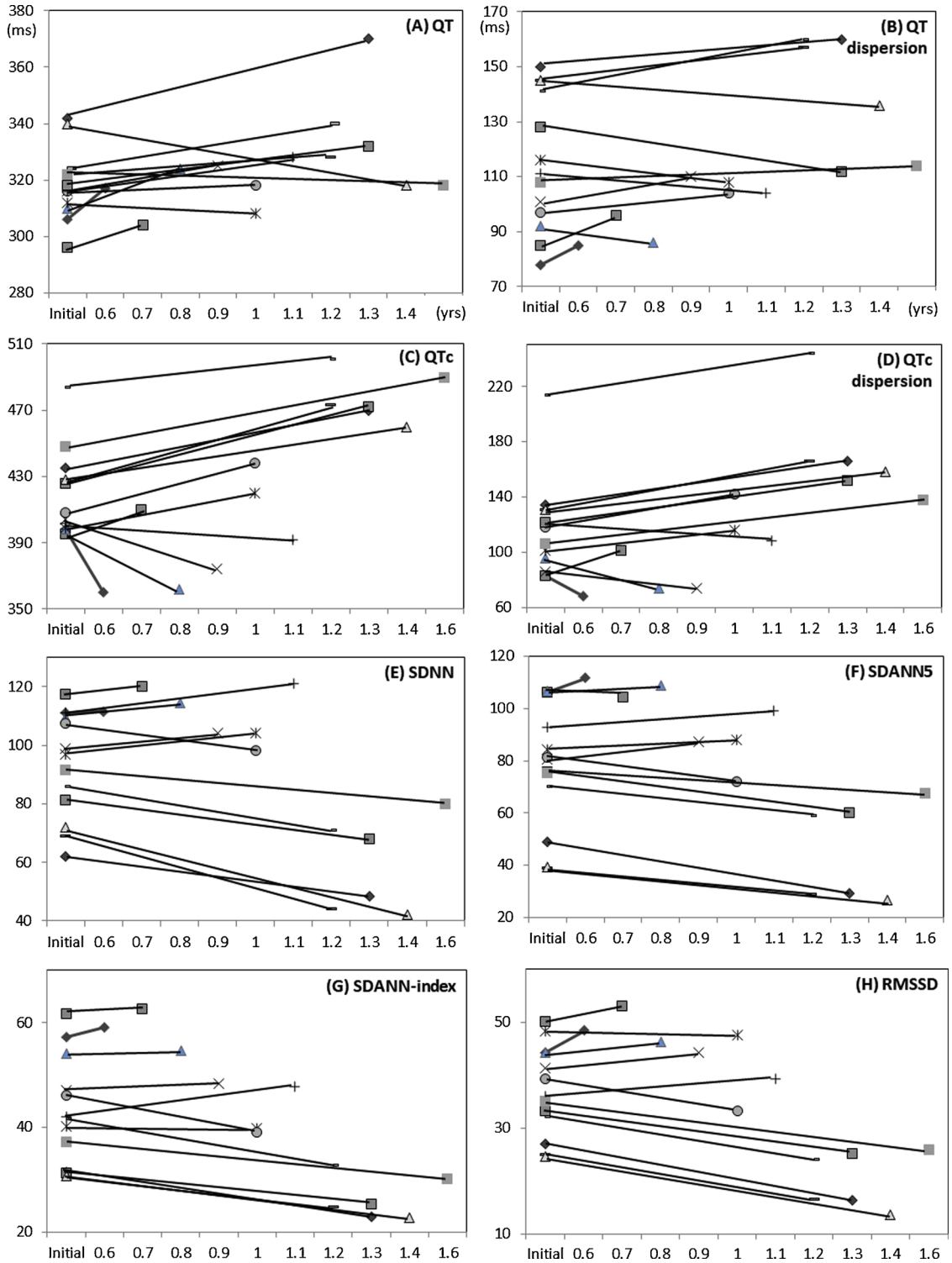

Fig. 2. Thirteen patients of Dravet syndrome were examined the cardiac electrical and autonomic studies (A–H) at the initial and follow-up visit. Each line presented the longitudinal data of the individual patient. The duration of follow-up studies was from 0.6 to 1.6 years (x-axis). The longitudinal change showed a tendency of increase of QTc and QTc dispersion (C, D), or of decrease of SDNN, SDANN5, SDNN-index, and RMSSD (E–H) in the patients with longer follow-up and epilepsy duration. The statistical significance of these patients' results was summarized in Fig. 1. (QT dispersion, the difference between the longest and the shortest QT interval; QTc dispersion, the difference between the longest and the shortest QTc interval; SDNN, standard deviation for all normal RR intervals; SDANN5, standard deviation of all RR intervals in successive 5-min segments of 24-hr ECG recording; SDANN-index, mean of the standard deviation of all RR intervals for all 5-min segments; RMSSD, root-mean square differences between adjacent RR intervals).

were as follows: significantly lower values of all HRV parameters (SDNN, SDANN5, SDANN-index, and RMSSD) and meaningfully higher P dispersion, QT and QTc dispersion in DS children than in healthy controls. Longer epilepsy duration (≥5 years), more numerous AEDs, and higher seizure frequency were independently associated with a significant decline of HRV among the DS children. In particular, longer epilepsy duration had a significant effect on longitudinal change of QTc, QTc dispersion, and HRV parameters on multivariate regression

Table 4
Multivariate regression for potential risk factors affecting the longitudinal change of different values between the initial and follow-up cardiac electrical and autonomic studies.

	Variables	Estimate	Standardized	T value	Pr(> |t|)
D-QTc					
	Duration	27.618	2.306	0.670	0.520
	Duration of ≥ 5 years	35.300	0.573	2.785	0.015*
	Sz frequency (/mo)	3.476	0.288	1.402	0.184
D-QTc-dispersion					
	Duration	5.158	0.988	0.292	0.777
	Duration of ≥ 5 years	15.784	0.588	2.986	0.011*
	Sz frequency (/mo)	1.593	0.303	1.541	0.147
D-SDNN					
	Duration	−3.421	−0.816	−5.284	< 0.001*
	Sz frequency (/mo)	1.899	0.082	0.304	0.767
D-SDANN5					
	Duration	−2.820	−0.832	−5.620	< 0.001*
	Sz frequency (/mo)	−0.564	−0.165	−0.357	0.730
D-SDANN-index					
	Duration	−1.321	−0.824	−5.433	< 0.001*
	Sz frequency (/mo)	−0.696	−0.431	−0.879	0.405
D-RMSSD					
	Duration	−1.105	−0.760	−0.140	0.025*
	Sz frequency (/mo)	−0.752	−0.297	−0.722	0.488

D-: difference of values between the initial and follow-up studies; Sz: seizure.
* $p < 0.05$: statistically significant.

analysis.

The underlying mechanisms of SUDEP remain uncertain, although both the respiratory and cardiac systems are thought to be involved (Delogu et al., 2011; Nashef et al., 2007). As seizures usually cause sinus tachycardia or tachyarrhythmia, impaired vagal activity and excessive autonomic changes during seizures would fail to restore a normal HR and may facilitate the development of ventricular arrhythmia or serious ischemia (Lotufo et al., 2012; Hirsch et al., 2011). Another study revealed that the presenting arrhythmia for sudden cardiac arrest in epileptic patients was more likely to be bradycardia/asystole, suggesting increased parasympathetic tone (Stecker et al., 2013). A potential link between some courses of epilepsy and life-threatening arrhythmias was recently suggested by the finding that their pathogenic mechanisms rely on the presence of genetic mutations of neuronal ion channels, which may appear in those responsible for genetically determined arrhythmogenic diseases associated with the risk of sudden cardiac death (Glasscock, 2014).

At least nine neurocardiac genes have been linked to SUDEP in human or animal studies (Glasscock, 2014). These nine genes can be grouped generally into five “brain” (*KCNA1, SCN1 A, SCN8A, HCN2,* and *PRRT2*) and four “heart” (*KCNQ1, KCNH2, SCN5A,* and *RYR2*) genes depending on their predominant expression pattern, but all show some degree of neurocardiac co-expression, such as epilepsy, arrhythmia, and SUDEP. *SCN1 A* encodes the α-subunit of voltage-gated Nav1.1 sodium channels, which show high levels of expression in the brain and lower levels in the heart (Noda et al., 1986). Nav1.1 channels are distributed throughout the human and rodent brain with the highest proportions in neurons of the hippocampus, thalamus, cerebellum, and brainstem (Ogiwara et al., 2007; Yu et al., 2006). The channels also exhibit specific localization to the transverse tubules of the ventricles and the sinoatrial node where they are important for excitation–contraction coupling and HR control, respectively (Maier et al., 2002, 2003). *SCN1 A*-related seizure disorders encompass a spectrum that ranges from simple febrile seizures and generalized epilepsy with febrile seizures plus at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures at the severe end (Meisler et al., 2010). The incidence of SUDEP in children is higher in DS than in other epilepsies (Delogu et al., 2011; Sakauchi et al., 2011). Particularly, patients with DS have decreased HRV and increased P interval and QT dispersion on ECG recordings, findings suggestive of augmented sympathetic tone that could contribute to neurocardiac dysfunction and SUDEP (Delogu et al., 2011; Ergul et al., 2013). Therefore, SUDEP risk is increased in cases of DS and a genetic influence of the *SCN1 A* mutation cannot be excluded.

HRV is the fluctuation in the time intervals between adjacent heartbeats generated by heart–brain interactions (Shaffer and Ginsberg, 2017). HRV is a known critical protective mechanism of the autonomic nervous system, and its optimal value is associated with self-regulatory capacity. The confirmed reference values of HRV among healthy children have not been evaluated until now (Shaffer and Ginsberg, 2017). Low HRV is strongly predictive of increased risk in coronary events or sudden cardiac death (Buccelletti et al., 2009). Repetitive seizures that repetitively stimulate cerebral autonomic centers and cardiac conducting system, which is more common in medically refractory epilepsy, may play a role in the interictal decreased HRV (Suorsa et al., 2011). Our results were able to confirm those of previous reports that HRV of patients with intractable epilepsy like DS demonstrated obvious lower values than healthy controls (Delogu et al., 2011; Ergul et al., 2013; Baysal-Kirac et al., 2017). It is known that increased QT and P dispersion can be a sign of autonomic dysfunction and that these conditions can lead to ventricular and atrial dysrhythmias (Li et al., 2002). The larger the QT dispersion, the higher the risk of reentry arrhythmia, a phenomenon that is not age- or sex-dependent (Surges et al., 2010). A seizure in the presence of pathologic QT dispersion can suddenly increase the risk of cardiac arrhythmia. To summarize, autonomic dysfunction–related augmented sympathetic tone can cause an increase in QT dispersion since it decreases HRV (Stein et al., 1994; Malik and Batchvarov, 2000).

Previous three studies (Delogu et al., 2011; Ergul et al., 2013; Myers et al., 2018) have evaluated autonomic dysfunction and electrical activities in children with DS. Delogu et al. (Delogu et al., 2011) reported that 20 DS patients had lower HRV than other epilepsy patients and healthy subjects. In the study by Ergul et al. (Ergul et al., 2013), the decreased HRV and increased P wave and QT dispersion seen in DS patients were important signs of autonomic dysfunction with increased adrenergic tone. Myers et al. (Myers et al., 2018) documented that awake HRV was lower in the SUDEP patients and in drug-resistant epilepsy patients with SCN mutations compared to those with non-SCN epilepsy. They suggest HRV has potential as a biomarker of SUDEP risk. Our 28 DS children had significantly lower values of all HRV parameters (SDNN, SDANN5, SDANN-index, and RMSSD) and much higher QT and QTc dispersion than healthy controls. We performed the longitudinally follow-up study in 54.2% (13/24) of our DS children, and they had a significant change of the values with increase of QTc and QTc dispersion and decrease of HRV parameters. In addition, longer epilepsy duration showed a significant effect on above longitudinal change between the initial and follow-up cardiac electrical studies on multivariate regression analysis, which can suggest that longer epilepsy duration can be potential risk factor associated with cardiac autonomic dysfunction. To our knowledge, our study is the first to investigate the longitudinal change through the follow-up study and the potential risk factors associated with cardiac autonomic dysfunction in DS children.

Our study had some limitations. First, it included a small number of patients. Second, we didn’t evaluate and compared with those of the patients with other drug-resistant epilepsy. Third, we lack a baseline study at the seizure onset or before the start of AEDs medication, so we cannot demonstrate the results of the longitudinal change compared to their baseline values of HRV and QTc/QTc dispersion. Finally, the follow-up studies were not performed in any control children. It was

practically difficult because they examined the cardiac test for their subjective symptoms including palpitation or chest discomfort. We were not able to demonstrate there were any changes or not in the examined parameters with aging. For these reasons, further long-time follow-up studies are necessary to assess whether the cardiac autonomic imbalance found in DS patients is closely associated with the risk of SUDEP in DS.

5. Conclusions

In conclusion, our children with DS, all of whom had the *SCN1 A* mutation, had lower HRV parameters and higher values of QT and QTc dispersion than those in the control group. Lower HRV can develop due to excessive sympathetic activity, and is considered a possible sign of cardiac autonomic dysfunction, thus it would be reasonable to speculate that *SCN1 A* mutation in DS patients may be linked to subclinical autonomic dysfunction by the interruption of cardiac adrenergic activity. In particular, DS children with long-term epilepsy duration may be exposed to risk of longitudinally deteriorating cardiac autonomic dysfunction with significant lower HRV. Therefore, there may be not only a genetic predisposition to these cardiac changes, but that the duration of epilepsy may be a factor that predisposes to SUDEP risk. Twenty-four-hr Holter ECG recordings could be useful for detecting an increased risk of cardiac autonomic dysfunction in DS children. To determine whether autonomic dysfunction is significantly correlated with SUDEP in DS, much long-term longitudinal and wider prospective studies are needed.

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We declare no financial relationships relevant to this article.

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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References

Babaoglu, K., Altun, G., Binnetoğlu, K., 2011. P-wave dispersion and heart rate variability in children with mitral valve prolapse. Pediatr. Cardiol. 32, 449–454. https://doi.org/10.1007/s00246-011-9892-0.

Baysal-Kirac, L., Serbest, N.G., Şahin, E., et al., 2017. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy Behav. 71, 60–64. https://doi.org/10.1016/j.yebeh.2017.04.018.

Buccelletti, E., Gilardi, E., Scaini, E., et al., 2009. Heart rate variability and myocardial infarction: systematic literature review and metaanalysis. Eur. Rev. Med. Pharmacol. Sci. 13, 299–307. https://www.researchgate.net/publication/26754890.

Delogu, A.B., Spinelli, A., Battaglia, D., et al., 2011. Electrical and autonomic cardiac function in patients with Dravet syndrome. Epilepsia 52 (Suppl. 2), 55–58. https://doi.org/10.1111/j.1528-1167.2011.03003.x.

Ergul, Y., Ekici, B., Tatli, B., et al., 2013. QT and P wave dispersion and heart rate variability in patients with Dravet syndrome. Acta Neurol. Belg. 113, 161–166. https://doi.org/10.1007/s13760-012-0140-z.

Glasscock, E., 2014. Genomic biomarkers of SUDEP in brain and heart. Epilepsy Behav. 38, 172–179. https://doi.org/10.1016/j.yebeh.2013.09.019.

Hirsch, L.J., Donner, E.J., So, E.L., et al., 2011. Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy. Neurology 31, 1932–1938. https://doi.org/10.1212/WNL.0b013e31821de7de.

Li, Z., Hertervig, E., Carlson, J., et al., 2002. Dispersion of refractoriness in patients with paroxysmal atrial fibrillation. Evaluation with simultaneous endocardial recordings from both atria. J. Electrocardiol. 35, 227–234. https://doi.org/10.1054/jelc.2002.33973.

Lotufo, P.A., Valiengo, L., Benseñor, I.M., et al., 2012. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 53, 272–282. https://doi.org/10.1111/j.1528-1167.2011.03361.x.

Maier, S.K., Westenbroek, R.E., Schenkman, K.A., et al., 2002. An unexpected role for brain-type sodium channels in coupling of cell surface depolarization to contraction in the heart. Proc. Natl. Acad. Sci. U. S.A. 99, 4073–4078. https://doi.org/10.1073/pnas.261705699.

Maier, S.K., Westenbroek, R.E., Yamanushi, T.T., et al., 2003. An unexpected requirement for brain-type sodium channels for control of heart rate in the mouse sinoatrial node. Proc. Natl. Acad. Sci. U. S. A. 100, 3507–3512. https://doi.org/10.1073/pnas.2627986100.

Malik, M., Batchvarov, V.N., 2000. Measurement, interpretation and clinical potential of QT dispersion. J. Am. Coll. Cardiol. 36, 1749–1766. https://doi.org/10.1016/S0735-1097(00)00962-1.

Marini, C., Mei, D., Temudo, T., et al., 2007. Idiopathic epilepsies with seizures precipitated by fever and SCN1A abnormalities. Epilepsia 48, 1678–1685. https://doi.org/10.1111/j.1528-1167.2007.01122.x.

Meisler, M.H., O'Brien, J.E., Sharkey, L.M., 2010. Sodium channel gene family: epilepsy mutations, gene interactions and modifier effects. J. Physiol. (Paris) 588, 1841–1848. https://doi.org/10.1113/jphysiol.2010.188482.

Myers, K.A., Bello-Espinosa, L.E., Symonds, J.D., et al., 2018. Heart rate variability in epilepsy: a potential biomarker of sudden unexpected death in epilepsy risk. Epilepsia 59, 1372–1380. https://doi.org/10.1111/epi.14438.

Nashef, L., Hindocha, N., Makoff, A., 2007. Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. Epilepsia 48, 859–871. https://doi.org/10.1111/j.1528-1167.2007.01082.x.

Noda, M., Ikeda, T., Kayano, T., et al., 1986. Existence of distinct sodium channel messenger RNAs in rat brain. Nature 320, 188–192. https://doi.org/10.1038/320188a0.

Ogiwara, I., Miyamoto, H., Morita, N., et al., 2007. Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J. Neurosci. 27https://doi.org/10.1523/JNEUROSCI.5270-06.2007. 5903 – 514.

Sakauchi, M., Oguni, H., Kato, I., et al., 2011. Mortality in Dravet syndrome: search for risk factors in Japanese patients. Epilepsia 52 (Suppl. 2), 50–54. https://doi.org/10.1111/j.1528-1167.2011.03002.x.

Shaffer, F., Ginsberg, J.P., 2017. An overview of heart rate variability metrics and norms. Front. Public Health 5, 258. https://doi.org/10.3389/fpubh.2017.00258.

Stecker, E.C., Reinier, K., Uy-Evanado, A., et al., 2013. Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: a community-based study. Circ. Arrhythm. Electrophysiol. 6, 912–916. https://doi.org/10.1161/CIRCEP.113.000544.

Stein, P.K., Bosner, M.S., Kleiger, R.E., et al., 1994. Conger BM. Heart rate variability: a measure of cardiac autonomic tone. Am. Heart J. 127, 1376–1381. https://doi.org/10.1016/0002-8703(94)90059-0.

Stöllberger, C., Finsterer, J., 2004. Cardiorespiratory findings in sudden unexplained/unexpected death in epilepsy (SUDEP). Epilepsy Res. 59, 51–60. https://doi.org/10.1016/j.eplepsyres.2004.03.008.

Suorsa, E., Korpelainen, J.T., Ansakorpi, H., et al., 2011. Heart rate dynamics in temporal lobe epilepsy-A long-term follow-up study. Epilepsy Res. 93, 80–83. https://doi.org/10.1016/j.eplepsyres.2010.10.005.

Surges, R., Taggart, P., Sander, J.W., et al., 2010. Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. Epilepsia 51, 738–744. https://doi.org/10.1111/j.1528-1167.2010.02571.x.

Yu, F.H., Mantegazza, M., Westenbroek, R.E., et al., 2006. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat. Neurosci. 9, 1142–1149. https://doi.org/10.1038/nn1754.