Journal of the Neurological Sciences 399 (2019) 118–124

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Prevalence and predictor factors of respiratory impairment in a large cohort of patients with Myotonic Dystrophy type 1 (DM1): A retrospective, cross sectional study

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ARTICLE INFO

Keywords:
DM1
Myotonic dystrophy type 1
Respiratory impairment
Respiratory
Restriction

ABSTRACT

Introduction: Respiratory complications are relevant in DM1, leading to a significantly increased morbidity and mortality risk in these patients; however, so far only few studies concerning respiratory function have been conducted in DM1 patients.

We report a retrospective, multicenter, cross sectional study on a large cohort of DM1 patients widely characterized in the phenotype, to assess prevalence and identify predictors of restrictive respiratory syndrome.
Methods: 268 DM1 subjects aged > 18 years, who had recently performed spirometric tests were included; restrictive syndrome was diagnosed if forced vital capacity (FVC) < 80% of predicted. This cut-off was used for statistical univariate and multivariate analysis.
Results: 51.9% patients showed a restrictive syndrome, and half of them had indication to non-invasive ventilation (NIV), yet only 50% resulted compliant to NIV. CTG expansion size in leukocytes, clinical muscle severity, most functional parameters of respiratory muscle involvement, presence of cardiac conduction disturbances, pacemaker (PMK), exertion dyspnea, obstructive sleep apnea, and indication and compliance to NIV were all significantly associated with restrictive syndrome at the univariate analysis; in the multivariate model only the first two factors resulted independent predictors.
Discussion: A high prevalence of restrictive syndrome in our DM1 cohort, mainly due to respiratory muscles weakness, was observed and documented; the severity of muscle impairment and the CTG expansion size confirmed to be independent predictors of respiratory restriction. Our data suggest that optimization of respiratory therapeutic management, particularly regarding launching of NIV, might help to reduce the rate of deaths due to respiratory complications in DM1.

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https://doi.org/10.1016/j.jns.2019.02.012
Received 7 December 2018; Received in revised form 4 February 2019; Accepted 6 February 2019
Available online 07 February 2019
0022-510X/

1. Introduction

Myotonic dystrophy type 1 (DM1, MIM #160900) represents the most common muscular dystrophy in adults: the worldwide estimated prevalence is about 1:8000 among Caucasians [1], and a recent study from our group assessed a prevalence in Italy of 10:100000 [2].

DM1 is an autosomal dominant, multisystem disorder affecting, besides the skeletal muscle, various other tissues and organs, being caused by the pathological expansion of an unstable trinucleotide (CTG) repeat sequence in the 3′ untranslated region of the myotonic dystrophy protein kinase gene (*DMPK*), on chromosome 19q13.3 (MIM #605377) [3]; its pathogenesis is mainly related to a toxic effect of the mutant pre-mRNAs containing expanded CUG sequences that disrupt the expression of other genes, eventually affecting tissues homeostasis [4].

Owing to the mitotic and meiotic instability of the pathological CUG expansions, DM1 has a wide phenotypic spectrum, ranging from oligosymptomatic forms to the most severe, life-threatening, congenital disease [3].

Overall, DM1 patients have a reduced life expectancy, mainly due to respiratory or cardiac causes [5]: the mortality rate secondary to respiratory problems in DM1 patients ranges between 51 and 76%, and respiratory involvement appears as the main cause of death in patients affected by the most severe, congenital form [6]. Chronic respiratory impairment is also associated with an increased morbidity in DM1 patients [6,7], particularly because of a high risk of pulmonary infections, and potentially life-threatening perioperative complications following general anesthesia [5].

The main etiology of ventilatory dysfunction in DM1 is the development of a chronic restrictive syndrome due to the progressive weakness of respiratory muscles; however muscle fatigue, as revealed by measuring Maximum Inspiratory and Expiratory Pressures (MIP and MEP), can also affect these muscles, and be the earliest manifestation of their impaired function [8,9]. Moreover, in DM1 patients respiratory fatigue could be worsened by other disease symptoms or manifestations, i.e. myotonia of respiratory muscles, obstructive sleep apnea (OSA), overweight, ineffective cough due to weakness of the expiratory muscles, or hemidiaphragm palsy secondary to dysfunction of the phrenic nerve [10–14].

The progressive decline of respiratory muscle strength leads over time to a reduction of both static and dynamic lung volumes and to increased stiffness of the thoracic wall [15]. The restrictive lung disease, defined as a reduction of Vital Capacity (VC), Total Lung Capacity (TLC) and/or Forced Vital Capacity (FVC) $< 80\%$ of the predicted at Pulmonary Function Tests (PFT), has a prevalence estimated between 36% and 60% in different cohorts of DM1 patients [7,16–21].

On the other hand, since DM1 affects the Central nervous system (CNS), some studies pointed out that an abnormal sensitivity of the central respiratory drive to chemical blood changes, particularly of [CO_2], might contribute to the pathogenesis of respiratory impairment in DM1 [22–24].

With regards to the management of respiratory function in DM1 patients, a recent consensus statement underlined the need of being aware, during medical history collection, of symptoms suggestive of respiratory impairment and/or sleep breathing disorders, and to take into account the effect of cognitive and behavioral problems on the subjective evaluation of symptoms and the compliance to medical prescriptions [6].

The relevance of respiratory involvement on DM1 prognosis emphasizes the importance of the identification of predictor factors of respiratory impairment to evaluate the risk of severe respiratory complications in this population. However, so far only few studies addressed this issue [16–19,21] by assessing associations or correlations between spirometric parameters and various clinical features; moreover, most of these studies included small cohorts of DM1 patients, and their conclusions were in some cases discordant.

Therefore, we performed a retrospective, multicenter, cross-sectional study on a large cohort of DM1 patients, followed-up in 6 Italian Neuromuscular Centers. Aims of our study were to assess I) the prevalence of restrictive syndrome in DM1 and II) the predictive value of many clinical/diagnostic features, including anthropometric and demographic data, common life habits, molecular genetic data and other various DM1-related manifestations.

2. Materials and methods

The study cohort included 268 DM1 patients (age ≥ 18 years), which were in neurological follow-up at one of the following Centers: Departments of Neurology, Policlinico A. Gemelli (Rome), Policlinico S. Andrea (Rome), Policlinico Tor Vergata (Rome), Ospedale S. Camillo-Forlanini (Rome), Unione Italiana Lotta alla Distrofia Muscolare (UILDM) sez. Laziale (Rome) and Ospedale Clinicizzato SS Annunziata (Chieti). All patients had received the molecular diagnosis of DM1: in 235 the test also included a precise estimation of the (CTG)n in leukocytes [25], whereas in the remaining 33 cases a pathological expanded allele was detected, but the precise size was not estimated.

Each patient included had performed at his/her Referring Center at least one clinical evaluation together with one pulmonary function test (PFT) by a pneumologist during the last 18 months; in case of serial evaluations, the most recent one was taken into account; PFT results from DM1 patients thought to be unreliable because of severe facial muscle weakness or poor compliance to the test, were not included in the analysis.

All PFT had been performed according to the standards of the American Thoracic Society/European Respiratory Society [26], in the upright-seated position in all patients. The flow/volume curve and lung volumes were assessed by an open-circuit spirometry.

For each patient, the available following spirometric parameters (compared with predicted normal values for age and sex and expressed as a percentage) were collected both for prevalence and association studies: FEV1 (Forced Expiratory Volume in 1 s); FVC (Forced Vital Capacity); FEV1/FVC (Tiffeneau index); TLC (Total Lung Capacity); VC (Vital Capacity); MIP (Maximum Inspiratory Pressure); MEP (Maximum Expiratory Pressure).

The indication to Non-Invasive Ventilation (NIV) was assessed by pneumologists in the presence of symptoms suggestive of chronic respiratory insufficiency [6] plus at least one of the following features:

- diurnal hypercapnia ($PaCO2 \geq 45$ mm Hg) at the ABG;
- evidence of nocturnal hypoventilation at nocturnal pulse-oxymetry, defined as $SpO2 \leq 88\%$ for > 5 consecutive minutes or $< 90\%$ for $> 10\%$ of the whole sleep time;
- FVC $< 50\%$ of predicted.
- AHI ≥ 10 events/h

Compliance to NIV (meaning the use of NIV for > 4 h/day) was assessed only in patients who had performed the last pneumological follow-up control after the indication to NIV.

For association studies, the following data were also computed:

- gender; age at onset of the disease; age, BMI assessed by weight [kg]/height $[m]^2$ and score of Muscular Impairment Rating Scale (MIRS) [27] at the time of the PFT; mean (CTG)n value in leukocytes;
- smoking habits and number of cigarettes per day; treatment of myotonia by mexiletine;
- specific cardiac manifestations including: left ventricular ejection dysfunction (LVED) (if ventricular ejection fraction $< 50\%$ by transthoracic echocardiogram); cardiac conduction disorders, including any atrioventricular and/or bundle branch blocks (except for isolated right bundle branch block, not included because of its high prevalence in the general population) at basal ECG and/or 24 h

Holter monitoring; cardiac rhythm disorders, including atrial fibrillation, atrial flutter and not sustained ventricular tachyarrhythmias at basal ECG or 24-h Holter monitoring; prophylactic Pacemaker (PMK) or Implantable Cardioverter Device (ICD);
- symptoms of I) rest dyspnea, defined as shortness of breath occurring during rest, referred by the patient or by caregivers; II) exertion dyspnea, defined as shortness of breath during physical activity, with a score ≥ 1 on Modified Medical Research Council (mMRC) Dyspnea Scale [28]; III) snoring; IV) Excessive Daytime Sleepiness (EDS) was considered if either reported by the patient or caregivers: Epworth Sleepiness Scale was not applied, given the poor reliability showed in DM1 patients [14];
- other respiratory comorbidities including Chronic obstructive pulmonary disease (COPD), if known in past medical history and confirmed by a pneumologist on the basis of FEV1/FVC < 70% of the predicted at PFT, asthma, obstructive sleep apnea (OSA) diagnosed by polysomnography (PSG) on the basis of an apnea-hypopnea index (AHI) ≥ 5 events/h [14];
- any defect of oro-pharyngeal muscles function, either assessed by oro-pharyngo-oesophageal scintigraphy (OPES) or by flexible laryngoscopy by an otolaryngologists;

All diagnostic parameters included for statistical analysis had been collected within six months from the pneumological assessment.

Arterial blood gas (ABG) tests were not included in the statistical analysis because not routinely performed in concomitance with PFT; moreover, most available data had been obtained in DM1 patients in NIV to verify effectiveness and compliance to treatment.

All data used for this study had been collected primarily for diagnostic purposes, and patients (or the caregivers in case of congenital forms) had given their consent to use their data also for clinical research purposes.

The study design was made according to the Declaration of Helsinki and approved by the Ethical Committees of each participating Institution.

Statistical analysis was performed using SPSS software version 24.0 and included:

- descriptive statistics concerning anthropometric, molecular, clinical and spirometric data;
- association studies: DM1 patients were divided in two groups, based on the diagnosis of a restrictive pattern using FVC < 80% of the predicted value as cut-off. Then, the two groups were compared with respect to the prevalence of the variables listed above, using univariate and multivariate models.

For univariate analysis, Mann-Whitney *U* test and Pearson's Chi-squared test were applied for numeric or categorial variables respectively; the level of significance was set at $p < .05$.

For multivariate analysis, we chose FVC < 80%, indicating a restrictive syndrome, as the dependent variable and we considered only those variables showing a significant association ($p < .05$) at the univariate analysis. For each variable, odds ratios, 95% confidence interval and *p* value were calculated. To measure reliability of the multivariate model, area under Receiver Operating Characteristic (ROC) curve was calculated.

3. Results

Of the 268 DM1 patients, 56.3% (151/268) were males and 43.7% females, with a mean age of 46.2 years ± 12.9. Mean age of disease onset was 25.2 years ± 13.4: 93.9% patients (257/268) had a juvenile or adult onset of the disease, whereas 4.1% (11/268) suffered from the congenital form. Mean (CTG)n value in leukocytes was 613 ± 622.6 (Table 1). Mean follow-up was 119.74 ± 151.14 months (median 97.5).

Table 1
Summary of available clinical and diagnostic data on the DM1 cohort of study. SD: standard deviation. For the remaining abbreviations, see Materials and Methods section.

	Patients	n (%)	Mean ± SD
Age (years)	268		46.2 ± 12.9
Male	268	151 (56.3)	
BMI (kg/m^2)	246		26.4 ± 4.9
Onset (years)	229		25.2 ± 13.4
(CTG)n	235		613.0 ± 622.6
MIRS	263		3.1 ± 0.9
Congenital cases	267	11 (4.1)	
Mexiletine use	262	18,0 (6.7)	
Smokers	205	55,0 (26.8)	
N° cigarettes/day	202		3.6 ± 7.6
LVEF dysfunction	256	29 (11.3)	
Tachyarrhythmias	255	29 (11.4)	
Conduction blocks	255	79 (31.0)	
PMK	263	43 (16.3)	
ICD	261	22 (8.4)	
COPD	250	33 (13.2)	
Rest dyspnea	225	27 (12.0)	
Exertion dyspnea	201	97 (48.3)	
EDS	219	138 (63.0)	
Snoring	143	85 (59.4)	
OSA	165	105 (63.6)	
Oro-pharyngeal muscles dysfunction	236	122 (51.7)	
Pulmonary function tests			
FEV1 (%)	262		79.0 ± 22.2
FEV1 (l)	260		2.5 ± 0.9
FEV1/FVC	245		85,7 ± 12.5
TLC (%)	142		76.9 ± 17.6
TLC (l)	140		4.5 ± 1.3
FVC% (%)	268		77.6 ± 22.1
FVC (l)	264		2.9 ± 1.1
VC (%)	234		77.2 ± 21.1
VC (l)	232		3.0 ± 1.1
MIP (%)	159		59.1 ± 32.0
MEP (%)	159		39.9 ± 22.7
NIV indication	233	83 (35.6)	
NIV compliance	238	48 (20.2)	

Our study cohort comprised the whole spectrum of skeletal muscle disease severity: 5.22% (14/268) patients had a MIRS score = 1, 19.4% (52/268) a score = 2, 40.3% (108/268) a score = 3, 29.1% (78/268) a score = 4 and 4.1% (11/268) a score = 5. Mean MIRS score was 3.1 ± 0.9.

In the whole cohort mean FVC value was 77.6 ± 22.1, mean values of other PFT parameters are listed in Table 1; data about MIP and MEP values were 59.1 ± 32 and 39.9 ± 22.7 of predicted, respectively (Table 1).

About 33% of patients evaluated for this parameter were overweight (25 ≤ BMI < 30) and 18% were obese (BMI ≥ 30). Mean BMI value was 26.4 ± 4.9 kg/m^2.

Clinical symptoms suggestive of chronic respiratory impairment were frequent in DM1 patients: indeed, when specifically requested to patients or their caregivers: 63% referred EDS, 59.4% snoring, 48.3% exertion dyspnea, and 12% rest dyspnea.

Regarding other factors influencing respiratory function (Table 1), 13.2% had COPD, either or not in association with the restrictive syndrome; 26.8% of patients referred to be smokers, with a low mean of number of cigarettes per day (3.6 ± 7.6). Finally, 63.6% (105/165) of patients who had performed PSG had OSA, being mild (> 5 AHI < 10) in 22/105 patients.

35.6% of the total cohort fulfilled the criteria to start NIV, either for ventilatory insufficiency and/or OSA, prescribed with preferred Bilevel mode [4], yet only 48 of them (57% with NIV indication, 20.2% of the total cohort) were fully compliant to treatment (Table 1).

Echocardiogram findings of LVED were observed in 11.3% of

Table 2
Summary of available clinical and diagnostic data on the DM1 cohort of study divided by the presence of restrictive respiratory impairment (cut-off FCV < 80% of predicted) and results of univariate analysis. According to the type of variable observed (numerical or categorical, respectively) Mann-Whitney or $\chi 2$ test were performed: results are indicated in the corresponding column. Significant values are bolded. SD: standard deviation; NS: not significant. For the remaining abbreviations, see Materials and Methods section.

	FVC < 80% (n = 139)			FVC ≥ 80% (n = 129)			Mann-Whitney	$\chi 2$ test
	Patients	n (%)	Mean ± SD	Patients	n (%)	Mean ± SD	p	p
Age (years)	139		46.7 ± 11.8	129		45.6 ± 14.1	NS	
Male	139	78 (56.1)		129	73 (56.6)			NS
BMI (kg/m2)	130		27.0 ± 5.0	116		25.7 ± 4.7	NS	
Onset (years)	129		24.5 ± 13.7	100		26.1 ± 13.0	NS	
(CTG)n	**125**		**686.0 ± 614.9**	**110**		**530.0 ± 623.7**	**< 0.001**	
MIRS	**138**		**3.4 ± 0.8**	**125**		**2.7 ± 1.0**		**< 0.001**
Congenital cases	138	9.0 (6.5)		129	2.0 (1.6)			NS
Mexiletine use	137	6.0 (4.4)		125	12.0 (9.6)			NS
Smokers	109	25.0 (22.9)		96	30.0 (31.3)			NS
N° cigarettes/day	108		3.1 ± 7.4	94		4.3 ± 7.8	NS	
Cardiopathy	134	16.0 (11.9)		122	13.0 (10.7)			NS
Tachyarrhythmias	132	19.0 (14.4)		123	10.0 (8.1)			NS
Conduction blocks	**132**	**53.0 (40.2)**		**123**	**26.0 (21.1)**			**0.005**
PMK	**139**	**32.0 (23.0)**		**124**	**11.0 (8.9)**			**0.001**
ICD	138	14.0 (10.1)		123	8.0 (6.5)			NS
COPD	129	19.0 (14.7)		121	14.0 (11.6)			NS
Rest dyspnea	115	19.0 (16.5)		110	8.0 (7.3)			NS
Exertion dyspnea	**102**	**62.0 (60.8)**		**99**	**35.0 (35.4)**			**0.001**
EDS	116	79.0 (68.1)		103	59.0 (57.3)			NS
Snoring	75	47.0 (62.7)		68	38.0 (55.9)			NS
OSA	**93**	**67.0 (72.0)**		**72**	**38.0 (52.8)**			**0.007**
Oro-pharyngeal muscles dysfunction	123	72.0 (58.5)		113	50.0 (44.2)			NS
Pulmonary function tests								
FEV1 (%)	**134**		**63.0 ± 16.5**	**128**		**95.7 ± 13.5**	**< 0.001**	
FEV1 (l)	**133**		**2.0 ± 0.7**	**127**		**3.0 ± 0.8**	**< 0.001**	
FEV1/FVC	125		86.2 ± 13.3	120		85.2 ± 11.7	NS	
TLC (%)	**78**		**65.5 ± 12.1**	**64**		**90.8 ± 12.6**	**< 0.001**	
TLC (l)	**76**		**3.8 ± 1.1**	**64**		**5.2 ± 1.2**	**< 0.001**	
FVC (%)	**136**		**60.8 ± 14.6**	**128**		**95.5 ± 12.5**	**< 0.001**	
FVC (l)	**136**		**2.3 ± 0.8**	**128**		**3.6 ± 0.9**	**< 0.001**	
VC (%)	**119**		**61.3 ± 14.3**	**115**		**93.5 ± 13.1**	**< 0.001**	
VC (l)	**118**		**2.4 ± 0.8**	**114**		**3.6 ± 0.9**	**< 0.001**	
MIP (%)	**75**		**52.4 ± 26.8**	**84**		**65.0 ± 35.2**	**0.014**	
MEP (%)	**75**		**34.6 ± 15.5**	**84**		**44.6 ± 26.8**	**0.030**	
NIV indication	**114**	**62.0 (54.4)**		**119**	**21.0 (17.6)**			**< 0.001**
NIV compliance	**118**	**37.0 (31.4)**		**120**	**11.0 (9.2)**			**< 0.001**

patients. In 31% of patients (79/255) there were ECG-documented conduction abnormalities and in 11.4% ECG-documented cardiac tachyarrhythmias (29/255); 16.3% patients (43/263) and 8.4% patients (22/261) had implanted a prophylactic PMK or ICD, respectively.

Signs of oropharyngeal muscles dysfunction were present in 51.7% of the patients assessed (122/236) (Table 1).

Only 6.7% patients (18/262) took mexiletine as treatment for myotonia, yet data regarding compliance to mexiletine treatment were not available.

PFT documented a restrictive syndrome in 51.9% DM1 patients (139/268), with a mean FVC value of 60.8 ± 14.6% (Table 2): in 34 of them (24,5%) PFT parameters indicated a severe restrictive syndrome causing chronic respiratory failure. On the other hand, in 48.1% DM1 patients (129/268) without a restrictive syndrome the mean FVC value was 95.5 ± 12.5% (Table 2).

By univariate analysis (Table 2), restricted and non-restricted DM1 patients significantly differed for most spirometric parameters including FEV1, TLC, VC, MIP, MEP.

Regarding the other features (Table 2), restricted patients showed higher mean (CTG)n value in leukocytes, MIRS score prevalence of exertion dyspnea, OSA, conduction abnormalities, and prophylactic PMK implantation. Finally, restricted DM1 patients had more frequent indication, also showing greater compliance to NIV.

By multivariate analysis, only MIRS and (CTG)n resulted independent predictive factors of restrictive syndrome in DM1 (Fig. 1, Table 3). Hosmer–Lemeshow test was 0.631.

4. Discussion

The development of chronic, progressive restrictive ventilatory failure can affect prognosis in terms of survival in many neuromuscular diseases: in this regard, progresses in its early diagnosis and therapeutic management by non-invasive therapeutic tools (NIV, respiratory physiotherapy and cough assist machine) have improved life expectancy of patients affected by various neuromuscular diseases [29]. In contrast, despite a slowly progressive restrictive lung syndrome [7], respiratory problems and related complications still represent the main cause of reduced life expectancy in DM1 [5].

Indeed, it might be possible that in DM1 patients the concurrence of other disease-related manifestations, i.e. sleep apneas or obesity associated to insulin resistance, would increase fatigue and favor the worsening of respiratory muscles function. Moreover, the weakness of the oropharyngeal muscles, besides predisposing to OSA, could increase the risk of aspiration pneumonia. Finally, frontal cognitive and behavioral symptoms in DM1 patients can affect awareness about their disease and related symptoms, adhesion to medical follow-up or compliance to the therapeutic indications for managing respiratory problems [6,30,31].

Although a consensus statement for the diagnosis and management

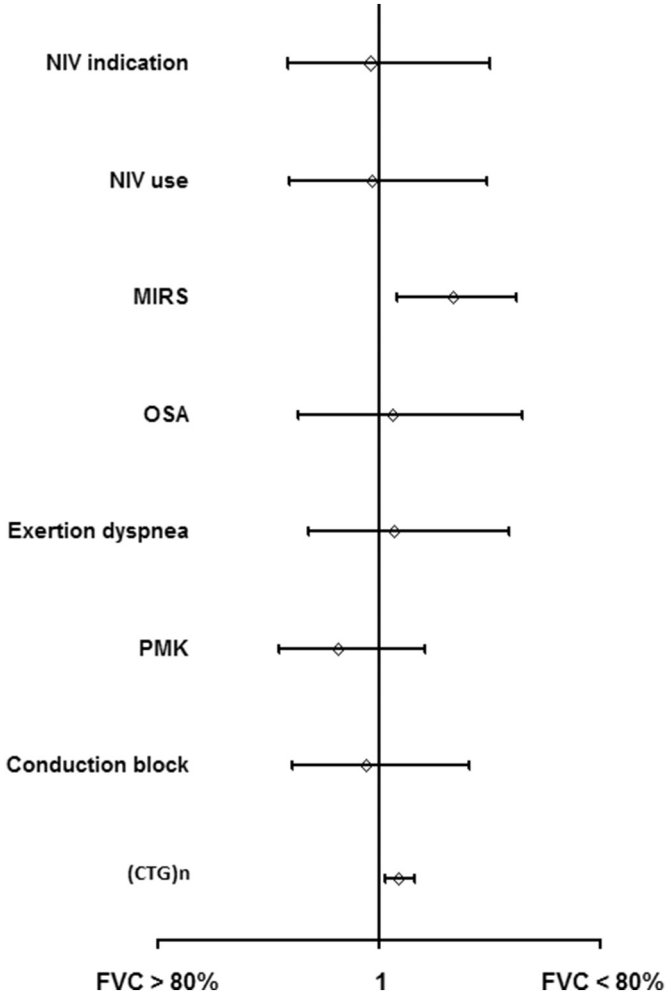

Fig. 1. Forrest plot of the multivariate analysis.

Table 3
Results of the multivariate analysis. OR: odds ratio; CI: confidence interval; NS: not significant. For the remaining abbreviations, see Materials and Methods section. Significant values are bolded.

	OR	p
MIRS	**1.619 (1.165–2.252)**	**0.004**
(CTG)n	**1.002 (1.000–1.003)**	**0.022**
Conduction blocks	0.634 (0.221–1.822)	NS
PMK	0.388 (0.106–1.419)	NS
NIV indication	0.602 (0.180–2.011)	NS
NIV compliance	0.624 (0.196–1.985)	NS
Exertion dyspnea	0.885 (0.360–2.178)	NS
OSA	0.795 (0.274–2.306)	NS

of respiratory problems in DM1 has been recently proposed [6] currently there are no specific established guidelines, and until now, only a limited number of clinical studies have been focused on the estimation of the prevalence and the characterization of respiratory involvement, or the identification of possible predictor factors of risk of respiratory failure in DM1 patients [16–19,21].

Aiming to clarify these issues, we performed a multicenter, retrospective, cross-sectional study analyzing a large (268 subjects) and well characterized cohort of DM1 patients in order to estimate the prevalence and to identify any predictors of restrictive lung disease in DM1. To our knowledge, this study includes the largest cohort of Italian DM1 patients assessed about respiratory function so far reported in the literature, being overall the third largest cohort together with two different French DM1 cohorts including 1409 [32] and 283 patients [19] respectively.

We used a FVC < 80% of the predicted as cut-off to diagnose restrictive lung disease, a cut-off value similar [21,33] or close [4,5,17,18] to those used in most respiratory studies concerning DM1. Indeed, a restrictive pattern was diagnosed in about 50% of our DM1 patients (Table 1); our findings thus indicate a high prevalence of respiratory impairment in DM1, higher than other studies [16,32], that however had used a FVC < 70% as cut-off value, but in agreement with the data by Kaminski et al. estimated in a cohort of 106 DM1 patients [17].

MIP and MEP data, available in 159 out of 268 DM1 patients, documented values below the respective cut-off in about 2/3 of cases (95/159 for MIP, 91/159 for MEP), showing that fatigue of respiratory muscles is also highly prevalent in DM1 patients. On the other hand, the absolute values of MIP and MEP resulted comparable in all patients (Table 2), suggesting a similar extent in the involvement of inspiratory and expiratory muscles. Our findings contrast with the study by Fregonezi et al., that documented a decreased MEP/MIP ratio in DM1 patients suggesting that expiratory muscles would be more affected than inspiratory muscles in DM1 [8], whereas agree with the results obtained by Cho et al. [34].

Regarding the severity of respiratory impairment, 25% of restricted DM1 patients in our cohort had a diagnosis of chronic ventilatory failure (FVC < 50% of predicted), and about 54% (62/114) of restricted patients had received indication to NIV according to the diagnostic criteria described in the methods section. Also 17.6% of non-restricted DM1 patients received indication to NIV for moderate/severe sleep apnea syndrome, as nocturnal hypoventilation can occurs as a consequence of fatigue aggravating weakness of respiratory muscles [6,14]. So, this study confirms a high prevalence of OSAS in DM1 patients, supporting previous studies [6,35].

To identify any predictor factors of respiratory impairment, we performed a statistical comparison between restricted and non-restricted DM1 patients, analyzing many clinical findings such as other features of DM1, common life-style habits and other respiratory conditions that could affect lung function (i.e. asthma or COPD) (Table 2).

In agreement with literature data [19,20,23] we documented a significant association between restrictive syndrome, MIRS score or (CTG)n in leukocytes; moreover, we found an association with OSA, cardiac conduction defects and PMK implant (Table 2). On the other hand, neither sex, age, disease onset, BMI, tachyarrhythmias, ICD implant, LVED, oropharyngeal muscles dysfunction, COPD, smoking habits or mexiletine treatment resulted independently associated with restrictive syndrome. Regarding the influence of gender on DM1 phenotype, our results are discordant from those by Dogan et al. [32] supporting a higher risk for restrictive syndrome in male DM1 patients; the larger cohort included in this study (1409 patients) would support their conclusions, but such discrepancy might also depend on different cut-off chosen to categorize restricted patients in the two studies.

Some studies suggested an association between respiratory impairment and BMI [17–19,30], whereas our results do not support these conclusions; indeed, we found a lack of association between restriction and BMI, similar to what assessed on a Spanish DM1 patients cohort that included a similar low prevalence of obese patients (BMI values ≥30) [21]. This observation would suggest that dietary habits (i.e. diffusion of the mediterranean diet in Italian and Spanish vs DM1 patients from non-Mediterranean countries) could influence the results of association studies concerning ventilatory restriction and BMI in DM1.

The apparent lack of association between ventilatory restriction and mexiletine treatment emerging by our study is certainly biased by the fact that, although clinical myotonia would occur in many DM1 patients, only few of them (18/262 in our cohort) probably decided to start mexiletine to alleviate this symptom. Thus, perspective studies are needed to assess the effects of mexiletine on ventilatory function in DM1.

Among subjective symptoms of chronic respiratory insufficiency only exertion dyspnea resulted significantly associated with the restrictive pattern; this, indeed is not surprising if we consider that such symptom can result either from respiratory insufficiency or skeletal muscle weakness, features tightly related in DM1 (Table 2).

As expected, indication to NIV is associated to restrictive pattern in DM1 patients; remarkably, compliance to NIV was also higher in this group (Table 2). Our findings agree with the conclusions by Boussaid et al. [30], who suggested that the presence of related symptoms would increase compliance to NIV in DM1 patients as these would appreciate a subjective benefit and improvement of their quality of life, differently from asymptomatic subjects receiving NIV indication based on the results of PFT or following an episode of acute respiratory failure.

Multivariate analysis confirmed, in agreement with previous studies [17,18], that in DM1 MIRS and (CTG)n would be the only independent predictors of restrictive respiratory syndrome; as these two variables would also predict the development of major cardiac conduction defects and OSA [14] this might explain their association to respiratory impairment at the univariate analysis (Table 2).

As stated above, our results highlight and confirm the poor compliance to NIV of DM1 patients, issue that could particularly affect the prognosis in terms of survival due to respiratory complications [30,36–38]; indeed, about 40% of restricted patients with indication to NIV in our cohort did not begin, quit or insufficiently use (< 4 h per night) it, thus being at higher risk for death or invasive mechanical ventilation.

Such poor compliance compared to other neuromuscular conditions is likely related to the CNS involvement affecting the frontal lobes, which causes in DM1 patients a reduced awareness about themselves and their disease, and an overall poor adherence to medical advices and/or prescriptions [31,39]. Moreover, weakness of facial muscles usually observed in DM1 patients could cause leak of air from the face mask, resulting bothersome and consequently reducing their compliance to this treatment [6].

In the attempt to improve patients' compliance, we suggest that it would be preferable to launch NIV and/or other respiratory devices during a brief hospitalization rather than in an outpatient setting, as the former would allow pneumologists to better manage I) the management of the devices by the patients and/or the caregivers II) the choice of the face-mask and, III) the set-up of ventilation pressures of ventilators.

The main limitation of our study, common to the most similar ones conducted in DM1 patients, is related to its retrospective design, not allowing availability of whole data from all cohort of study for any variable included in the study, as in the case of the lack of ABG data. Of course, perspective studies will help to clarify still unsolved questions regarding the contribution of specific in the respiratory impairment or in the respiratory prognosis, in order to eventually improve their diagnostic and therapeutic management of DM1.

5. Conclusions

In conclusion, our study documents a high prevalence of restrictive syndrome in DM1 patients, with respiratory muscles involvement being the main determinant of ventilatory dysfunction, and it confirms that both the severity of muscle impairment and the extent of the CTG expansion in leukocytes can help to stratify the risk of respiratory problems in these patients.

Acknowledgements

we thank Dr. Isabella Miele for revising the English form of the manuscript. This work was partially supported by grants from M.I.U.R (Italian Ministry for the University and Scientific Research), Fondi Linea D1 2017.

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