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Myotonic dystrophy type 1: A comparison between the adult- and late-onset subtype

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Abstract

Introduction/Aims: Although the extent of muscle weakness and organ complications has not been well studied in patients with late-onset myotonic dystrophy type 1 (DM1), adult-onset DM1 is associated with severe muscle involvement and possible life-threatening cardiac and respiratory complications. In this study we aimed to compare the clinical phenotype of adult-onset vs late-onset DM1, focusing on the prevalence of cardiac, respiratory, and muscular involvement.

Methods: Data were prospectively collected in the Dutch DM1 registry.

Results: Two hundred seventy-five adult-onset and 66 late-onset DM1 patients were included. Conduction delay on electrocardiogram was present in 123 of 275 (45%) adult-onset patients, compared with 24 of 66 (36%) late-onset patients ($P = .218$). DM1 subtype did not predict presence of conduction delay (odds ratio [OR] 0.706; confidence interval [CI] 0.405 to 1.230, $P = .219$). Subtype did predict indication for noninvasive ventilation (NIV) (late onset vs adult onset: OR, 0.254; CI, 0.104 to 0.617; $P = .002$) and 17% of late-onset patients required NIV compared with 40% of adult-onset patients. Muscular Impairment Rating Scale (MIRS) scores were significantly different between subtypes (MIRS 1 to 3 in 66% of adult onset vs 100% of late onset [$P < .001$]), as were DM1-activ^{C} scores (67 ± 21 in adult onset vs 87 ± 15 in late onset; $P < .001$).

Discussion: Although muscular phenotype was milder in late-onset compared with adult-onset DM1, the prevalence of conduction delay was comparable. Moreover, subtype was unable to predict the presence of cardiac conduction delay. Although adult-onset patients had an increased risk of having an NIV indication, 17% of late-onset patients required NIV. Despite different muscular phenotypes, screening for multiorgan involvement should be equally thorough in late-onset as in adult-onset DM1.

Abbreviations: DM1, myotonic dystrophy type 1; DMPK, myotonic dystrophy protein kinase; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MIRS, Myotonic Dystrophy Impairment Rating Scale; NIV, noninvasive home mechanical ventilation; PFT, pulmonary function testing; PM, pacemaker; SRDB, sleep-related breathing disorder.

KEYWORDS
cardiomyopathy, conduction delay, muscle weakness, myotonic dystrophy, noninvasive ventilation, phenotype

1 | INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a muscle disease caused by a CTG repeat expansion on chromosome 19 in the myotonic dystrophy protein kinase (*DMPK*) gene.[1] The number of CTG repeats in healthy individuals ranges up to 35, whereas repeat expansions larger than 50 are associated with DM1.[2] Although the main symptoms of DM1 consist of muscle weakness and myotonia, multisystemic involvement is a relevant feature, including cardiac, respiratory, and gastrointestinal dysfunction with a highly variable clinical phenotype.

Based on age of onset and length of the CTG repeat expansion, DM1 is often divided into four subtypes.[3–5] The classical/adult, childhood/juvenile, and congenital subtypes are associated with repeat expansions larger than 100 ranging up to several thousand, with CTG repeat size overlap between different phenotypes.[3,4] Clinically, these subtypes have been linked to profound muscle weakness and systemic involvement, which can have life-threatening complications.[3,4,6] The late-onset subtype gives rise to symptoms after 40 years of age and has been associated with CTG repeat expansions of 50 to 150.[3–5,7,8] Clinical findings consist of early-onset cataracts and mild muscular involvement, whereas the prevalence of other organ complications in this subtype remains unclear.[5,8] Moreover, insufficient data are available on the life expectancy of patients with late-onset DM1, whereas patients affected by the adult subtype have been demonstrated to have a markedly reduced survival.[9]

As a reduced lifespan in DM1 is most frequently the result of cardiac or respiratory complications, disease management focuses on early detection of organ involvement.[9] Yearly follow-up by a coordinating physician (neuromuscular neurologist) is advised, including an annual electrocardiogram (ECG) to detect possible cardiac conduction delay.[10,11] In the case of conduction disorders or cardiac symptoms, referral to a cardiologist is indicated.[10,11] Regular pulmonary function testing (PFT) is also recommended and referral to a pulmonologist is advised in patients with respiratory symptoms.[11]

Due to large differences in DM1 phenotypes, subtype treatment stratification has been suggested.[7,12] Although the prevalence of organ complications has not been well studied in late-onset DM1, some studies have suggested that cardiac and respiratory involvement may be present as frequently as in adult-onset DM1.[7,13] Not all multisystemic abnormalities may have treatment consequences, but it would be of added value to further specify the frequency and severity of organ involvement in the late-onset subtype. Therefore, the aim of the current study was to compare the clinical phenotype of adult-onset and late-onset DM1, focusing on the prevalence of cardiac, respiratory, and muscular involvement.

2 | METHODS

2.1 | Participants

Data were prospectively collected as part of the observational Myotonic Dystrophy type 1: Dutch Registry and Follow-up Study (MYODRAFT study) at the Maastricht University Medical Centre+ (MUMC+) and Radboudumc Nijmegen. The MUMC+ and Radboudumc form the national Myotonic Dystrophy Expertise Centre in The Netherlands. Data collection for the MYODRAFT study started in March 2017. All participants were 18 years of age or older and had a genetically confirmed diagnosis of DM1. For the current study, all consecutive patients diagnosed with adult-onset or late-onset DM1 who joined the MYODRAFT study up until March 2021 were included.

The research protocol was approved by the institutional medical ethics committee (METC 16-4-001). Written informed consent was obtained from all included participants. For legally incapacitated patients, written informed consent was signed by a legal guardian.

2.2 | MYODRAFT protocol and subtype classification

As standard of care, DM1-affected individuals visit the neurology outpatient clinic annually to determine disease progression. MYODRAFT data were collected during these standard follow-up visits. Upon inclusion (baseline), data on the diagnosis, age of first symptoms, age of diagnosis, CTG repeat size, and DM1 subtype were collected. DM1 subtype classification was performed by a trained neuromuscular specialist and was based on age of onset and CTG repeat size.[3,4] The late-onset subtype was defined as an age of onset over 40 years with a CTG repeat expansion between 50 and 150.[3,4] The adult-onset subtype was defined as an age of onset between 10 and 40 years with a CTG repeat expansion between 100 and 1000.[3,4] Patients in whom the DM1 subtype remained unclear, as is sometimes the case for asymptomatic genetically confirmed patients under 40 years of age in whom symptoms may still arise, were not included (n = 1).

To define neuromuscular progression, the Muscular Impairment Rating Scale (MIRS) score was determined for each patient annually. The MIRS score is a disease-specific rating scale, based on manual muscle testing.[14] MIRS scores between 1 and 3, indicating no or distal muscle weakness, were categorized as low. MIRS scores of 4 to 5, indicating both distal and proximal muscle weakness, were categorized a high. The most recently determined MIRS score for each participant was used for analysis. Moreover, data on the presence of clinical myotonia were collected. Patients also completed the DM1-activ^{C}

questionnaire at baseline and during annual follow-up. This disease-specific patient-reported outcome measure determines activity and social participation in patients with DM1.[15] DM1-activ^{C} raw scores were translated into centrile metric scores ranging from 0 (most severe limitations in activity and social participation) to 100 (no activity and social limitations).[15] Centrile metric scores over 70 indicated few limitations, and scores less than or equal to 30 indicated severe limitations in activities of daily living.[16] The most recently determined DM1-activ^{C} score for each participant was used.

2.3 | DNA analysis

DNA analysis took place at DM1 diagnosis as part of standard care. All CTG repeat lengths were determined by analyzing DNA extracted from peripheral blood samples through polymerase chain reaction (PCR), followed by fragment length analysis and Southern blot analysis.[2] In the case of a CTG repeat length expressed as CTG > *X*, value *X* was used for statistical analysis. In case of a CTG repeat length expressed as a range, mean CTG repeat length was used for statistical analysis.

2.4 | Cardiac follow-up

During annual visits, patients were evaluated by a DM1-experienced cardiologist as standard of care. History-taking and resting 12-lead ECG were performed. The presence of cardiac symptoms (palpitations, dyspnea, light-headedness, dizziness, syncope) was assessed.

Cardiac conduction delay was defined as a PR interval over 200 milliseconds, widened QRS complex >120 milliseconds, and/or prolonged QTc time of at least 450 milliseconds in men or at least 460 milliseconds in women, on at least one of the ECGs during follow-up. In case of atrioventricular (AV) conduction delay, this was further classified into first-degree, second-degree Wenckebach, second-degree Mobitz, or third-degree AV block. Baseline left ventricular ejection fraction (LVEF) and data on the presence of a pacemaker (PM) or implantable cardioverter-defibrillator (ICD) were collected. LVEF was considered abnormal if less than 50%.[17]

2.5 | Respiratory follow-up

Respiratory involvement was assessed through history-taking by the coordinating neuromuscular neurologist upon yearly visits. In case of (suspected) respiratory involvement, patients were referred to the pulmonologist for detailed screening consisting of PFT, polysomnography, and blood-gas analysis. PFT was considered abnormal in case of a forced vital capacity (FVC) less than 80% of predicted on at least one PFT during follow-up.[18]

Data on noninvasive home mechanical ventilation (NIV) indications were collected. The indication for NIV was based on the 207th European Neuromuscular Centre Workshop (21-07-2014),[18,19] comprising the presence of at least one or more daytime or night-time symptoms suggestive of chronic respiratory insufficiency in combination with: (1) daytime hypercapnia; (2) FVC less than 50% of predicted; or (3) evidence of nocturnal hypoventilation on polysomnography.

2.6 | Statistical analysis

Statistical analysis was performed using IBM SPSS version 25 (IBM Corp, Armonk, NY). The distribution of continuous variables was assessed for normality by visual inspection of histograms and standardized normal probability plots. Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) in cases of skewness. Categorical variables are expressed as number (percent). Differences between groups were compared using the chi-square test or the Fisher exact test (categorical data), and the unpaired Student *t* test or Mann-Whitney *U* test (continuous variables). Univariable binary logistic regression using predefined variables was performed to identify predictors for the presence of conduction disorders on ECG and for the presence of an NIV indication. Selected variables were age, gender, DM1 subtype (adult- or late-onset DM1), CTG repeat size, and having a high MIRS score (MIRS 4 to 5). Variables with $P < .20$ on univariable analysis were considered important and were included in the multivariable logistic regression analysis for identification of independent predictors, presented as odds ratios (ORs) with confidence intervals (CIs). Missing data were not imputed. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

The MYODRAFT population consisted of 481 DM1 patients, among whom all consecutive 341 participants diagnosed with adult- or late-onset DM1 were selected for the current study. Two hundred seventy-five (81%) patients had been diagnosed with the adult-onset subtype and 66 (19%) patients with the late-onset subtype. Clinical characteristics of included patients are presented in Table 1.

3.2 | Age of onset and clinical symptomatology

Adult-onset DM1 patients first noted DM1-related features at a median age of 25 years, which consisted of myotonia (54%), muscle weakness (21%), fatigue (11%), cataracts (4%), or other symptoms, such as gastrointestinal abnormalities, apathy, or dysphagia (12%). Seven late-onset DM1 patients were subjectively asymptomatic and showed no signs of DM1 upon evaluation. In the other 59 late-onset patients, DM1-related features were reported to start at a median age of 50 years, and consisted of cataracts (31%), fatigue (20%), mild muscle weakness (17%), myotonia (12%), or dysphagia (3%). The remaining

TABLE 1 Clinical characteristics

	Total (n = 341)	Adult-onset DM1 (n = 275)	Late-onset DM1 (n = 66)	*P* value
Age at inclusion (years), mean ± SD	48 ± 13	46 ± 13	57 ± 13	<.001
Male, number (%)	172 (50%)	125 (45%)	47 (71%)	<.001
CTG repeat size, median [IQR]	150 [96-200]	150 [120-200]	72 [61-97]	<.001
Follow-up time (years), mean ± SD	3 ± 1	3 ± 1	2 ± 1	.006
Age of onset (years), median [IQR]	27 [16-38]	25 [16-34]	50 [42-52]	<.001
Age at diagnosis (years), median [IQR]	33 [25-43]	30 [24-39]	51 [43-59]	<.001
Symptom duration (years), median [IQR]	18 [10-27]	20 [11-28]	12 [6-14]	<.001

Abbreviations: DM1, myotonic dystrophy type 1; IQR, interquartile range; SD, standard deviation.

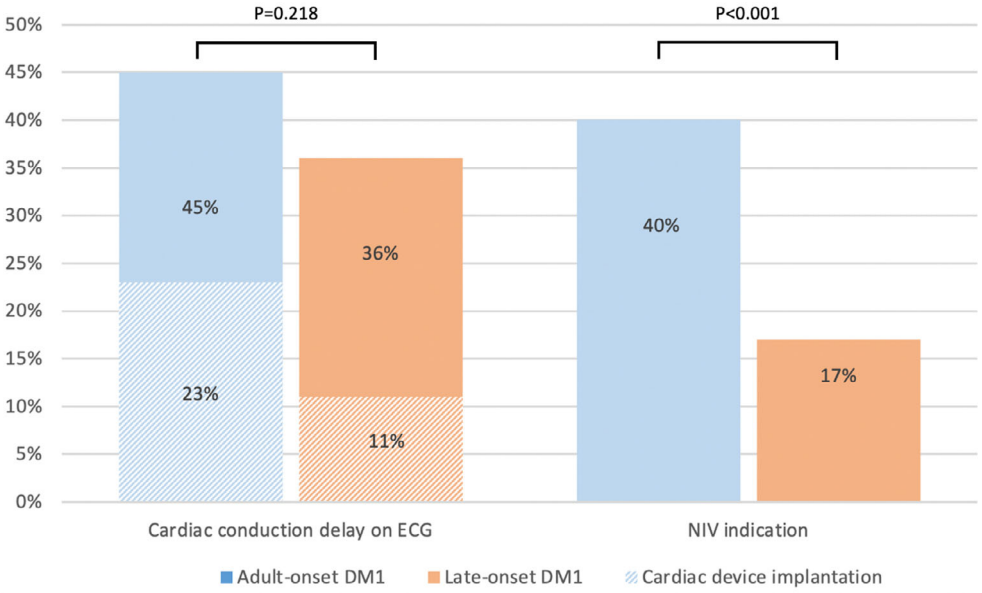

FIGURE 1 Prevalence of cardiac conduction delay and NIV indications in patients diagnosed with adult-onset vs late-onset myotonic dystrophy type 1. Abbreviations: ECG, electrocardiogram; NIV, noninvasive ventilation; DM1, myotonic dystrophy type 1.

17% of late-onset patients were asymptomatic but showed multiorgan involvement as a sign of DM1 on evaluation.

3.3 | Cardiac involvement

Conduction delay on ECG was present in 123 of 275 patients with adult-onset DM1, as compared with 24 of 66 patients with late-onset DM1 by the end of follow-up (Figure 1). First-degree AV block was the most commonly observed conduction delay on ECG in both subtypes, frequently combined with bundle branch blocks (Table 2). In 24 of 147 (16%) patients with conduction delay, ECGs were completely normal on baseline evaluation.

As displayed in Table 3, both age and MIRS category independently predicted the presence of conduction delay. DM1 subtype was not a predictor for conduction delay on ECG.

In the adult-onset subgroup, 62 of 275 patients had a PM or ICD, as compared with 7 of 66 in the late-onset subtype group (Figure 1). Two of the late-onset subtype patients with a cardiac device had no subjective symptoms of DM1 on presentation, making asymptomatic cardiac conduction delay the sole expression of disease at the evaluation.

TABLE 2 Conduction delay

	Adult-onset subtype (n = 123)	Late-onset subtype (n = 24)
First-degree AV block	59 (48%)	13 (54%)
First-degree AV block and bundle branch block	37 (30%)	4 (17%)
First-degree AV block and prolonged QTc	0	1 (4%)
Second-degree AV block	3 (2%)	0 (0%)
Bundle branch block	24 (20%)	6 (25%)

Abbreviations: AV, atrioventricular; ECG, electrocardiogram.

Cardiac symptoms were present in only 34 of the total 147 (23%) patients with conduction abnormalities on ECG. These symptoms consisted of recurrent dizziness (47%), palpitations (23%), chest pain (18%), or syncope (12%). LVEF was reduced in 10% of adult-onset patients vs 4% of late-onset patients ($P = .205$).

TABLE 3 Binary logistic regression analysis

	Univariate			Multivariate		
	OR	CI	*P* value	OR	CI	*P* value
For the presence of cardiac conduction delay on ECG						
Age	1.053	1.034-1.072	<.001	1.049	1.030-1.068	<.001
Sex (female vs male)	1.146	0.746-1.760	.533			
CTG repeat length	1.002	0.999-1.004	.222			
DM1 subtype (late onset vs adult)	0.706	0.405-1.230	.219			
High MIRS score (4, 5)	2.687	1.649-4.379	<.001	2.251	1.355-3.740	.002
For presence of an NIV indication						
Age	1.026	1.009-1.044	.003	1.051	1.026-1.077	<.001
Sex (female vs male)	1.431	0.916-2.236	.115	0.649	0.376-1.119	.120
CTG repeat length	1.007	1.003-1.011	.001	1.007	1.002-1.012	.002
DM1 subtype (late onset vs adult)	0.300	0.150-0.599	.001	0.254	0.104-0.617	.002
High MIRS score (4, 5)	2.198	1.351-3.576	.002	1.015	0.540-1.905	.964

Abbreviations: CI, confidence interval; DM1, myotonic dystrophy type 1; ECG, electrocardiogram; MIRS, Muscular Impartment Rating Scale; NIV, noninvasive ventilation; OR, odds ratio.

TABLE 4 NIV indications

	Adult-onset subtype (n = 110)	Late-onset subtype (n = 11)
Nocturnal hypoventilation	34 (31%)	0 (0%)
Daytime hypercapnia	4 (4%)	1 (9%)
Obstructive sleep apnea	37 (34%)	7 (64%)
Central sleep apnea	26 (23%)	2 (18%)
Mixed sleep apnea	9 (8%)	1 (9%)

Abbreviation: NIV, noninvasive ventilation.

3.4 | Respiratory involvement

In the adult-onset group, 108 of 275 (39%) had an FVC of less than 80% of predicted, compared with 3 of 66 (5%) in the late-onset group ($P < .001$). An FVC lower than 50% of predicted was observed in 29 adult-onset patients (11%) and none of the late-onset patients.

NIV indications were present in 110 of 275 adult-onset patients and in 11 of 66 late-onset patients (Figure 1). NIV indication was most frequently based on the presence of sleep-related breathing disorders (SRBDs; Table 4). Only age, CTG repeat length, and DM1 subtype independently predicted the presence of an NIV indication (Table 3).

3.5 | Muscular involvement and disability

All late-onset DM1 patients had a low MIRS score, compared with 66% of the adult-onset patients ($P < .001$; Figure 2). Mean DM1-activ^C scores were significantly different among subtypes, with a mean score of 67 ± 21 in adult-onset patients compared with 87 ± 15 in late-onset patients ($P < .001$). Also, late-onset DM1 patients did not experience severe limitations in activities of daily living (DM1-activ^C less than or equal to 30; Figure 2). Myotonia was present in 231 of 275 (84%) adult-onset patients vs 17 of 66 (26%) late-onset patients ($P < .001$).

4 | DISCUSSION

Cardiac and respiratory involvement were common in both adult- and late-onset DM1, despite clear differences in muscular status. The prevalence of conduction delay on ECG was comparable between both groups and the presence of conduction abnormalities was independent of DM1 subtype. Although patients with adult-onset DM1 were more likely to have an NIV indication, 17% of late-onset patients still required NIV treatment.

Cardiac conduction defects are described to be present on 17% to 50% of ECGs in the general DM1 population, which is in line with our results.[7,20–22] For late-onset DM1, however, less is known about the frequency of cardiac abnormalities because multiorgan involvement has not been well studied. A study investigating patients with small CTG repeat expansions found ECG abnormalities in 17% to 21% of participants, but ECG evaluation criteria were not specified.[13] In the French DM-scope registry, cardiac conduction delay was present in 50.1% of adult-onset and even in 55.8% of late-onset DM1 patients.[7] Yet again, ECG criteria were not provided.

For DM1 cardiac screening, an annual ECG has been accepted as the most valuable tool.[10,23] In our study population, a large proportion of patients with ECG abnormalities was asymptomatic and had a normal ECG at baseline, stressing the need for standard follow-up. Although percentages of cardiac device implantation were high in both subtypes, guidelines on when to perform an invasive measurement of the cardiac conduction system are still lacking.[23] Consequently, the true number of patients requiring device implantation

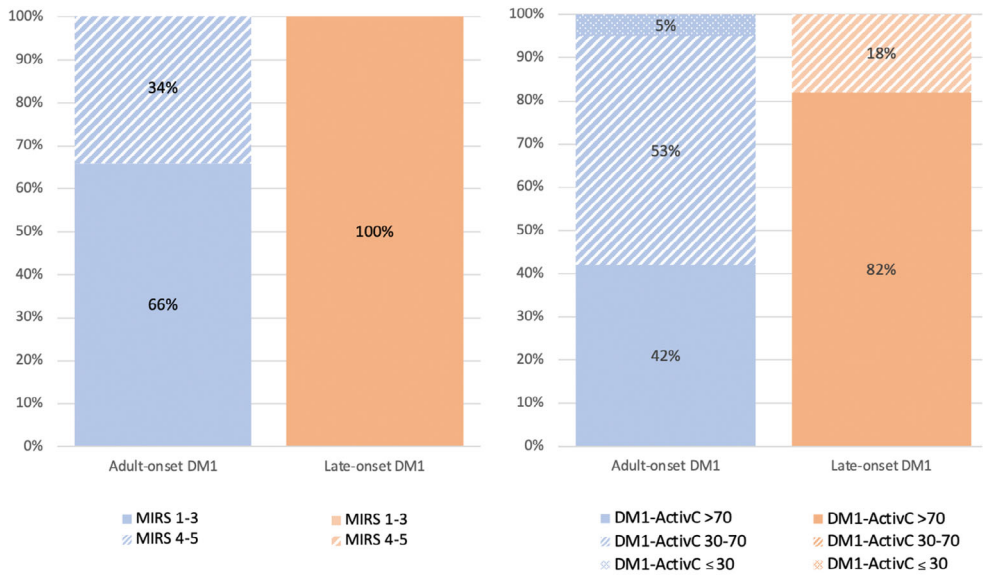

FIGURE 2 MIRS and DM1-activ^C scores in patients diagnosed with adult-onset vs late-onset myotonic dystrophy type 1. Abbreviations: DM1, myotonic dystrophy type 1; MIRS, muscular impairment rating scale.

may be higher. Indications for device implantation were not revised, and ICD implantation may be based on prevention of ventricular arrhythmias instead of conduction delay.

There was a clear distinction between the fraction of patients with FVC values less than 80%. Respiratory insufficiency is described in approximately 30% of the general DM1 population,[7,24] whereas the prevalence of SRBD is highly variable among studies reporting percentages between 16% and 75%.[24,25] In the DM-scope registry, prevalence was comparable between both groups (32%) possibly resulting from the regular performance of PFTs, regardless of symptoms.[7] In the current study, patients were referred only in cases of suspected respiratory involvement, possibly inducing screening bias. A specification of respiratory symptoms was not included in the MYODRAFT registry, nor in the DM-scope article. Unfortunately, NIV indications were not included in the DM-scope report.[7]

It should be noted that the value of PFT as a screening modality in neuromuscular disorders is still being debated, as PFT seems unable to predict the presence of SRBD.[26] Most NIV indications were based on sleep apnea ascertained through polysomnography.

Although the degree of multiorgan involvement was more comparable than previously known, a difference between MIRS, DM1-activ^C scores, and presence of myotonia between subtypes was expected. None of the late-onset patients had MIRS scores over 3, confirming that severe muscle weakness is rare in late-onset DM1.[5,7,13] The current study also demonstrated a difference in functioning and participation between subtypes through DM1-activ^C scores.

Although CTG repeat length is presumed to play a major role in the severity of DM1 subtypes, other factors are likely to influence phenotype establishment as well. Previous studies have described the phenomenon of disease manifestations arising in a relatively short period of time in late-onset DM1.[7,11] This may result from RNA toxicity passing a threshold for deregulation of cell function.[5,27] Also, tissue-specific sensitivity to RNA foci may be related to variability in organ sensitivity and muscular sensitivity.[6]

Although RNA toxicity is likely to increase over a patient's lifetime, the effects of general aging must be taken into account. As patients affected by late-onset DM1 develop symptoms after 40 years of age, they were consequently older than adult-onset patients. Activity and participation are affected by age, but these are taken into account in the DM1-activ^C scoring system. In the Dutch general population, the frequency of ECG abnormalities increases after 65 years of age.[28] As the median age was 57 years in the late-onset group, however, first-degree AV block and bundle branch block could have been expected for approximately 4% and 1% of ECGs, respectively, as is the case in the Dutch population.[28] In our study, age increased the risk of having ECG abnormalities, yet the prevalence of conduction disorders was clearly higher than in healthy Dutch adults.[28] In addition, respiratory function is known to be influenced by aging, and age increased the risk of having an NIV indication in our study population.[29,30] Although age is taken into account in FVC predicted values, the prevalence of SRBD was also higher than in the aging Dutch population.[31] Despite the effects of aging, our study has demonstrated a high prevalence of multiorgan involvement among all patients, stressing the need for adequate screening and follow-up despite age or DM1 subtype.

Another limitation is that subtype determination may be challenging in clinical practice. CTG repeats are known to overlap between subtypes, to demonstrate tissue-specific expansions, and to be unstable throughout life.[32,33] Also, many different classifications have been used in the literature. In our study, age of onset was used as the primary feature for subtype differentiation, yet CTG repeat size was taken into account.

Although the late-onset group was considerably smaller than the adult-onset group, a relatively large number of patients of both subtypes were included, even though late-onset DM1 patients can remain unknown to health-care providers. Nevertheless, this may have influenced cohort characterization because more affected patients are more likely to be under follow-up. In addition, other

multisystemic complications such as central nervous system involvement and metabolic abnormalities were not evaluated,[34] as well as use of medication and its possible effects on cardiac conduction.

In conclusion, the prevalence of cardiac conduction delay in late-onset DM1 was comparable with the prevalence of conduction delay in adult-onset DM1. Moreover, DM1 subtype was unable to predict the presence of conduction delay on ECG. As most of the patients with cardiac abnormalities remained clinically asymptomatic, yearly screening through ECG is essential. Although patients diagnosed with the adult-onset subtype were more likely to have an NIV indication, 17% of late-onset DM1 patients still required NIV treatment. As a result, screening for multiorgan involvement in DM1 should be equally thorough and frequent in late-onset as in adult-onset DM1.

AUTHOR CONTRIBUTIONS

Isis B.T. Joosten: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Corinne Horlings:** Supervision. **Bettine Vosse:** Investigation; methodology; validation. **Anouk Wagner:** Data curation; investigation. **David S.H. Bovenkerk:** Data curation; investigation. **Reinder Evertz:** Investigation; supervision; validation. **Kevin Vernooy:** Investigation; supervision; validation. **Baziel G. van Engelen:** Conceptualization; investigation; methodology; project administration; supervision. **Catharina Gerritdina Faber:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; validation.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data underlying this article will be shared on reasonable request to the corresponding author.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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