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ORIGINAL ARTICLE
Miscellaneous

CTG repeat length underlying cardiac events and sudden death in myotonic dystrophy type 1

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Aims Myotonic dystrophy Type 1 (DM1) is caused by the expansion of CTG repeats (CTGn) in the DM1 protein kinase (DMPK) gene, while it remains unclear whether CTGn may be associated with the incidence of cardiac events or sudden death in Japan as well as Europe. The aim of this study was to investigate the association between CTGn and cardiac involvements.

Methods and results This cohort study included patients with DM1 who were retrospectively recruited from nine Japanese hospitals specializing in neuromuscular diseases. A total of 496 patients with DM1 who underwent a genetic test in the DMPK gene were analysed. Patients with congenital form or under 15 years old were excluded and patients were assigned into the quartiles. When we compared the incidence of cardiac events including advanced/complete atrioventricular block, pacemaker implantation, and ventricular tachycardias or mortality among four groups, patients with 1300 or longer CTGn experienced composite cardiac events [hazard ratio (HR): 3.19, 95% confidence interval (CI): 1.02–9.99, $P = 0.014$] more frequently and had significantly higher mortality rate (HR: 6.79, 95% CI: 2.05–22.49, $P < 0.001$) than those under 400 CTGn while the rate of sudden death was not significantly different.

Conclusion Regarding the cardiac events and mortality in patients with DM1, patients with 1300 or longer CTGn are at especially high risk.

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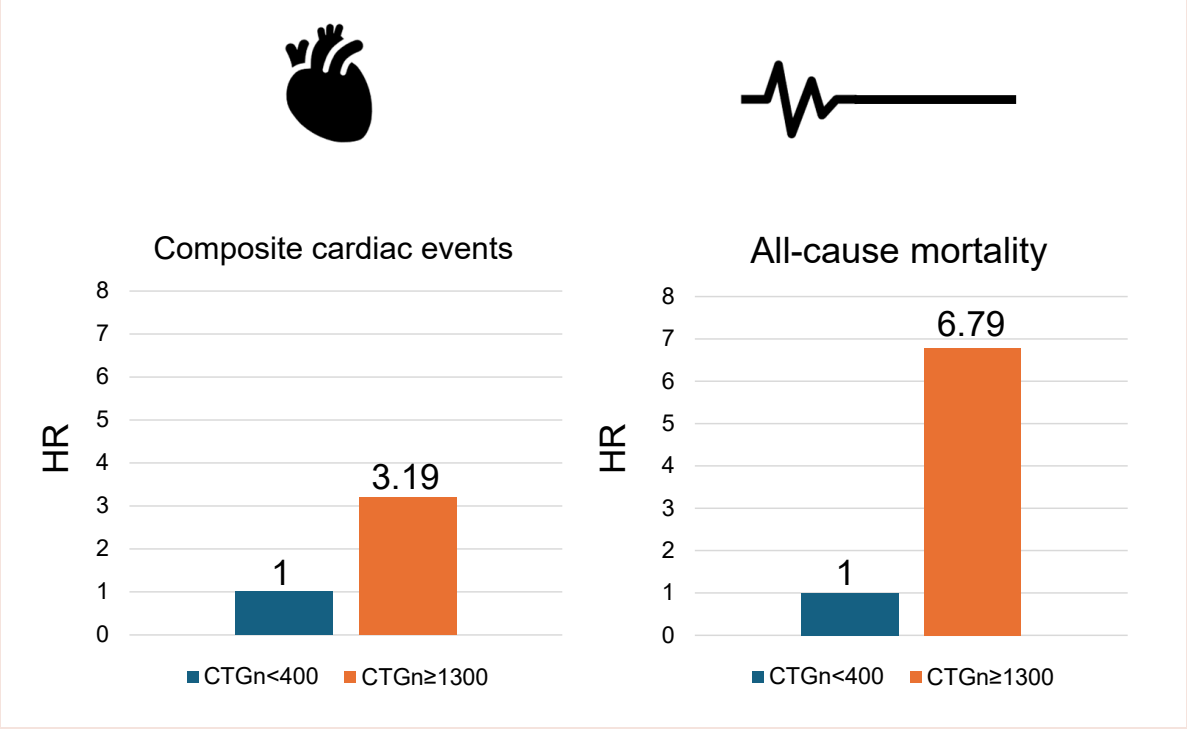
Graphical abstract



Keywords Myotonic dystrophy • Conduction disease • Sudden death

Introduction

Myotonic dystrophy is a multisystemic disorder characterized by muscle stiffness and wasting, central nervous system dysfunction, impaired glucose metabolism, cardiac conduction diseases, sudden death, or respiratory failure. This is the most common neuromuscular disease, with an incidence rate of 1 case per 3000–8000 individuals.[1,2] Genetic analysis has revealed two genetic subtypes underlying myotonic dystrophy: myotonic dystrophy Type 1 (DM1) and DM2. Myotonic dystrophy Type 1 is established as Steinert's disease with an autosomal dominant inheritance that is associated with the length of CTG repeats (CTGn) in the DM1 protein kinase (DMPK) gene (i.e. >50 CTGn in DM1 vs. <35 CTGn in normal controls).[3] The mRNA transcription from the expanded CTGn in the 3′ untranslated region led to the aggregation of muscleblind-like protein 1 (MBNL1), which is associated with alternative splicing of the cardiac sodium channel gene sodium voltage-gated channel alpha subunit 5, *SCN5A*. Consequently, the inhibition of MBNL1 fails to result in alteration in the expression of adult sodium channels instead of foetal sodium channels through alternative splicing.[4] Compared with the adult type, the foetal cardiac sodium channel abolishes its function by the shift of the activation curve to the depolarized side.[5] This causes cardiac sequelae, including conduction disorders, ventricular tachyarrhythmias, or sudden death.[6]

The length of CTGn ranges from several dozens to thousands of repeats among patients with DM1.[7] A French retrospective study which examined the correlation between CTG length and clinical phenotypes among patients with DM1 have demonstrated that extreme CTGn are linked to several phenotypes when compared with shorter CTGn.[8] In our previous study of patients with DM1 treated in nine hospitals, cardiac events (e.g. pacemaker implantation, advanced atrioventricular block, or ventricular tachyarrhythmias) were associated with cardiac conduction disorders, such as PQ interval of ≥240 ms or QRS width of ≥120 ms in the electrocardiogram (ECG)[9] while it remains unclear whether the CTG repeat size corresponding to the length of CTGn could be associated with cardiac conduction disorders, cardiac events, or mortality in Asia. The purpose of this study is to evaluate the correlation between CTGn and cardiac involvements or mortality among 496 patients with DM1 in Japan.

Methods

Patients

As mentioned in our previous report,[9] the institutional review board of each participating centre approved this retrospective study (approval number, R2015-058 in Shiga University of Medical Science). This study was publicly declared and written informed consent was waived because of its retrospective design. None of the patients refused to participate in the study.

A total of 528 patients with DM1 who had attended or been hospitalized from January 2006 to October 2016 in nine hospitals specializing in neuromuscular diseases were recruited in this study. Patients underwent Southern blot as a genetic test to confirm that the length of CTGn in the 3′ untranslated region of DMPK was ≥50. Notably, 32 patients were excluded from this analysis. The exclusion criteria were the presence of congenital DM1 or age <15 years ($n = 28$), Charcot–Marie–Tooth disease ($n = 1$), double entry ($n = 1$), and unclear number of CTGn ($n = 2$).

Consequently, 496 patients with DM1 were retrospectively analysed during the follow-up. We evaluated the following clinical and genetic characteristics: age, sex, smoking, number of CTGn, medical history including the implantation of pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy, consecutive ECGs, activities of daily living, nutritional support, respiratory support including oxygen, tracheotomy, non-invasive positive pressure ventilation, or ventilator, and medications. The durations of the clinical follow-up periods were 95 ± 66, 98 71, 88 ± 65, and 104 ± 83 months from Groups 1 to 4 ($P = 0.324$). The times of ECG examinations were 7.2 ± 6.2, 9.2 ± 8.0, 10 ± 10, and 12 ± 10 from Groups 1 to 4 ($P = 0.002$).

Depending on the quartiles of CTGn, patients were assigned into four groups: Group 1 (<400 CTGn; $n = 106$), Group 2 ($400 \leq$ CTGn < 800; $n = 124$), Group 3 ($800 \leq$ CTGn < 1300; $n = 134$), and Group 4 ($1300 \leq$ CTGn; $n = 132$). Cardiac events were defined as advanced/complete atrioventricular block, pacemaker implantation, or documented ventricular tachyarrhythmias. Sudden death was defined as death occurring suddenly (within 1 h after the onset of new symptoms) and unexpectedly (even if unwitnessed) in patients who were stable for 24 h prior to the event.[6] The first-degree atrioventricular block was defined as PR interval over 200 ms. Regarding supraventricular tachyarrhythmias, we evaluated the occurrence of atrial fibrillation or atrial flutter in this study. Atrial fibrillation was defined as an ECG with f-wave instead of P-wave and irregular RR interval. Atrial flutter was a narrow QRS tachycardia with saw-tooth pattern of inverted flutter wave or as an arrhythmia with F-wave. Sustained ventricular tachycardia was defined as wide QRS tachycardia which consisted of consecutive ventricular beats with 30 s or longer and a higher heart rate than 100 b.p.m. Ventricular fibrillation was defined as ventricular contractions with 300 beats or more per minute.

Genetic analysis

DNA analysis for the CTG repeat expansion size was performed in certified clinical laboratories. In Japan, only Southern blot analysis is approved by the government for health insurance purposes. High molecular weight DNA was extracted from peripheral blood samples, digested using two or three restriction enzymes (EcoRI and BamH1, or EcoRI, BglI, and PstI), and then electrophoresed. Southern blotting was subsequently performed. The number of repeats was determined based on the band sizes obtained. Samples that did not show expansion or were suspected of premutation by Southern blotting were subjected to fragment analysis. After PCR amplification of the DMPK CTG repeat region, capillary electrophoresis was performed using GeneMapper software (Thermo Fisher Scientific) for the analysis.

Electrocardiogram

A total of 4906 ECGs were collected in this study. PR, QRS, QT, and RR intervals were measured in the initial ECG, and the QTc interval was calculated using the Bazett formula.[10] JTc interval was calculated as (QTc − QRS). Electrocardiograms performed during pacemaker stimulations were excluded from the measurements. Complete right bundle branch block (RBBB) and left bundle branch block (LBBB) were classified according to the criteria based on previous reports.[11,12]

Statistical analysis

Baseline characteristics were presented as means and standard deviations for continuous variables and as numbers and percentages for categorical variables. Differences in characteristics between four groups were evaluated using an analysis of variance for continuous variables and χ^2 test, or Fisher's exact test for categorical variables. The differences between initial and last ECG data were evaluated by the paired *t*-test. Survival curves were plotted using the unadjusted Kaplan–Meier method and compared among four groups using the log-rank test. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome across groups (the group with the number of CTG repeat <400 as a reference). We also tested for trends across four groups based on assigning a median value for each group and modelling this variable as a continuous variable. In addition, we performed sequential adjustment analyses. Model 1 was adjusted for age and sex. Model 2 was further adjusted for current smoking, oxygen administration, tracheotomy, respiratory support, bed rest, nutritional support, hypertension, dyslipidaemia, diabetes mellitus, chronic kidney disease, and cardiovascular disease. The covariates were selected *a priori* as they have known associated with CTG repeat length and are considered independent predictor for cardiac event and mortality in patients with DM1 as well as previous reports. The analyses were performed using the STATA 17.0 software (StataCorp LP, College Station, TX, USA). Two-tailed *P*-values of <0.05 denoted statistical significance.

Results

Patient characteristics corresponding to the length of CTG repeats

Table 1 shows the clinical characteristics of DM1 at the initial examination. The length of CTGn in each group was 215 ± 86, 584 ± 121, 993 ± 145, and 1784 ± 528 from Group 1 to Group 4, respectively ($P < 0.001$). There was no significant difference in sex among four groups ($P = 0.863$). Ages at onset were different among four groups and patients in Group 1 were older when compared with the other groups (36 ± 12, 29 ± 12, 30 ± 12, and 30 ± 13 years in Groups 1–4, $P < 0.001$). The number of smokers was larger in patients with less CTGn (19, 13, 3, and 0% in Groups 1–4, respectively, $P < 0.001$). Regarding the medical history, diabetes mellitus or the frequency of atrial fibrillation/flutter was also similar between the groups. In terms of the cardiac function, ejection fractions were similar among four groups ($P = 0.760$). The end-diastolic diameters were statistically a significant difference ($P = 0.023$) but within a normal limit. Overall cardiac functions were similar among four groups at the first examination.

Electrocardiogram showed different findings between four groups at the initial ECG examination. As shown in *Table 1*, the PR and QRS were significantly different among four groups (PR interval, $P = 0.001$ and QRS width, $P < 0.001$, respectively) and both values in Group 4 were longer than those in the other three groups (PR interval in Group 4, vs. Group 1, $P = 0.048$, vs. Group 2, $P < 0.001$, vs. Group 3, $P = 0.002$; QRS interval in Group 4, vs. Group 1, $P < 0.001$, vs. Group 2, $P < 0.001$, vs. Group 3, $P = 0.005$) (*Figure 1*). Regarding the change of each parameter in the last ECG when compared with the initial ECG, HR did not change in each group, while both PR and QRS intervals in the last ECG were longer than those in the initial ECG (*Table 2*). The first atrioventricular block and RBBB/LBBB were significantly more frequent in Group 4 than the other three groups ($P < 0.001$, $P = 0.031$, and $P = 0.033$, respectively). QTc interval was longer in Group 4 than those in the other three groups, while JTc was similar among four groups. Regarding the utilization of each cardiac device (i.e. pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy), there were not statistically differences among four groups. In terms of other related disorders except for cardiac involvements, patients with longer CTGn required nutritional support more frequently than those with milder CTGn (3, 1, 7, and 7% from Group 1 to Group 4, $P = 0.034$, respectively). Forced vital capacity was lower in patients in the longer CTGn group than the milder CTGn group ($P < 0.001$). Moreover, the use of oxygen administration was more frequent in Group 4 than the other groups (0, 2, 5, and 7% from Group 1 to Group 4, $P = 0.010$, respectively). The use of medications was similar among four groups, and most patients were not receiving medication at the initial examination.

Incidence of cardiac conduction disorders and cardiac events

In this study, pacemakers were implanted in seven of nine patients with advanced/complete atrioventricular block, while the follow-up period was too short to be evaluated in one of the other two patients. And another one without a pacemaker had complete atrioventricular block with atrial fibrillation and died at 64 years old for congestive heart

Table 1 Baseline characteristics of 496 patients with myotonic dystrophy Type 1

Number of CTG repeat	Group 1 <400	Group 2 ≥400, <800	Group 3 ≥800, <1300	Group 4 ≥1300	*P*-value
Number of patients	106	124	134	132	
Age (years), mean ± SD	43 ± 12	37 ± 11	41 ± 12	42 ± 10	<0.001
Age at onset (years), mean ± SD	36 ± 12	29 ± 12	30 ± 12	30 ± 13	<0.001
Infantile, 1 month–10 years	0	2 (2)	7 (6)	8 (8)	0.007
Juvenile, >10–20 years	11 (12)	27 (26)	24 (22)	21 (21)	
Adult, >20–40 years	51 (56)	56 (54)	60 (56)	53 (53)	
Late onset, >40 years	29 (32)	18 (17)	17 (16)	18 (18)	
Female sex, *n* (%)	54 (51)	60 (48)	72 (54)	67 (51)	0.863
CTGn, mean ± SD	215 ± 86	584 ± 121	993 ± 145	1784 ± 528	<0.001
Current smoking, *n* (%)	15 (19)	12 (13)	3 (3.7)	0 (0)	<0.001
Medical history, *n* (%)					
Hypertension	5 (5)	1 (1)	6 (5)	5 (5)	0.197
Dyslipidaemia	64 (62)	72 (59)	74 (56)	76 (58)	0.839
Diabetes mellitus	19 (18)	24 (19)	33 (25)	39 (30)	0.115
Cerebrovascular disease	5 (5)	3 (2)	8 (6)	6 (5)	0.575
Chronic kidney disease	13 (14)	8 (7)	16 (15)	17 (17)	0.131
Atrial fibrillation/flutter	3 (3)	3 (2)	7 (5)	5 (4)	0.664
VT/VF/cardiac arrest	1 (1)	0 (0)	1 (1)	0 (0)	0.587
Pacemaker, *n* (%)	1 (1)	0 (0)	1 (1)	2 (2)	0.686
ICD, *n* (%)	1 (1)	0 (0.0)	1 (1)	0 (0)	0.587
CRT-D/P, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA
ECG					
HR (b.p.m.), mean ± SD	67 ± 14	68 ± 14	72 ± 13	74 ± 15	<0.001
PR (ms), mean ± SD	190 ± 36	187 ± 37	188 ± 37	206 ± 61	0.001
QRS (ms), mean ± SD	99 ± 18	101 ± 20	106 ± 24	117 ± 29	<0.001
QTc (ms), mean ± SD	426 ± 36	424 ± 46	438 ± 34	451 ± 42	<0.001
JTc (ms), mean ± SD	322 ± 32	318 ± 41	322 ± 34	322 ± 37	0.762
First-degree AV block	28 (27)	30 (25)	34 (26)	59 (47)	<0.001
RBBB	2 (2)	5 (4)	7 (5)	14 (11)	0.031
LBBB	1 (1)	2 (2)	4 (3)	10 (8)	0.033
Bifascicular block	1 (1)	3 (2)	2 (1)	4 (3)	0.727
Advanced/complete AV block	0 (0)	0 (0)	0 (0)	2 (2)	0.178
Echocardiography					
EF, %	64 ± 9	64 ± 10	65 ± 10	64 ± 11	0.760
Dd, mm	44 ± 5	45 ± 6	42 ± 6	44 ± 8	0.023
Bedridden, *n* (%)	2 (2)	0 (0)	5 (4)	5 (4)	0.107
Nutritional support, *n* (%)	3 (3)	1 (1)	9 (7)	9 (7)	0.034
Respiratory function, *n* (%)					
%FVC	84 ± 21	76 ± 21	66 ± 20	53 ± 20	<0.001
FEV1.0%	82 ± 13	82 ± 16	82 ± 17	83 ± 22	0.964
Oxygen administration	0 (0)	2 (2)	7 (5)	9 (7)	0.010
Tracheotomy	2 (1)	1 (1)	6 (4)	8 (6)	0.085
Respiratory support	5 (5)	8 (6)	12 (9)	14 (11)	0.352
Medication, *n* (%)					
ACEI	0 (0)	0 (0)	0 (0)	1 (1)	0.468
Beta-blocker	0 (0)	1 (1)	0 (0)	1 (1)	0.731
Class I drugs	0 (0)	0 (0)	0 (0)	0 (0)	NA
Amiodarone	1 (1)	0 (0)	0 (0)	0 (0)	0.230

RBBB, complete right bundle branch block; LBBB, left bundle branch block; AV, atrioventricular; ACEI, angiotensin-converting enzyme inhibitor; CRT-D/P, cardiac resynchronization therapy with defibrillator/pacemaker; CTGn, CTG repeats; DM1, myotonic dystrophy type 1; ECG, electrocardiogram; FEV, forced expiratory volume; FVC, forced vital capacity; ICD, implantable cardioverter defibrillator; NA, not available; SD, standard deviation.

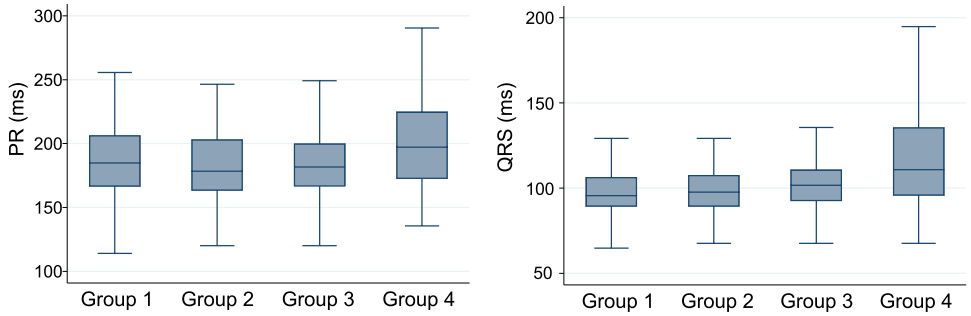


Figure 1 PR and QRS intervals in each group corresponding to the CTG repeat length.

Table 2 Comparison between initial and last electrocardiogram data

Number of CTG repeat	Group 1 <400	Group 2 ≥400, < 800	Group 3 ≥800, < 1300	Group 4 ≥1300
HR				
Initial value (b.p.m.), mean ± SD	68 ± 14	68 ± 14	72 ± 13	75 ± 15
Last value (b.p.m.), mean ± SD	69 ± 16	69 ± 14	70 ± 15	72 ± 16
Initial vs. last, *P*-value	0.409	0.503	0.358	0.158
PR interval				
Initial value (ms), mean ± SD	187 ± 29	182 ± 34	189 ± 38	201 ± 36
Last value (ms), mean ± SD	195 ± 35	193 ± 45	202 ± 46	214 ± 49
Initial vs. last, *P*-value	<0.001	<0.001	<0.001	<0.001
QRS duration				
Initial value (ms), mean ± SD	100 ± 18	101 ± 21	106 ± 25	116 ± 27
Last value (ms), mean ± SD	105 ± 23	107 ± 25	115 ± 30	127 ± 36
Initial vs. last, *P*-value	<0.001	0.004	<0.001	<0.001

failure. Among 14 patients with ventricular arrhythmias/cardiac arrest, 4 patients had an implantable cardioverter defibrillator (ICD), and all patients were alive during the follow-up. Three patients received a pacemaker implantation and two suddenly died. Seven patients did not receive any device therapies, and five of seven patients were alive under the medical treatment. Other two patients died for sudden death or cancer.

Table 3 shows the incidence rates of each cardiac event, composite events, or mortality in four groups. In terms of each cardiac event in four groups, advanced/complete atrioventricular block occurred in two of Group 1 and seven of Group 4, respectively. Also, ventricular tachycardia, ventricular fibrillation, or cardiac arrest occurred in two, two, two, and eight from Groups 1 to 4, respectively. A pacemaker device was implanted in five, zero, two, and nine from Groups 1 to 4, respectively, and the difference was not statistically significant. The composite cardiac outcome (i.e. advanced/complete atrioventricular block, pacemaker implantation, ventricular tachyarrhythmias, or cardiac arrest) was more frequently observed in Group 4 when compared with Group 1 (Model 2; HR 3.19, 95% CI 1.02–9.99, $P = 0.014$); the incidence rate was 111 in Group 1 and 252 in Group 4 per 100 000 person-years, respectively (*Table 2*). All-cause mortality depended on the severity of CTGn and the mortality rates were 147, 211, 260, and 529 from Groups 1 to 4, respectively (Model 2; HR 6.79, 95% CI 2.05–22.49, $P < 0.001$). Among 73 patients who expired during the follow-up period, 18 patients expired suddenly. There was no statistically significant finding among four groups. As shown in *Figure 2*, the composite cardiac events and mortality rate were statistically different among four groups (the composite events in *Figure 2A*, log-rank test, $P = 0.014$ and all-cause mortality in *Figure 2B*, log-rank test, $P < 0.001$); however, the incidence of sudden cardiac death was not significantly different (*Figure 2C*, log-rank test, $P = 0.076$).

Discussion

This Japanese multicentre study of DM1 yielded two major findings. Firstly, in terms of the genetic severity corresponding to the length of CTGn, especially patients with 1300 or longer CTGn was associated with frequent cardiac events including conduction disorders or life-threatening cardiac events as well as Europe. Secondly, CTG repeat length was associated with the total mortality rate in patients with DM1; however, it was not linked to the frequency of sudden death unlike Europe.

A previous study has investigated the role of CTGn length in the occurrence of cardiac events in DM1. Chong-Nguyen *et al.*[8] evaluated the relationship between genetic background and the severity of clinical phenotypes among 855 patients with DM1. They concluded that the length of the CTGn was associated with conduction disorders and

Table 3 Association of CTG repeats with outcomes

Number of CTG repeat	Group 1 <400	Group 2 ≥400, <800	Group 3 ≥800, <1300	Group 4 ≥1300	*P* for trend
Composite endpoints					
No. of cases (%)/no. at risk	6 (5.7)/106	2 (1.6)/124	4 (3)/134	17 (12.9)/132	
Incidence rate (/100 000 person-years)	111.1	35.3	61.3	252.6	
Model 1, HR (95% CI)	Ref (1)	0.30 (0.06–1.53)	0.46 (0.12–1.69)	2.16 (0.84–5.59)	0.017
Model 2, HR (95% CI)	Ref (1)	0.37 (0.07–2.02)	0.21 (0.04–1.27)	3.19 (1.02–9.99)*	0.014
Advanced/complete atrioventricular block					
No. of cases (%)/no. at risk	2 (1.9)/106	0 (0)/124	0 (0)/134	7 (5.3)/132	
Incidence rate (/100 000 person-years)	37	0	0	104	
Model 1, HR (95% CI)	Ref (1)	—	—	2.64 (0.53–13.19)	NA
Model 2, HR (95% CI)	ref (1)	—	—	2.28 (0.14–37.36)	NA
VT/VF/cardiac arrest					
No. of cases (%)/no. at risk	2 (1.9)/106	2 (1.6)/124	2 (1.5)/134	8 (6.1)/132	
Incidence rate (/100 000 person-years)	37.0	35.3	30.7	118.9	
Model 1, HR (95% CI)	ref (1)	0.64 (0.09–4.74)	0.52 (0.07–3.89)	2.38 (0.49–11.47)	0.100
Model 2, HR (95% CI)	ref (1)	0.94 (0.10–8.40)	NA	3.74 (0.42–33.35)	0.166
Pacemaker implantation					
No. of cases (%)/no. at risk	5 (4.7)/106	0 (0)/124	2 (1.5)/134	9 (6.8)/132	
Incidence rate (/100 000 person-years)	92.5	0	30.7	133.7	
Model 1, HR (95% CI)	Ref (1)	—	0.31 (0.06–1.68)	1.64 (0.53–5.14)	0.169
Model 2, HR (95% CI)	Ref (1)	—	0.26 (0.04–1.79)	2.21 (0.56–8.81)	0.122
All-cause mortality					
No. of cases (%)/no. at risk	8 (7.6)/106	12 (9.7)/124	17 (12.7)/134	36 (27.3)/132	
Incidence rate (/100 000 person-years)	147.6	211.4	260.0	529.4	
Model 1, HR (95% CI)	Ref (1)	1.42 (0.57–3.53)	1.37 (0.57–3.27)	4.13 (1.88–9.04)‡	<0.001
Model 2, HR (95% CI)	Ref (1)	1.91 (0.56–6.48)	1.76 (0.50–6.22)	6.79 (2.05–22.49)†	<0.001
Sudden death					
No. of cases (%)/no. at risk	1 (0.9)/106	4 (3.2)/124	4 (3.0)/134	9 (6.8)/132	
Incidence rate (/100 000 person-years)	18.5	70.5	61.2	132.3	
Model 1, HR (95% CI)	Ref (1)	3.59 (0.39–32.92)	2.39 (0.25–22.45)	6.97 (0.87–55.58)	0.038
Model 2, HR (95% CI)	Ref (1)	1.38 (0.13–14.43)	0.48 (0.03–8.01)	2.95 (0.30–28.67)	0.259
Respiratory-associated death					
No. of cases (%)/no. at risk	3 (2.8)/106	5 (4.0)/124	3 (2.2)/134	15 (11.4)/132	
Incidence rate (/100 000 person-years)	55.4	88.1	45.9	220.6	
Model 1, HR (95% CI)	Ref (1)	1.61 (0.37–6.98)	0.71 (0.14–3.69)	5.94 (1.61–21.89)†	0.003
Model 2, HR (95% CI)	Ref (1)	0.75 (0.11–4.85)	0.38 (0.04–3.68)	5.21 (0.96–28.32)	0.009
Other causes of death					
No. of cases (%)/no. at risk	4 (3.8)/106	2 (1.6)/124	8 (6.0)/134	12 (9.1)/132	
Incidence rate (/100 000 person-years)	73.8	35.2	122.4	176.5	
Model 1, HR (95% CI)	Ref (1)	0.49 (0.09–2.72)	1.20 (0.34–4.25)	2.49 (0.78–7.99)	0.038
Model 2, HR (95% CI)	Ref (1)	8.61 (0.51–145.21)	22.01 (1.43–339.19)[a]	47.25 (2.49–894.85)*	0.005

P-values for Cox model are given below.
*<0.05.
‡<0.001.
†<0.01.
Model 1, adjusted for age and sex.
Model 2, adjusted for age, sex, current smoking, oxygen administration, tracheotomy, respiratory support, bed rest, nutrition support, hypertension, dyslipidaemia, diabetes mellitus, chronic kidney disease, and coronary artery disease.
CI, confidence interval; CTGn, CTG repeats; HR, hazard ratio; LBBB, left bundle branch block; RBBB, right bundle branch block; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

sudden death or supraventricular arrhythmias. In this our study, the PR and QRS intervals as markers of conduction disturbance were also significantly prolonged in DM1 patients with 1300 CTGn or longer among the quartile at baseline. The available amount of MBNL1 may be associated with cardiac events in patients with 1300 CTGn or longer. MBNL1 contributes the alternative splicing of the cardiac sodium

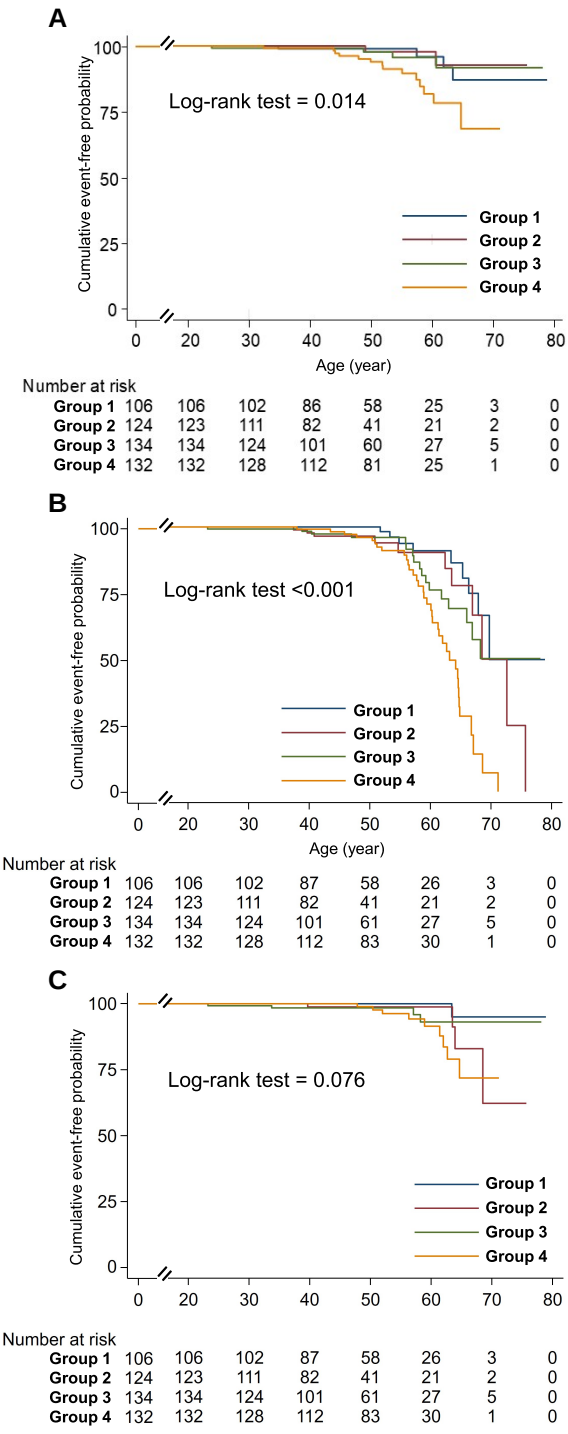


Figure 2 Cumulative event-free probabilities for composite cardiac events (*A*), all-cause mortality (*B*) and sudden death (*C*) among four groups depending on the underlying CTGn. DM1, myotonic dystrophy Type 1.

channel gene and paly a dose-dependent splicing manner.[13] Free MBNL1 in the nuclei may be less in patients with 1300 CTGn or longer than others because of the aggregation of CTGn and MBNL1. The incidence rates of bundle branch block or composite cardiac events were also higher in the longer CTGn group than the other CTGn groups. In addition, the length of CTGn was strongly associated with the occurrence of cardiac events including advanced/complete atrioventricular block, pacemaker implantation, or documented ventricular tachyarrhythmias. Our previous study involving a multivariate analysis demonstrated that cardiac events were associated with cardiac conduction disorders[9] and overall the genetic severity underlying in patients with DM1 could be associated with cardiac conduction disorders and consequently cause cardiac events including cardiac conduction disorders or ventricular arrhythmias. These results were concordant with those of another study conducted in a different country.

The incidence rate of sudden death was expectedly high in DM1 patients when compared with healthy Japanese individuals. A previous study evaluated trends in the rate of sudden cardiac death in Japan from 2001 to 2005[14] and revealed the incidence of sudden death among those aged 30–64 years was 17 per 100 000 person-years. When patients with DM1were classified into the quartile, the incidence of sudden death was 18, 70, 61, and 132 from the milder CTGn to the longer CTGn. This finding indicated that the incidence of sudden death among patients with DM1 was markedly higher than that recorded among healthy individuals in Japan. Nevertheless, we were unable to detect an association between sudden death and CTG repeat size in Japanese patients with DM1. Groh *et al.*[6] also reported that the incidence of sudden death was not associated with the length of CTGn; instead, it was associated with conduction disturbance, including QRS interval ≥120 ms and atrial tachyarrhythmias. Contrary, Chong-Nguyen *et al.*[8] identified a strong relationship between the length of CTGn and sudden death in a French cohort. As shown in *Table 2*, the incidences of other causes of death were significantly different among four groups depending on the underlying genetic severity and it will be possible the cause of mortality except sudden death may mask the incidence of sudden death. Regarding the association between CTGn and cardiac function in DM1, several studies[15–17] reported that patients with left ventricular dysfunction could be associated with increased mortality, cardiac arrhythmias, or cardiac conduction defects. Among patients who enrolled in our study, ejection frication or the volume of left ventricle were normal except several patients. Thus, patients with left ventricular dysfunction were few in our study and we failed to reveal a significant finding between cardiac functions and cardiac events. Our echocardiographic data were a concordant result when compared with the data in France.[8] Chong-Nguyen *et al.*[8] reported that 21% (181/855) of the patients received a pacemaker during the follow-up period. This rate was markedly higher than that recorded in the Japanese DM1 cohort (~3%; 16/496). Regarding the indication of pacemaker, the guideline of the Japanese Circulation Society[18] recommends the pacemaker implantation for patients who advanced/complete atrioventricular block regardless of bradycardia-induced symptoms in cases with myotonic dystrophy. Moreover, the Japanese Society of Neurology recommends the implantation of a pacemaker for not only patients corresponding to the criteria as mentioned above but also patients with HV interval with 70 ms or longer in the electrophysiological study. As reported in the previous article,[9] the incidence of the pacemaker implantation is less in Japan when compared with France and this is because most patients hesitate to undergo an electrophysiological study and there are not any patients who undergo pacemaker implantation. However, it is noted that the incidence of sudden death was not frequent than expected when compared with patients in France who receive the pacemaker under considering the result of the electrophysiological study, and the reason of this fact remains unclear. Overall, patients with DM1 receive pacemakers in Japan when they are diagnosed as advanced/complete atrioventricular block or severe bradyarrhythmias in the ECG and the incidence of sudden death in Japan is low despite the lower rate of pacemaker implantation compared with France.[9,19] Regarding the indication of ICD, the guideline of the Japanese Circulation Society[18] recommends ICD implantation for

patients with documented ventricular tachycardias as the indication of secondary prevention. These therapeutic strategies were built under considering various complications at the procedure of ICD/pacemaker implantation, e.g. infection and skin problems. For the ICD indication considering the primary prevention, the intolerance of medications or cardiac dysfunction need to be considered as additional implications, and there were no patients corresponding to the indication of the primary prevention in our cohort while one asymptomatic patient with both DM1 and Brugada ECG received an ICD for the primary prevention.

Differences in healthcare between countries may also explain the lack of an association of CTG repeat length with the incidence of sudden death among patients with DM1. In our study, atrial tachyarrhythmias were also not associated with the length of CTGn. Hence, the roles of other risk factors which induce atrial tachyarrhythmias (e.g. hypertension, valve disease, obesity, diabetes mellitus, alcohol consumption, obesity, etc.) may be investigated. Furthermore, variations in genetic severity, therapy selection, and care among different ethnic groups should be considered when updating the guidelines for the management of patients with DM1.[20] A recent work[21] suggested that the pleomorphic phenotypical expressivity of DM1 could be better predicted according to a classification system, based on the age of disease onset, e.g. congenital, infantile, juvenile, adult, and late onset. Chong-Nguyen *et al.*[8] reported the onset age depended on the underlying genetic severity and our study was also similar result. Overall, these studies means there should be a relationship between the CTGn and the onset age.

Limitation

The genetic severity could be one of the factors to affect cardiac conduction defects, and sudden death in patients with DM1[6,8] while it remains controversial. This could be explained by hypothesizing that the only genetic burden due to the expansion of CTGn could not be sufficient to contribute the cardiac and arrhythmic risk of patients with DM1 and that other factors, e.g. polygenic risk and so on, may play an important role for the arrhythmic risk. Furthermore, it is noted that DM1 is subjected to the biological phenomenon of somatic mosaicism of the CTGn repeats and CTGn in the heart may not be as same as those in other organs. CTGn is not only age-dependent, but also time-dependent and tissue-specific.

Conclusions

In this Japanese multicentre study which involved 496 patients with DM1, 1300 or longer CTGn was associated with the incidence of cardiac events, including advanced atrioventricular block, pacemaker implantation, and ventricular tachyarrhythmias. Nevertheless, we were unable to detect the association between the expansion of CTGn and sudden death, though the length of CTGn was associated with all-cause mortality. In spite of less occasions of the pacemaker implantation, the occurrence of sudden death was not frequent in Japan than other countries.

Clinical and research implications

This cohort study included 496 patients with DM1 who were retrospectively recruited from hospitals specializing in neuromuscular diseases. During the mean follow-up period of 8 years, the incidences of cardiac events were significantly higher in patients with1300 or longer CTGn when compared with other patients in Japan. We are able to estimate the occurrence of cardiac conduction diseases or ventricular arrhythmias corresponding to the expansion of CTGn, while further research studies are warranted for elucidating differences in healthcare provision and genetic background when compared with countries on the prognosis or sudden death of DM1.

Data availability

The data supporting the findings in this article will be shared on reasonable request to the corresponding author.

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