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Research Report

# DM1 Patients with Small CTG Expansions are also at Risk of Severe Conduction Abnormalities

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**Abstract**.
**Background and Objectives:** A high risk of cardiac arrhythmias was reported in myotonic dystrophy type 1 (DM1). The purpose of the study was to evaluate the risk of severe electrocardiographic abnormalities in DM1 patients with small CTG expansions.
**Methods:** We assessed the ECG done at DM1 diagnosis for 127 patients with ≤200 CTG repeats and for 82 of them who had ≥1 ECG over a period of follow-up of 11.7 ± 7.6 years (mean ± SD). Criteria of severe ECG abnormality are at least one of the following features: PR interval ≥240 msec, QRS duration ≥120 msec, second-degree or third-degree atrioventricular block, atrial fibrillation or flutter, insertion of a pacemaker or cardioverter-defibrillator.
**Results:** At baseline, ECG was normal for 109 patients out of 127 (85.8%) and only 4 patients (3.1%) presented severe ECG abnormalities. At follow-up, 46 patients out of 82 (56.1%) had a normal ECG and 25 (30.5%) developed severe ECG abnormalities ($p < 0.0001$) including 6 of them who needed permanent pacemaker insertion. There were also 3 sudden deaths during the follow-up period. Using multivariate Cox regression analysis, age at entry (relative risk RR, 1.05; (95% CI 1.01–1.08; $p = 0.012$) and muscular weakness (MIRS) at the entry (RR, 2.03; 95% CI 1.28–3.22; $p = 0.003$) were significant risk factors for the development of severe ECG abnormality.
**Conclusions:** An increased risk of severe ECG abnormalities and cardiac events is observed even in DM1 patients with small CTG expansions and warrants close cardiac follow-up similar to DM1 patients with larger CTG expansions.

Keywords: Myotonic dystrophy, cardiac arrhythmias, electrocardiogram

## INTRODUCTION

Myotonic dystrophy type 1 (DM1]) is the most frequent type of muscular dystrophy affecting adults [1]. The prevalence is estimated between 2.1 to 14.3 per 100,000 persons worldwide. In the Saguenay-Lac-Saint-Jean region (SLSJ), the prevalence of the disease is much higher, affecting 158 per 100,000 persons [2]. DM1 results from the expansion of an unstable trinucleotide cytosine-thymine-guanine (CTG) repeat mutation located in the 3' untranslated region of a gene (19q13.3) encoding a putative protein kinase (DMPK) [3]. When transcribed into CUG-containing RNA, mutant transcripts aggregate as nuclear foci that sequester RNA-binding proteins, including members of the muscleblind (MBNL) family, resulting in a spliceopathy of downstream effector genes [4].

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DM1 is a progressive and pleiotropic disease that can affect several systems including the muscular, respiratory, cardiac, endocrine, ocular and central nervous systems [1]. Typical symptoms of the disease include a progressive loss of muscle strength from distal to proximal, ptosis, weakness of facial, jaw and anterior neck muscles, myotonia, daytime sleepiness, fatigue and cataract [1].

Different clinical phenotypes are recognized in DM1 according to age of onset: congenital (present at birth), childhood (onset before 10 years of age), early adult (onset between 11 and 20 years of age), adult (onset from 21 to 40 years of age) and late or mild (onset after 40 years of age). CTG repeats in DM1 patients can range from 50 to several thousands and the length of the CTG repeats is partly correlated to the severity of the disease and the age at onset of symptoms [5]. It is unclear however if the severity and progression of cardiovascular manifestations are also related to the number of CTG repeats [6–12].

Cardiac involvement is frequent in DM1, with findings on endocardial biopsy of interstitial fibrosis, fatty infiltration, myocardiocyte hypertrophy and focal areas of myocarditis [13, 14]. These changes predispose to the degeneration of conduction tissue, causing prolonged PR and QRS intervals, which may lead to the development of various heart blocks and many different tachyarrhythmias [14, 15], including atrial flutter and/or fibrillation, and ventricular tachycardia and/or fibrillation [13, 14, 16–18]. These have been associated with an increased risk of mortality from sudden cardiac death [12, 19, 20]. Although reduction of these deaths have been a point of interest in recent years, no clear consensus has emerged on the means to achieve it. The selection of patients for prophylactic insertion of a pacemaker or an implantable cardioverter-defibrillator (ICD) remains controversial, however recent studies have suggested a possible benefit in prophylactic insertion of a device in patients with an HV interval >70 msec on an electrophysiological study [21, 22].

Since a striking increase of individuals with the mild phenotype of DM1 have been reported in relationship with the availability of genetic counselling and predictive testing [2], it is relevant to better describe the clinical features of these milder patients as they will represent a very common phenotype of DM1 population in the near future. The present study aims to determine if patients with small CTG expansions (defined as $\leq$200 repeats [23, 24]) are also at risk of developing severe electrocardiographic (ECG) changes. This could help in the future to decide if less affected patients warrant as close a follow up as those with larger expansions and more severe phenotypes.

Table 1
Baseline clinical characteristics of patients with DM1 ($n = 127$)

| | | |
|---|---|---|
| Age, *years* | | |
| Median (range) | 48.6 | (16.6–80.5) |
| Male, *n* (%) | 56 | (44.1) |
| CTG repeat length (median, range) | | |
| Median (range) | 95.0 | (55–200) |
| Muscular Impairment Rating Scale, *n* (%) | | |
| 1- No clinical muscular impairment | 85 | (66.9) |
| 2- Minimal signs without distal muscular weakness | 28 | (22.0) |
| 3- Distal muscular weakness | 11 | (8.7) |
| 4- Mild to moderate proximal weakness | 3 | (2.4) |
| 5- Severe proximal muscular weakness | 0 | |

## METHODS

### *Patients*

The DM1 patients living in the Saguenay-Lac-Saint-Jean (SLSJ) region are all followed at the Neuromuscular Clinic (NMC) of Jonquiere Hospital. We included in the present study 127 consecutive DM1 patients diagnosed at the NMC with $\leq$200 CTG repeats. The clinical characteristics of these patients were ascertained from history and examination. The severity of weakness was scored by a standardized five-point muscular-impairment rating scale (MIRS) as described in Table 1 [25].

### *ECG testing*

Cardiac testing included a resting 12-lead ECG. ECG tracings were analyzed by two investigators (MTP and RB). Among the 127 patients, 82 of them (64.6%) had $\geq$1 follow-up ECG. For the purpose of the present study, we only analyzed the first and the last ECG and the average time between these two ECG was $11.7 \pm 7.6$ years (0.12 – 29.3 years). Criteria of severe ECG abnormality were any of the following: a) PR segment $\geq$240 msec, b) QRS width $\geq$120 msec, c) second or third degree atrioventricular block, d) atrial flutter or fibrillation [19]. We added to these criteria the insertion of a permanent pacemaker or implantable cardioverter-defibrillator (ICD).

### *DNA analysis*

Genomic DNA was extracted from peripheral blood samples using QIAamp DNA blood kit (Qiagen Science, MD) according the manufacturer's instructions.

The DNA (3 to 5 μg) was digested with *Eco*RI (new England Biolabs), electrophoresed on 0.8% agarose gels, Southern transferred onto nylon membrane (Hybond, Amersham) and probed overnight with radiolabeled 2.2 kb *Bam*HI/*Eco*RI subclone of probe pGB2.66, as previously described. PCR amplification of the CTG repeat provides a more accurate assessment of its size. Genomic DNA (1μg) was PCR-amplified with primers 406 and 409 using a standard protocol [26].

*Statistical analysis*

Analysis for age and number of CTG repeats between groups was performed using the Mann-Whitney U test. PR prolongation and QRS widening between groups was analyzed by the non-parametric Wilcoxon signed-ranks test. Analysis of Muscular impairment rating scale and sex were done by using a $\chi^2$ test. Statistical analysis was performed using SPSS software version 21, 2012. Cox proportional hazards models were used to take into account the simultaneous effect of age and other predictor variables of outcome identified by univariate analysis, and to estimate the age-adjusted relative risks of severe ECG abnormality and confidence intervals (CI). Because a severe ECG abnormality was defined by the rhythm, PR interval, QRS duration, and presence of atrioventricular block, these individual covariates were not included in the multivariate models.

## RESULTS

*Patients' baseline characteristics*

The patients' baseline characteristics are summarized in Table 1. Average age at time of first ECG was 48.6 years (range 16.6 to 80.5 years), and 56 patients (44.1%) were male. All patients enrolled in this study have small CTG expansions, ranging from 55 to 200, and, accordingly, the MIRS show that the majority of these patients present no significant muscular weakness.

*ECG findings at baseline*

At time of DM1 diagnosis, ECG was normal for 109 patients out of 127 (85.8%) (Table 2). Fourteen (14) patients (11%) had minor ECG abnormalities and 4 patients (3.2%) had severe ECG abnormalities: 2 patients with PR interval ≥240 msec and 2 patients with QRS duration ≥120 msec.

Table 2
ECG findings at baseline ($n = 127$) and at follow-up ($n = 82$)

| Resting twelve-lead ECG findings | Baseline ECG | ECG at follow-up | *p* value |
|---|---|---|---|
| Normal, *n* (%) | 109 (85.8) | 46 (56.1) | |
| Minor ECG abnormality, *n* (%) | 14 (11.0) | 11 (13.4) | |
| First degree AV block, *n* | 11 | 7 | |
| Left anterior fascicular block(LAFB), *n* | 1 | 3 | |
| Non specific intraventricular conduction delay*, *n* | 1 | 1 | |
| Left bundle branch block (LBBB), *n* | 0 | 0 | |
| Right bundle branch block (RBBB), *n* | 1 | 0 | |
| Severe ECG abnormality, *n* (%) | 4 (3.2) | 25 (30.5) | <0.0001¥ |
| PR interval ≥240 msec, *n* | 2 | 8 | |
| QRS duration ≥120 msec, *n* | 2 | 18 | |
| Second-degree or third-degree atrioventricular block, *n* | 0 | 1 | |
| Atrial fibrillation or flutter, *n* | 0 | 2 | |
| Pacemaker insertion, *n* | 0 | 6 | |
| Cardioverter-defibrillator insertion, *n* | 0 | 1 | |
| PR interval, *msec* | | | |
| Median (range) | 160 (80–256) | 173.0 (120–374) | <0.0001¶ |
| QRS duration, *msec* | | | |
| Median (range) | 86 (60–154) | 94.0 (64–174) | <0.0001¶ |

¥Chi-square test. ¶Non parametric Wilcoxon signed-ranks test. *Defined as QRS >110 ms, but not fulfilling criteria for LBBB, RBBB, LAFB.

*ECG findings at follow-up*

Eighty-five (85) patients had at least one follow up ECG during a period of $11.7 \pm 7.6$ years. Thirty-six (36) of these patients (43.9%) developed minor or severe ECG abnormalities (25 patients (30.5%) had severe abnormalities) (Chi-square, $p < 0.0001$). Among the 4 patients with severe abnormalities at baseline, 3 of them remained with a severe ECG abnormality, and 1 was lost to follow up. These 3 patients were excluded from the subsequent analyses ($n = 82$).

*Atrio-ventricular (AV) conduction*

Median PR interval went from 160 msec (80–256) to 173 msec (120–374) ($p < 0.0001$). First degree AV block was initially present on 11 patients (8.7%), but in only 7 patients at follow-up (5.5%). PR interval ≥240 msec was present in greater frequency on the last ECG [2 patients (1.6%) at baseline vs. 8 patients (6.3%) at follow-up). The median PR interval progression was 1.24 (0–27.6) msec/year, and was identical for both genders (Mann-Whitney, $p = 0.7$).

No correlation was found between PR interval progression and the number of CTG repeats (Spearman $r = 0.009$, $p = 0.941$), the baseline MIRS (Spearman $r = -0.003$, $p = 0.983$), the baseline PR interval (Spearman $r = -0.147$, $p = 0.204$), the baseline QRS duration (Spearman $r = 0.008$, $p = 0.994$) or the QRS interval progression (Spearman $r = 0.168$, $p = 0.148$).

*Ventricular conduction*

The median QRS duration increased during the study period, from 86 msec (60–154) to 94 msec (64–174) ($p < 0.0001$). The proportion of patients with QRS $\geq$120 msec increased substantially during the study, from 2 (1.9%) to 18 (21.9%). Left anterior fascicular block was present in 3 patients at follow-up, up from 1 (0.8%). No patients developed left bundle branch block. One patient presented right bundle branch block on the initial ECG, which surprisingly disappeared on follow-up. The median QRS interval progression was 0.49 (0–17.4) msec/year. The baseline QRS duration was found to be negatively correlated with the median QRS widening (Spearman $r = -0.301$, $p = 0.007$) but this relationship was not found to be significant in linear regression analysis adjusted for the other factors ($p = 0.27$).

*Tachyarrhythmias*

No patients had atrial fibrillation or flutter on the first ECG. Two (2) patients developed atrial fibrillation and/or flutter during the study (2.4%). No ventricular arrhythmias were noted on the ECGs.

*Pacemaker and implantable cardioverter-defibrillator (ICD) insertion*

Six (6) patients necessitated a pacemaker (7.3%) during the study. All device insertions were for clinical reasons: high grade second degree AV block was present in three patients, symptomatic bradycardia in two and one patient had a pacemaker insertion after an unexplained syncope. One of these patients later developed severe left ventricular dysfunction and the pacemaker was upgraded to an ICD with biventricular pacing. None had prophylactic insertion of a pacemaker during that period.

*Predictive factors of severe ECG abnormality*

In univariate analysis, the only factor identified as being predictive of severe ECG changes was PR length at baseline (Table 3). Age, gender, CTG repeats length, MIRS or baseline QRS were not predictors of severe ECG abnormality. Multivariate Cox regression analysis adjusted for sex, age at baseline, MIRS score, CTG repeats length, showed that age at baseline (relative risk RR, 1.05 (95% CI 1.01–1.08); $p = 0.012$, per each year increase of age) and muscular weakness (MIRS) at baseline (RR,2.03 (95% CI 1.28–3.22); $p = 0.003$, per each MIRS score increase) were significant risk factors for the development of severe ECG abnormality.

*Deaths*

During the follow-up period, 22 patients (17.3%) out of 127 died, including 3 sudden deaths. The other causes of death were: pneumonia (4 patients), neoplasms (4 patients), acute cerebrovascular disease (2 patients), acute myocardial infarction (1 patient), congestive heart failure (1 patient) and death of unknown cause (6 patients). Mean age at death was $68.8 \pm 12.2$ years. Patients who died of sudden death were younger than the other patients (42, 45 and 56 years old), but sample size is too small to validate statistically.

Table 3
Clinical characteristics and ECG findings according to the presence or absence of a severe ECG abnormality at follow-up

| Characteristics | No severe abnormality ($N = 57$) | Severe abnormality ($N = 25$) | $p$ value |
|---|---|---|---|
| Age at entry, *years* | | | |
| Median (range) | 47.3 (16.6–79.4) | 51.7 (18.9–71.4) | 0.375¶ |
| Male, *n* (%) | 23 (40) | 8 (32) | 0.122¥ |
| CTG repeat length | | | |
| Median (range) | 90 (55–200) | 100 (55–200) | 0.301¶ |
| Baseline MIRS, *n* (%) | | | |
| 1 or 2 | 51 (89.5) | 21 (84) | 0.652¥ |
| 3 or 4 | 6 (10.5) | 4 (16) | |
| Progression of PR interval, msec/year | | | |
| Median (range) | 1.03 (0.0–27.51) | 1.93[a] (0.0–27.61) | 0.136¶ |
| Progression of QRS duration, msec/year | | | |
| Median (range) | 0.15 (0.0–17.38) | 3.17[b] (0.0–7.12) | <0.0001¶ |

MIRS: Muscular Impairment Rating Scale. ¶Non parametric Mann-Whitney test. ¥Chi-square test. [a]$n = 19$. [b]$n = 23$.

## DISCUSSION

Several studies have examined the relation between the number of CTG repeats and ECG changes in populations of DM1 patients [6, 8–11, 27, 28], with conflicting results, possibly suggesting that there are external factors affecting the ECG changes. ECG changes showed a strong association with the severity of disease as evaluated by the MIRS; the highest frequency of ECG abnormalities occurring in patients with grades III and IV [7]. However, no linear correlation has been reported between the extent of the CTG repeats and various conduction measurements either on the surface ECG or intracardiac measurements [29]. The present study is the first one which specifically examined if patients with small CTG expansions were also at risk of developing severe ECG changes and if there is a need to do ECG monitoring in this population.

We used the cut-off value of $\leq$200 CTG to define a small CTG expansion because in previous work [24] we observed that patients with a very small expansion (50–99 CTG) were nearly asymptomatic except for the presence of cataracts, and that mild symptoms were more prevalent among patients with 100 to 200 CTG repeats, with half of them having mild to moderate weakness.

Predictors of developing severe ECG changes or adverse events were age at baseline and muscular weakness at baseline as measured by the MIRS. These results are consistent with those observed by Groh et al. in a larger DM1 population where patients with severe ECG abnormalities were older, had more CTG repeats, and had more severe muscular impairment [19]. No factor correlated with rate of PR progression per year, including initial PR segment length. Initial QRS interval and progression of the QRS interval were also not shown to predict outcomes. However, Clarke et al. [8] have shown that DM1 patients who experienced a cardiac event during follow-up had more rapid rates of PR interval increase ($9.9 \pm 11.1$ vs $1.6 \pm 2.9$ msec/year, $p = 0.008$) and a trend to greater QRS complex widening ($3.6 \pm 4.5$ vs $0.9 \pm 1.5$ msec/year; $p = 0.06$) than those who did not.

The PR and QRS interval progressions in this study were slower than those found by Groh et al. [19], which were respectively of $5.2 \pm 5.8$ msec/year and $2.2 \pm 3.0$ msec/year in those who developed no ECG abnormalities, and $8.8 \pm 12.9$ msec/year and $3.4 \pm 5.4$ msec/year in those who presented at least one severe ECG abnormality. This difference could be related to the lesser severity of disease in our patients, as determined by the lower number of CTG repeats (mean CTG length repeats of 95 in our study vs 600–700 in Groh' study) and a lower MIRS score (at baseline, 89% patients with score 1 and 2 in our study vs 63–78% with score 3 or 4 in Groh's study).

However, even if the PR and QRS interval progression in this study was slower than in previous studies, a significant portion of the individuals required a pacemaker insertion during the follow up period (7.3%). This portion is similar to the one found by Nazarian et al. [12], and higher than in Groh et al.'s study, where approximately two thirds of the pacemakers were installed prophylactically. These findings indicate that patients with a low number of CTG repeats are also at risk of developing serious bradyarrhythmias.

Cardiac mortality in most studies is estimated as being in between 10 and 20 percent of patients with DM1 [12, 19, 30]. It was lower in our study, affecting only 3.9% of patients (5/127), and sudden cardiac death accounted for the majority of these deaths (3/5). This is lower than Lazarus' (8.2%), Groh's (8.6%) or Mathieu's (11%) findings. This may be explained by the lower number of CTG repeats or lesser disease severity in our study population. Also, only two patients developed atrial tachyarrhythmias (2.7%), which is much lower than estimates in literature where up to 25% of patients are reported to develop these arrhythmias [31]. As mentioned earlier, atrial tachyarrhythmias are an important risk factor for cardiac death. It is possible that the low number of supraventricular arrhythmias may have driven the low percentage of cardiac deaths, as the number of bradyarrhythmic events and pacemaker implantations were similar to previous studies. These results may also indicate that bradyarrhythmias and atrio-ventricular blocks are independent to the number of CTG repeats, whereas atrial tachyarrhythmias are.

Limitations of this study should be the use of a "severe ECG abnormality" as a surrogate endpoint rather than a clinical endpoint such as sudden death or symptomatic arrhythmia and the absence of any control population. Despite a low positive predictive value (12.1%), essentially explained by the low prevalence of sudden death in DM1, Groh already documented that the presence of severe ECG abnormality in DM1 was a significant and powerful predictor of sudden death with an adjusted relative risk of 3.30, a sensitivity of 74.1% for the prediction of sudden death, a specificity of 61.7% and a negative predictive value of 97.1% (Groh et al., NEJM 2008). As our study focused on a relatively small sub-population of DM1 (patients with a low number of CTG repeats) and an expected low

prevalence of sudden death, we preferred to use ECG parameters as endpoint to increase chances of providing meaningful data instead of only descriptive results. Also, a severe ECG abnormality was defined with clinically relevant and easily measured parameters, which are easily transferable on clinical ground for clinicians with less experience with DM1. Otherwise, the inclusion of DM1 patients with larger CTG expansions as control groups have been already done (Groh, NEJM 2008) and demonstrated that patients with severe ECG abnormalities were older, had more CTG repeats, and had more severe muscular impairment. Our work highlights the development of significant ECG abnormalities in patients with a milder DM1. This result is partially unexpected since it happens in a population where we already reported a lower incidence of sudden death in patients with larger CTG repeats [27] and the present work may suggest that CTG expansions have a limited role in predicting either conduction abnormalities or sudden death.

Considering that patients with a low number of CTG expansions are generally more functional and less at risk of developing respiratory problems than their counterparts with an elevated number of CTG expansions, prevention of unfavorable cardiac events in this population becomes very important, as it may have a pronounced effect on long term survival. Therefore, patients with $\leq$200 CTG repeats, as those with minimal neuromuscular findings and those with minor or absent ECG changes at the moment of the diagnosis, warrant careful follow-up, similarly to other DM1 patients who require an ECG at least yearly [32]. Otherwise, as the proportion of patients with a mild phenotype significantly increased over the last years in direct relationship with the availability of genetic testing, allowing the detection of asymptomatic patients, it is relevant to better characterise these milder patients as they will represent a more common phenotype in DM1 population in a near future [33]. These observations on the progression of cardiac abnormalities in patients with small CTG expansions may also be seen as an additional argument to promote genetic screening of the asymptomatic adults who are at-risk of DM1.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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