International Journal of Cardiology 168 (2013) 1147–1153

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The frequency and severity of cardiac involvement in myotonic dystrophy type 2 (DM2): Long-term outcomes ☆

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ARTICLE INFO

Article history:
Received 21 September 2012
Accepted 11 November 2012
Available online 23 December 2012

Keywords:
Myotonic dystrophy type 1
Myotonic dystrophy type 2
Cardiac arrhythmias
Sudden cardiac death

ABSTRACT

Background: Frequency and severity of cardiac involvement in DM2 are still controversial. The aims of our study were to determine the frequency and progression of cardiac and muscle involvement in a relatively large cohort of patients with DM2 throughout Italy and Germany and to provide long-term outcomes in this disorder.
Methods: 104 DM2 and 117 DM1 patients underwent baseline and follow-up assessments of, ECG, 24 h Holter monitoring, 2D echocardiography and electrophysiological study (EPS) when appropriate, and manual muscle strength testing (mean follow-up: 7.4 ± 4.1 for DM2 and 5.7 ± 4 years for DM1).
Results: Overall, 10% of DM2 patients vs 31% of DM1 patients had PR ≥ 200 ms and 17% of DM2 patients vs 48% of DM1 patients had QRSD ≥ 100 ms. Six patients with DM2 vs 28 patients with DM1 required PM/ICD implantations. DM2 patients were stronger than DM1 patients at baseline, but muscle strength worsened significantly over time ($p<0.0001$), just as in DM1, although at a slower annual rate.
Conclusion: Our data demonstrate that the frequency and severity of cardiac involvement and of muscle weakness are reduced in DM2 compared to DM1 and that progression is slower and less severe. Nonetheless, careful cardiac evaluation is recommended in this patient population to identify patients at risk for potential major cardiac arrhythmias.

1. Introduction

Myotonic dystrophy type 1 (DM1) and type 2 (DM2) are autosomal dominant disorders, characterized by muscle weakness, myotonia and early-onset cataracts. Multiple organs are affected and, among these, the heart. While cardiac involvement is well documented in DM1 [1–15] and predictors of AV conduction disturbances, cardiac arrhythmias and sudden death are being defined in DM1 [4,16–21] there are still limited data in DM2 [22–26]. In DM2, cardiac abnormalities have been reported to be similar to those described in DM1 [22–25] but less frequent. This has led some authors [21,25] to suggest that DM2 may be a more favorable and milder disease compared to DM1. A more recent study including 25 patients with DM2 [27] demonstrated that, despite the older age and greater prevalence of cardiovascular disease (coronary heart disease and heart failure) among these patients, they had a similar rate of severe ECG abnormalities as patients with DM1. How and if the degree of cardiac involvement relates to muscle impairment is still unclear.

We performed an observational study in a relatively large cohort of patients with DM2 throughout Italy and Germany on the frequency, severity and progression of cardiac and muscle involvement in this disease so as to provide long-term outcomes in patients with DM2.

2. Methods

2.1. Patients

Patients with the diagnosis of DM1 and DM2 attending the Neuromuscular Clinic at IRCCS Policlinico San Donato from 1997 till present were identified through the clinic database and manual review of patients' charts.

After obtaining informed consent, we included in the study a random sample of 104 DM2 patients (54 DM2 patients from the Italian cohort and 50 DM2 patients from the Neuromuscular Center in Munich; mean age: 58.75 ± SD 12.8 years; range: 24–92 years). All patients were ambulatory at baseline.

The German and Italian populations were similar with respect to age and follow-up but the two populations were not identical when considering disease duration. Disease duration was in fact longer in the Italian population compared to the German one (20 ±

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcard.2012.11.076

8.8 vs 14.8 ± 12.3, p = 0.0006) but this was clinically irrelevant given the long period of disease affection in both groups.

Data were compared to 117 DM1 patients (mean age: 48.5 ± SD 13.6 years; range: 16–74 years), all ambulatory at baseline (Muscle Impairment Rating Scale, MIRS: 2.7 ± 1.1 SD) [28]. There was no a priori selection based on their cardiac history or degree of muscle involvement or CTG/CCTG-expansion.

The diagnosis of DM1 was genetically determined according to standard procedures [29] and patients were classified according to degree of CTG expansion as E1 (50–100), E2 (100–1000), and E3 (>1000): 37 in E1 range; 76 in E2 range; and 4 in E3 range. The diagnosis of DM2 was made according to clinical Consortium criteria [30] and genetically confirmed by FISH.

Disease duration was taken as the time elapsed from onset of symptoms and last available clinical follow-up. Symptoms at onset of disease could be classified in 4 fields: genetic diagnosis with no symptoms, muscle symptoms, cardiac symptoms and other symptoms. Muscle symptoms which were considered from the patients' histories were muscle weakness, myotonia, muscle pain, rhabdomyolysis; cardiac symptoms reported were dyspnea, palpitations, syncopes, dizziness, and vertigo. Other symptoms considered to determine onset of disease were cataracts or symptoms of multisystem organ involvement. For asymptomatic patients, in whom the diagnosis was made during family screening, onset was taken as the time of genetic diagnosis. For asymptomatic patients, in whom the diagnosis was made during family screening, but medical history documented that signs (high Creatine Kinase, CK or myotonic discharges on EMG) or symptoms were retrospectively present before the time of genetic diagnosis, that time was taken as the time at onset rather than the time of genetic testing.

For patients who were no longer attending the clinic, their status was determined by referring to an internal neuromuscular and cardiac database.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by local ethics committee.

2.2. Cardiac evaluation

At study entry all patients underwent complete clinical cardiac evaluation including: physical examination, standard 12-lead ECG, 24-hour Holter monitoring and 2D-echocardiography.

On resting ECG any alteration was noted. Specifically, patients were identified as having mild ECG abnormalities if they had a PR interval ≥ 200 ms and a QRS duration ≥ 100 ms. The following abnormalities were considered severe, according to Groh et al. [4]: PR interval ≥ 240 ms, QRS duration ≥ 120 ms, second or third degree AV block, and a rhythm other than sinus.

On 24-hour Holter monitoring the following variables were considered: average heart rate, longest RR interval, any degree of AV block, number of supraventricular (SV) and ventricular (V) ectopic beats, and runs of SV or V tachycardia.

Electrophysiological study (EPS) was performed in patients presenting at least one of the following criteria: occurrence of syncope, recurrent episodes of palpitations, history of sudden death (SD) in relatives affected by DM 1 or 2; presence of PR ≥ 280 ms, second degree AV block, pauses ≥ 3 s, trifascicular block, non-sustained/sustained atrial fibrillation/flutter, or SV or V tachycardia on Holter recording. In each patient sinus node function, AV conduction, and atrial and ventricular inducibility were evaluated. Recommendations for PM and ICD implantation were based on guidelines recently published [31].

On echocardiograms the following parameters were measured, according to the recommendations of the American Society of Echocardiography [32]: wall thickness, cavity diameters and ejection fraction (EF). Left ventricular (LV) systolic dysfunction was diagnosed when EF was lower than 50%.

There was a blind reading of ECG, 24-h Holter monitoring and 2D-echocardiography by either of 2 independent cardiologists (LDA, GDA, FB). The analyses were performed without the cardiologists knowing the diagnosis and the clinical status of the patients.

To better identify cardiac involvement cardiovascular risk factors such as smoking, cholesterol and triglyceride levels, hypertension, family history for vascular disease and sudden cardiac death, diabetes and ongoing treatment were also assessed.

2.3. Neuromuscular assessment

Muscle strength was determined using the modified Medical Research Council (MRC) scale on 15 muscle groups on the right and on the left side. The total normal Mega MRC score was 150.

Myotonia was quantified using an arbitrary 4-point self-assessment scale (from 0 = no myotonia to 3 = severe myotonia) in 5 different body parts (eyes, tongue, jaw muscles, hands, and lower limbs). Body parts are listed in this subjective scale to facilitate the patients in thinking of their symptoms.

2.4. Cardiac and muscle follow-up assessments

Patients in our Neuromuscular Clinic are subjected on a routine basis to annual manual muscle strength testing, annual ECG, 24-hour Holter ECG monitoring and 2D-echocardiograms, unless otherwise required.

Neuromuscular and cardiac follow-up was fully available in 75% of patients with DM2 and in 70% of patients with DM1. In the remaining patients, neuromuscular and cardiac parameters were noted as 'unchanged' over time in the annual update of database or charts, but the exact values were not reported and thus this data was not included in the statistical analysis. Mean follow-up period was of 7.4 ± 4.1 years (range: 1–25 years) for DM2 patients and 5.7 ± 4 (range 1–16 years) for DM1 patients.

2.5. Statistical analysis

Patient characteristics were reported as mean and standard deviation (SD) and percentage if qualitative. For all the quantitative measurements a comparison between DM2 and DM1 patients was performed applying parametric unpaired t test (with Satterthwaite's correction for degrees of freedom) or the analogous non-parametric Wilcoxon–Mann–Whitney's test (U). For the qualitative variables, the chi-squared test or Fisher's exact test was applied. Changes between two points in time (follow-up with respect to baseline) were described by means of parametric paired t test or analogous nonparametric Wilcoxon sign test and were considered separately for DM2 and for DM1. In addition, a two-way repeated-measures analysis of variance was applied to evaluate differences in time between DM2 and DM1 patients with the appropriate correction for degrees of freedom if it was necessary. Finally, the effect of age at onset on weakness progression over time was investigated adjusting for sex, symptoms at onset and disease duration applying a multiple regression model.

The survivor time to death (overall), the time the patient ended up needing a wheelchair, the time non-invasive ventilation (NIV) was started and PM or ICD were implanted were taken as parameters of severity of disease. The Nelson–Aalen estimator was applied to describe the cumulative hazard for overall death, PM and ICD implantation, NIV and use of wheelchair in DM1 and DM2 patients. Difference in the cumulative hazard estimates was evaluated by the more appropriate test.

A p-value less than 0.05 was considered significant (two-side). All the analyses were carried out using STATA 10 (Stata Corporation. STATA 10. College Station, Texas (US); 2008).

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Patients

There was a higher proportion of females in the DM2 cohort than in the DM1 cohort (Table 1; chi-squared = 2.45 p = 0.117). DM2 patients were on average older than DM1 patients (t = 5.71, p < 0.0001): the age ranged from 24 to 92 years in DM2 with respect to age range from 16 to 74 years in the DM1 population (Table 1). Disease duration was statistically shorter in DM2 patients with respect to DM1 patients but clinically irrelevant (mean 17.5 ± 10.9 for DM2 vs 20.9 ± 12.1, t = 2.18, p = 0.03). Both DM2 and DM1 were mostly inherited by paternal transmission, but with a lower proportion in DM2 compared to DM1 patients (chi-squared = 9.71, p = 0.002). Finally, age at onset was on average greater in DM2 patients than in DM1 ones (41.2 ± 14.1 years vs. 27.6 ± 15.4 years; t = 6.83, p < 0.0001). Inheritance information was available for 74/104 DM2 patients and 62/117 DM1 patients. In all the remaining patients (except for 2 patients with DM1 and 3 patients with DM2 who were adopted) parents were unavailable for genetic studies or refused medical attention.

3.2. Symptoms at onset

In our cohort of DM2 patients, almost half of the patients complained of muscles weakness as their symptom at onset, especially in the proximal district and in the lower limbs. Forty percent presented with muscle pain or myotonia (Table 2). DM1 patients instead, more frequently presented myotonia at the beginning of their clinical history (36.8%), followed by muscle weakness and none complained of muscle pain. In general, the different clinical presentation between two cohort was relevant (p-value for

Table 1
Demographic characteristics of DM2 (n = 104) and DM1 patients (n = 117).

	DM2	DM1	p
Females (%)	52.3%	42%	0.117
Age in years (mean ± SD)	58.7 ± 12.8	48.5 ± 13.6	<0.0001
Age at onset (mean ± SD)	41.2 ± 14.1	27.6 ± 15.4	<0.0001
Disease duration in years (mean ± SD)	17.5 ± 10.9	20.9 ± 12.1	0.03
Paternal transmission (%)	55.4	80.7	0.002