Dyspnea assessment in myotonic dystrophy type 1

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Highlights

- Dyspnea scores are low in Myotonic Dystrophy type 1 (DM1) patients
- A mMRC score ≥ 2 (dyspnea in daily living) is associated with lower Vital Capacity
- A mMRC score ≥ 2 is associated with a lower six-minute walking test distance
- A mMRC score ≥ 2 is associated with more severe motor handicap
- The mMRC scale might be an useful tool to assess dyspnea in daily living in DM1

Abstract

In Myotonic Dystrophy type 1 (DM1), combining respiratory symptom screening and respiratory function testing, is crucial to identify the appropriate time for ventilatory support initiation. Dyspnea has been little investigated in DM1. To provide a multidimensional description of dyspnea, questionnaires assessing dyspnea were administered to 34 consecutive adult patients with DM1 (median(25^{th}-75^{th} centile) age of 36(28-49), Vital Capacity (VC) of 74(64-87)% of predicted value). Dyspnea scores were low whatever the questionnaire used: Multidimensional Dyspnea Profile score of 2(0-4.7)/50 for dyspnea sensory descriptor and of 0(0-4.7)/60 for the emotional descriptor, Visual Analogue Scale score of 0(0-0)/10 in sitting and supine position and Borg score after six-minute walk test (6MWT) of 2.2(1.8-4.2)/10. Eleven patients (32%) reported disabling dyspnea in daily living (modified Medical Research Council (mMRC) score $\geq$ 2). In comparison with patients with mMRC score < 2, patients with mMRC score $\geq$ 2 had a more severe motor handicap (Muscular Impairment Rating score of 4.0(4.0-4.0) *vs* 3.0(2.0-3.5), p<0.01), a lower 6MWT distance (373(260-424) *vs* 436(346-499)m, p=0.03) and a lower VC (64(48-74)% *vs* 75(69-89)%, p=0.02). These data suggest that the mMRC scale might be an easy-to-use and useful tool to assess dyspnea in daily living in DM1 patients. However, the interest of integrating the mMRC dyspnea scale in clinical practice to guide therapeutic management of DM1 patients remains to be assessed in further studies.

Keywords

Myotonic Dystrophy type 1, dyspnea, mMRC, respiratory impairment, non-invasive ventilation, quality of life

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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.

Disclosure of interest

None of the authors has any conflict of interest to disclose.

Abbreviations

- DM1: Myotonic dystrophy type 1
- CTG: Cytosine-Thymine-Guanine repeat
- DMPK: Dystrophia myotonica protein kinase
- CPAP: Continuous Positive Airway Pressure
- NIV: Non-Invasive Ventilation
- MMSE: Mini Mental State Examination
- BMI: Body Mass Index
- mMRC: modified Medical Research Council
- MDP: Multidimensional Dyspnea Profile
- VAS: Visual Analogue Scale
- ES: Epworth Sleepiness
- PF: Pichot fatigue
- PSQI: Pittsburgh Sleep Quality Index
- HAD: Hospital Anxiety and Depression Scale
- AS: Apathy Scale
- QOL-gNMD: Quality Of Life in genetic Neuromuscular Disease
- MIRS: Muscular Impairment rating scale
- SQ: Sensory Qualities
- 6MWT: 6-minute walk test
- PFTs: Pulmonary function tests
- VC: Vital Capacity
- FEV_1: Forced Expiratory Volume in one second
- MIP: Maximal Inspiratory Pressure
- MEP: Maximal Expiratory Pressure

- SNIP: Sniff nasal inspiratory pressure
- AHI: Apnea Hypopnea Index
- ALS: Amyotrophic Lateral Sclerosis

1- Introduction

Myotonic dystrophy (dystrophia myotonica) type 1 (DM1) is one of the most common genetic muscular disease in populations of European descent (1). It is caused by expansion of a CTG triplet repeat in the 3' non coding region of DMPK (2), the gene encoding the DM protein kinase. DM1 is a multisystem disorder characterized by myotonia with dysfunction of skeletal and smooth muscles, as well as dysfunction of the cardiac, endocrine, nervous, digestive and respiratory systems (1).

The main cause of death is a respiratory failure (3) which can be caused by dysfunction in the central control of ventilation (4) (5) (6), weakness of the respiratory muscles (7) (6) (8), weakness of pharyngeal muscles associated with swallowing disorders (9) and aspiration pneumonia and concurrent obstructive apneas (10). Combining respiratory symptom screening and respiratory function testing allows to identify the appropriate time to initiate adequate ventilatory care including non-invasive ventilation (NIV) (11).

Dyspnea, a major respiratory symptom, has not been extensively investigated in patients with DM1. Dyspnea is a subjective experience of breathing discomfort with qualitatively distinct sensations that vary in intensity and emotional and behavioral significances (12). Many tools exist to evaluate the dyspnea experienced including, the modified Medical Research Council (mMRC) (13) (14) to assess the functional impact of dyspnea, the Borg scale (15) (16), the Visual Analogic Scale (VAS) (17) (18) to quantify its sensory intensity, and the Multidimensional Dyspnea Profile (MDP) (19) to analyze both sensory and affective dimensions.

The main objective of this pilot study was to provide a multidimensional assessment of dyspnea in patients with DM1, including sensory and affective dimensions of dyspnea and its functional impact. The secondary objectives were to analyze the relationships between

dyspnea in daily living according to the mMRC scale and clinical history of DM1, number of CTG repeats, muscular impairment, respiratory assessment, emotional/cognitive disorders and quality of life. We also investigated respiratory symptoms according to NIV indication.

2- Methods

Adult DM1 patients were recruited from the Neuromuscular Diseases referral center of Reims. This study was performed in accordance with the declaration of Helsinki and approved by the Ethics Committee (Comité de Protection des Personnes - Ile de France 1, No. N2020-A01221-38) and was registered on clinicaltrials.gov (NCT04835298). DM1 patients referred to the Department of Pulmonary Medicine between July 2020 and July 2021 were considered for inclusion in this study. All patients received detailed information and gave their written consent.

2.1. Patient selection

Inclusion criteria were age older than 18 years, a diagnosis of DM1 confirmed by molecular analysis, absence of the Continuous Positive Airway Pressure (CPAP) or NIV, and the absence of legal protection measures (guardianship, curatorship). Exclusion criteria were an ongoing or recent (i.e. within the last 4 weeks before study recruitment) unstable medical condition and a significant cognitive impairment defined by a Mini Mental State Examination (MMSE) score < 20.

2.2. Patient demographic and clinical characteristics

Demographic data (age, sex), body mass index (BMI), characteristics of the DM1 (age at beginning of symptoms, age at diagnosis of DM1, number of CTG expansion triplet), education level, professional activity, comorbidities, treatments, smoking status, and clinical characteristics were systematically recorded.

With the help of a junior doctor (BD), patients filled in questionnaires on dyspnea (*modifed Medical Research Council dyspnea scale: mMRC, Multidimensional Dyspnea Profile : MDP,*

Visual Analogue Scale : VAS), daytime sleepiness (*Epworth Sleepiness scale: ES*), asthenia (*Pichot fatigue scale: PF*), sleep quality (*Pittsburgh Sleep Quality Index: PSQI*), anxiety and depression (*Hospital Anxiety and Depression Scale: HAD*), apathy (*Apathy Scale: AS*), quality of life (*Quality of Life in genetic Neuromuscular Disease scale: QOL-gNMD*), cognitive functioning (*Mini Mental State Examination : MMSE*). Muscular Impairment Rating Scale (MIRS) was also collected.

2.2.1. Modifed Medical Research Council Dyspnea Scale

The mMRC scale (13) (14) consists of five statements that almost entirely describe the range of dyspnea from none (grade 0) to almost complete incapacity (grade 4). Significance thresholds ≥ 2 have been used to categorize patients according to their dyspnea.

2.2.2. Multidimensional Dyspnea Profile

The MDP (19) (20) consists of eleven items, each evaluated on a 0–10 numerical rating scale, that describe the unpleasantness of dyspnea (one item [A1], maximum score of 10), its sensory qualities (5 items [SQ], maximum score of 50), and its emotional qualities (5 items [A2], maximum score of 50). MDP scores can be grouped in two dimensions (sensory dimension [SQ], maximum score of 50; affective dimension [A1+A2], maximum score of 60) or in two domains (immediate perception response [SQ+A1], maximum of 60; emotional response [A2], maximum score of 50), which is analogous to pain conceptual models.

2.2.3. Visual analogue scale

Patients were asked to rate their breathing discomfort on a non-graduated 100-mm visual analogue scale anchored by "no breathing discomfort" at the left end, and "intolerable breathing discomfort" at the right end (17) (18). VAS was first applied with the patients

seated in a comfortable chair and then reapplied after they had assumed a fully supine position. A second non graduated 100-mm visual analogue scale was used to evaluate the changes in breathing comfort (in either direction) between the sitting and the supine positions ("transitional" scale; from "extreme deterioration" on the left end to "extreme improvement" on the right, with a middle marker to indicate "no change").

2.2.4. Epworth Sleepiness scale

The ES (21) is a questionnaire assessing the likelihood of falling asleep under various circumstances in daily life. The scale is composed of 8 items scored from 0 to 3 for a total score from 0 to 24. Excessive daytime sleepiness is defined by a score ≥11.

2.2.5. Pichot fatigue scale

The PF (22) is a questionnaire composed of 8 items scored from 0 to 4 for a total score from 0 to 32 distinguishing physical or psychic fatigue perception. A global score > 22 is in favor of excessive fatigue.

2.2.6. Pittsburgh Sleep Quality Index

The PSQI (23) is a questionnaire, which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of the component scores yields a global score from 0 to 21. A global PSQI score > 5 indicates impaired sleep quality.

2.2.7. Hospital Anxiety and Depression Scale

The HAD (24) scale is designed for patients with physical illnesses. It consists of 14 items:

seven items relating to depression and seven items relating to anxiety with cut-off points for severity. For each domain (A or D), scores of 0–7 indicate no disorders, 8–10 indicate suspected disorders, and 11–21 indicate confirmed disorders.

2.2.8. Apathy Scale

Apathy was assessed by the AS scale (25). The AS consists of 14 items phrased as questions that are to be answered on a four-point Likert scale. Scores on the AS range from 0 to 42, with higher scores reflecting greater apathy symptoms, with a recommended cut-off score of 14.

2.2.9. Mini Mental State Examination

The items of the MMSE (26) (27) include tests of orientation, registration, recall, calculation and attention, naming, repetition, comprehension, reading, writing and drawing. If all items are answered correctly, the score is 30. A score greater than 25 is considered normal and a score between 20 and 25 indicates the presence of mild cognitive impairment.

2.2.10. Quality of life in genetic neuromuscular disease scale

The QOL-gNMDs (28) a specific quality of life (QoL) questionnaire structured in 3 domains (Impact of Physical Symptoms, Self-Perception, Activities and Social Participation) including 26 items with 2–4 response options: 2 general items, 7 items concerning impact of Physical Symptoms (sum 0 to 18), 8 items concerning self-perception (sum 0 to 24), and 9 items concerning activities and social participation (sum 0 to 27). Each domain has an ordinal scale, which has been transformed by an interval score (0 bad QoL, 100 best QoL) according to Rasch measurement theory. The Minimal Clinical Difference for these interval scores is between 10 to 12 points.

2.2.11. Muscular Impairment Rating scale

The MIRS (29) is a rating scale from 1 (asymptomatic) to 5 (severe proximal involvement), established in accordance with the clinically recognized distal to proximal progression of the muscular involvement in DM1, based partly on a manual muscle testing of 11 muscle groups.

2.3. Lung function tests

2.3.1. Arterial blood gases

Arterial Blood Gases were measured in a sitting position on room air.

2.3.2. Six-minute walk test

The six-minute walk test (6MWT) was performed in a 30-meter long, flat, covered corridor, marked meter-by-meter, according to the American Thoracic Society guidelines (30). Oxygen saturation and modified Borg scale (15) (16) subjectively assessing the degree of dyspnea graded from 0 to 10 were collected at the beginning and the end of the 6MWT. The distance covered was calculated at the end of the test.

2.3.3. Pulmonary function testing

PFTs were performed according to the American Thoracic Society/European Respiratory Society guidelines (31) (BodyBox 5500 Medisoft Sorinnes, Belgium). Vital capacity (VC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, were measured during spirometry, which was performed both in upright seated and in supine positions. Results were expressed as the percentage of predicted values.

2.3.4. Evaluation of inspiratory and expiratory muscle strength

Respiratory muscle strength consisted of measuring Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) (32). The maximum value of three available tests that varied by less than 20% was recorded. Results were expressed in cmH2O and percentage of predicted values.

2.3.5. Ventilatory response to carbon dioxide

Ventilatory response to carbon dioxide was measured by the Read rebreathing method (33) (34). The patients were seated comfortably and attached to a mouth-piece with a nose clip. They were instructed to breathe room air as quietly as possible until the end-tidal CO_2 tension ($PetCO_2$) stabilized. After this complete sitting rest of 5 minutes, the circuit was closed and they started rebreathing as quietly as possible the content of a bag with a gaseous mixture (approximately 7% of CO_2 and 93% of O_2) for 4 minutes. The gradual increase in $PetCO_2$ and ventilation (L/min) was measured by a fast response metabographe (Medisoft, Sorinnes, Belgium), with normal values between 1.5 and 3 L/min/mmHg (35).

2.3.6. Overnight respiratory recording

Home or in-hospital overnight respiratory recording was performed including overnight polysomnography (Resmed Nox A1), overnight respiratory polygraphy (Resmed Nox T3) or nocturnal SpO_2 and $PtcCO_2$ (SenTec Inc., Terwil, Switzerland). These recordings were not systematically performed and were prescribed by clinicians according to patients' symptoms, results of lung function tests and results of previous overnight respiratory recordings. Overnight polysomnography or respiratory polygraphy recordings were analyzed according to the 2015 update of the American Academy of Sleep Medicine rules for scoring respiratory events in sleep. Apnea was defined as the absence of airflow ≥ 10 s, hypopnea was defined as a reduction of airflow ≥ 30 % associated with a decrease in oxygen saturation ≥ 3% (or micro-

awakening if polysomnography recording). The Apnea Hypopnea Index (AHI) was calculated as the number of apneas and hypopneas per hour (of total sleep time in polysomnography and night recording on respiratory polygraphy).

2.3.7. Criterions for Non Invasive Ventilation initiation

Criteria for initiating NIV were defined only by objective respiratory parameters: $PaCO_2$ > 45mmHg and/or VC < 50% and/or nocturnal desaturation defined by overnight time with SpO_2 < 90% > 10%.

2.4. Statistical analyses

Quantitative variables were described as median and interquartile range and qualitative variables as number and percentage. Patients were separated into two groups according to their mMRC dyspnea scale: mMRC < 2 (no disabling dyspnea in daily living) and mMRC ≥ 2 (disabling dyspnea in daily living). Comparison of clinical and genetic characteristics and quality of life and respiratory assessment between patients with mMRC < 2 and patients with mMRC ≥ 2 were studied using Student or Wilcoxon or Khi2 or Fisher exact tests according to application's conditions. Comparison of clinical and genetic characteristics and respiratory symptoms between patients with no NIV indication and patients with NIV indication were studied using Student or Wilcoxon or Khi2 or Fisher exact tests according to application's conditions. Comparison of MIR scale and 6MWT distance and vital capacity between patients with mMRC = 0, patients with mMRC = 1 and patients with mMRC ≥ 2 were studied using Kruskal Wallis tests.

A p-value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3- Results

3.1.Patient demographic and clinical characteristics

Ninety adult patients with DM1 were referred to our medical center. Twenty-three patients were not eligible for the study including legal protection measure (n=3), CPAP (n=5), NIV (n=20). Twenty-eight patients refused to participate in the study. One patient was excluded because of a MMSE score < 20. Finally, data of thirty-four patients were analyzed.

Patient characteristics are presented in **Table 1.** The median (25^{th}-75^{th} centile) age of the patients was 36 (28-49) years, including 21 men and 13 women. The median BMI was 24 (21.6-26.3) kg/m². Regarding the DM1, first symptoms occurred at 19 (10-31) years. The median number of CTG triplets affecting DMPK gene was 550 (300-900). The median MIRS score was 3 (2-4).

Three patients (9%) didn't go to school or stopped in primary school, 20 patients (59%) went to high school and 11 patients went to university (32%). Mini-mental state examination was completed by all patients with a median score of 27 (24-29). Seven patients (21%) had an anxiety HAD score > 10, 5 patients (15%) a depression HAD score > 10, and 34 patients (100%) an apathy score ≥ 14.

3.2.Dyspnea assessment

Results of dyspnea assessment are presented in **Table 2.**

Eleven patients (32%) had a mMRC score ≥ 2, which is usually considered as disabling dyspnea in daily living and eight patients (25%) had a Borg scale score at the end of the 6MWT ≥ 5 which corresponds to severe dyspnea on exertion. The median score of dyspnea according to Borg scale after 6MWT was 2.2 (1.8-4.2), which corresponds to slight dyspnea on exertion.

At rest, the median score was 0 (0-0) in sitting position according to VAS, 0 (0-0) in supine position according to VAS, 0 (0-0) according to Borg scale before the 6MWT, 0 (0-0) according to A1 "immediate unpleasantness" of MDP. Twenty-nine patients (87%) according to VAS in sitting position, 27 patients (79%) according to VAS in supine position had a score of 0 at rest. Eight (23%) patients described worsening dyspnea when moving from sitting to lying (orthopnea).

The SQ and A2 scores of MDP (sensory and emotional descriptors, respectively, both with a maximal score of 50) were 2.0 (0.0-4.7) and 0.0 (0.0-4.7). For SQ, the most commonly chosen «best descriptor» was "breathing a lot" (n=11 (32%), median score 0 (0-3)), and for A2, "breathing sensations make feel angry" was the most chosen as «best emotional descriptor», (n=5 (15%), median score of 0 (0-0)).

3.3.Objective respiratory assessment parameters

Results of objective respiratory assessment parameters are presented in **Table 3.**

Eight patients presented criterion for initiating NIV, defined either by $PaCO_2$ > 45mmHg (n=5), or by VC < 50% (n=3), or by nocturnal desaturation defined by overnight time with SpO_2 < 90% > 10 % (n=4).

3.4.Comparison of clinical and genetic characteristics, quality of life and respiratory assessment between patients with mMRC < 2 and patients with mMRC ≥ 2

Compared with patients with mMRC < 2, patients who experienced disabling dyspnea in daily living (mMRC ≥ 2) had a higher BMI (25.9 (25.0-29.9) kg/m² *vs* 22.7 (19.6-25.2) kg/m², p<0.01), a clinically significant more severe motor handicap (MIRS score of 4.0 (4.0-4.0) *vs* 3.0 (2.0-3.5), p<0.01), 6MWT distance of 373 (260-424) m *vs* 436 (346-499) m, p=0.03) and a more impaired quality of life **(Table 4a, Figure 1).**

Regarding respiratory assessment **(Table 4b)**, patients with mMRC ≥ 2, experienced also more severe dyspnea according to VAS, MDP and Borg score at the end of the 6MWT than patients with mMRC < 2. They had also a lower VC (median 64 (48-74) % *vs* 75 (69-89) %, p=0.024)

The mMRC scale was correlated with higher MIRS score (correlation coefficient + 0,55, p < 0.001), lower 6MWT distance (correlation coefficient - 0,53, p < 0.01) and a lower CV (correlation coefficient -0,42, p= 0.016).

There was no difference between these 2 groups of patient regarding smoking status, medical history, MMSE score, HAD score and apathy score (data not shown).

3.5. Comparison of clinical and genetic characteristics, quality of life and respiratory symptoms between patients with no NIV indication and patients with NIV indication

Patients with no NIV indication and those with NIV indication were compared in terms of demographic and clinical characteristics, number of CTG and respiratory symptoms **(Table 5).** Compared with patients with no NIV indication, patients with NIV indication had a decreased sleep quality (PSQI median score of 7 (6.2-8.0) *vs* 3.5 (3.0-5.7), p=0.04).

4- Discussion

This study focused on dyspnea assessment in adult DM1 patients using several multi-dimensional questionnaires. Regarding sensory dimension of dyspnea, at rest, and whatever the scale used (VAS in siting position, VAS in supine position, Borg and SQ MDP), most of patients reported a dyspnea intensity score at zero. On exertion, Borg score after 6MWT was 2.2 (1.8-4.2) /10 which corresponds to slight dyspnea. Concerning affective dimension of dyspnea according to MDP, A1 + A2 intensity score was also very low 0.0 (0.0-4.7) /60. One-third of patients reported disabling dyspnea in daily living (mMRC $\geq$ 2), which is closely to that a previous study in DM1 patients (presence of dyspnea during activities of daily living in 22% of patients) (36).

Several hypotheses can be formulated to explain the absence or the low intensity of dyspnea for most of DM1 patients.

First, it could have been hypothesized that cognitive deficits, emotional disturbances and avoidant or passive personalities traits may induce a lack of interest in answering dyspnea scales and/or cause difficulties in understanding the questionnaires (37) (38). In our study, all patients had an apathy score $\geq$ 14, however voluntarily participated to the study and appeared to do their best to fill in scales, with the help of a junior doctor. Patients with moderate to severe cognitive deficit were excluded from the study and 90% of analysed patients went to high school. Regarding emotional disturbance, only 15% of patients had a depression HAD score > 10. Moreover, if MDP and mMRC may have introduced a difficulty regarding recall over a focal period, VAS and Borg scales explore immediate unpleasantness breathing sensation and are known to be easy to use in clinical practice.

Second, the low dyspnea intensity could be explained by moderate respiratory function impairment of the DM1 patients included in this study. Nevertheless, patients with NIV indication in our study had also very low scores in dyspnea scales, except for mMRC, compared to other neuro-muscular patients with NIV indication. For example, Amyotrophic Lateral Sclerosis (ALS) patients with NIV indication (39) (median FVC of 46% predicted) had median SQ score of 28.0 (16.0-40.0) (sensory dimension of dyspnea) and A2 score of 15.0 (5.5–23.5) (affective dimension of dyspnea) (39), while DM1 patients in our study had median SQ score of 4 (1.5-12.0) and A2 score of 9.5 (0.7-19.2) for a median FVC of 47% predicted.

Third, it is possible that, notably because of muscular impairment, physical activity level is too low to induce dyspnea. Patients may also have adapted their gait speed to avoid dyspnea.

Finally, we propose that some DM1 patients could have an alteration of breathing sensations. Breathing sensations arise from one or several stimuli, the transmission of these stimuli to the brain, and cognitive and affective processing of this interoceptive information arising from the respiratory system. In DM1 patients, several types of central nervous system lesions (brain lesions with notably limbic system lesions (40) and brainstem lesions (41) with a reduced ventilatory response to CO_2 (5)) could interfere with this process and explain blunted breathing sensations. Baldanzi *et al* (42) showed that a high percentage of DM1 suffer from anasognosia (52%), *ie* were unaware of symptoms across different physical and life domains. Moreover, while patients with other neuromuscular disorders like ALS have rapidly progressing symptoms, the relative slowly progression of disease is likely to induce an adaptation to thoracic mechanical load induced by respiratory muscle impairment and/or an adaptation to daytime hypercapnia (respiratory gating mechanism or in other words an habituation process, that blunt the perception of dyspnea) (43). It is also possible that the long

duration of disease may cause less anxiety, a factor that is known to increase dyspnea level (44). Only 21 % of DM1 patients had an anxiety HAD score > 10 in our study.

Our results provide evidence for the use of the mMRC scale, an easy-to-use and not time-consuming scale, in the assessment of dyspnea in daily living in DM1 patients. First, our results demonstrated associations between mMRC and data that reflect disease severity, *ie* follow-up duration from diagnosis, muscle impairment severity (MIRS, 6MWT distance) and decrease quality of life (**Figure 1, Table 4a)**. Second, in our between group comparisons, the mMRC scale was associated with other dyspnea scales (VAS, MDP and Borg after 6MWT) and with pulmonary function parameters which might be involved in dyspnea in DM1 (VC) **(Figure 1, Table 4b)**. Of note, there was a lack of clinically significant respiratory symptomatic differences between patients with and without NIV indication, except for dyspnea according to mMRC scale (no statistically significant difference probably due to the low power of our study) and quality of sleep according to PSQI. It would be interesting to investigate the mMRC score modifications after NIV initiation. Nevertheless, it has already been shown that respiratory sleep-related symptoms did not worsen during one month NIV withdrawal period in DM1 patients and did not improve thereafter (45). The lack of expected symptomatic benefit from NIV, might explain in part the difficulties with NIV treatment adherence in DM1 patients (46) (23).

Discriminating DM1 patients having a higher level of respiratory dysfunction from those having a lower risk of respiratory involvement remains a challenge. We believe that a mmRC score ≥ 2 could be an element that might alert clinicians and help them in identifying potential candidates for intervention. It would be interesting to investigate in further larger multicentric studies if the combination of different scales could improve respiratory involvement

detection. For example, mMRC scale might be used in association with Respicheck (47), a new scale designed to quickly capture symptoms of respiratory involvement in DM1.

This study has several limitations. First, a large number of patients considered for inclusion refused to participate to the study, reflecting probably particular personality traits typically reported in DM1, and may represent a selecting bias. Second, the study was conducted in a single center, including a small number of patients, who, most often, had moderate respiratory function impairment, were ambulant and presented no severe cognitive disorders, which limit the generalizability of the results.

5- Conclusion

This first-in-kind analysis has yielded new data on the associations between dyspnea according to mMRC scale, muscular impairment severity, quality of life and VC in DM1 adult ambulant patients, without severe cognitive disorder. The mMRC scale might be a useful and easy-to-use tool to assess dyspnea in daily living in these DM1 patients. Additional studies are needed to determine the interest of integrating the mMRC dyspnea scale in clinical practice to guide therapeutic management of DM1 patients.

References

1. Turner C, Hilton-Jones D. Myotonic dystrophy: diagnosis, management and new therapies. Curr Opin Neurol. oct 2014;27(5):599-606.

2. Mahadevan M, Tsilfidis C, Sabourin L, Shutler G, Amemiya C, Jansen G, et al. Myotonic dystrophy mutation: an unstable CTG repeat in the 3' untranslated region of the gene. Science. 6 mars 1992;255(5049):1253-5.

3. Mathieu J, Allard P, Potvin L, Prévost C, Bégin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 12 mai 1999;52(8):1658-62.

4. Bogaard JM, van der Meché FG, Hendriks I, Ververs C. Pulmonary function and resting breathing pattern in myotonic dystrophy. Lung. 1992;170(3):143-53.

5. Poussel M, Thil C, Kaminsky P, Mercy M, Gomez E, Chaouat A, et al. Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord. mai 2015;25(5):403-8.

6. Zifko UA, Hahn AF, Remtulla H, George CF, Wihlidal W, Bolton CF. Central and peripheral respiratory electrophysiological studies in myotonic dystrophy. Brain. déc 1996;119 (Pt 6):1911-22.

7. Lo Mauro A, Aliverti A. Physiology of respiratory disturbances in muscular dystrophies. Breathe (Sheff). déc 2016;12(4):318-27.

8. Henke C, Spiesshoefer J, Kabitz H-J, Herkenrath S, Randerath W, Brix T, et al. Characteristics of respiratory muscle involvement in myotonic dystrophy type 1. Neuromuscul Disord. janv 2020;30(1):17-27.

9. Pilz W, Baijens LWJ, Kremer B. Oropharyngeal dysphagia in myotonic dystrophy type 1: a systematic review. Dysphagia. juin 2014;29(3):319-31.

10. West SD, Lochmüller H, Hughes J, Atalaia A, Marini-Bettolo C, Baudouin SV, et al. Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis. 29 nov 2016;3(4):529-37.

11. Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.

12. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 15 févr 2012;185(4):435-52.

13. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. mars 1988;93(3):580-6.

14. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the

Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. juill 1999;54(7):581-6.

15. Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. Clin Sci (Lond). mars 1989;76(3):277-82.

16. Hareendran A, Leidy NK, Monz BU, Winnette R, Becker K, Mahler DA. Proposing a standardized method for evaluating patient report of the intensity of dyspnea during exercise testing in COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:345-55.

17. Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. Rehabil Nurs. déc 1989;14(6):323-5.

18. Attali V, Collet J-M, Jacq O, Souchet S, Arnulf I, Rivals I, et al. Mandibular advancement reveals long-term suppression of breathing discomfort in patients with obstructive sleep apnea syndrome. Respiratory Physiology & Neurobiology. mai 2019;263:47-54.

19. Banzett RB, O'Donnell CR, Guilfoyle TE, Parshall MB, Schwartzstein RM, Meek PM, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. Eur Respir J. juin 2015;45(6):1681-91.

20. Williams MT, Johnston KN. Multidimensional measurement of breathlessness: recent advances. Curr Opin Support Palliat Care. sept 2019;13(3):184-92.

21. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. déc 1991;14(6):540-5.

22. Pépin J-L, Georgiev O, Tiholov R, Attali V, Verbraecken J, Buyse B, et al. Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial. Chest. avr 2021;159(4):1598-609.

23. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. mai 1989;28(2):193-213.

24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. juin 1983;67(6):361-70.

25. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1992;4(2):134-9.

26. Foreman MD, Fletcher K, Mion LC, Simon L. Assessing cognitive function. Geriatr Nurs. oct 1996;17(5):228-32; quiz 233.

27. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. QJM. août 2007;100(8):469-84.

28. Dany A, Rapin A, Lavrard B, Saoût V, Réveillère C, Bassez G, et al. The quality of life in genetic neuromuscular disease questionnaire: Rasch validation of the French version.

Muscle Nerve. déc 2017;56(6):1085-91.

29. Mathieu J, Boivin H, Meunier D, Gaudreault M, Bégin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology. 13 févr 2001;56(3):336-40.

30. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 1 juill 2002;166(1):111-7.

31. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. European Respiratory Journal. 1 sept 2005;26(3):511-22.

32. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 15 août 2002;166(4):518-624.

33. Read DJ. A clinical method for assessing the ventilatory response to carbon dioxide. Australas Ann Med. févr 1967;16(1):20-32.

34. Read DJ, Maloney JE, Fowler KT. REPRODUCIBILITY OF TRANSIENT RESPONSE TO CO2 INHALATION IN MAN. J Appl Physiol. juill 1964;19:750-4.

35. Laza F, Tamisier R, Wuyam B, Borel J-C, Saint Raymond C, Labarre-Vila A, et al. [Chronic respiratory failure and Steinert's myotonia]. Rev Mal Respir. janv 2009;26(1):83-6.

36. De Mattia E, Lizio A, Falcier E, Sannicolò G, Gualandris M, Rossi G, et al. Screening for early symptoms of respiratory involvement in myotonic dystrophy type 1 using the Respicheck questionnaire. Neuromuscul Disord. avr 2020;30(4):301-9.

37. Miller JN, Kruger A, Moser DJ, Gutmann L, van der Plas E, Koscik TR, et al. Cognitive Deficits, Apathy, and Hypersomnolence Represent the Core Brain Symptoms of Adult-Onset Myotonic Dystrophy Type 1. Front Neurol. 2021;12:700796.

38. Leddy S, Cercignani M, Serra L, Bozzali M. Social cognition in type 1 myotonic dystrophy - A mini review. Cortex. sept 2021;142:389-99.

39. Morélot-Panzini C, Perez T, Sedkaoui K, de Bock E, Aguilaniu B, Devillier P, et al. The multidimensional nature of dyspnoea in amyotrophic lateral sclerosis patients with chronic respiratory failure: Air hunger, anxiety and fear. Respir Med. déc 2018;145:1-7.

40. Weijs R, Okkersen K, van Engelen B, Küsters B, Lammens M, Aronica E, et al. Human brain pathology in myotonic dystrophy type 1: A systematic review. Neuropathology. févr 2021;41(1):3-20.

41. Ono S, Takahashi K, Jinnai K, Kanda F, Fukuoka Y, Kurisaki H, et al. Loss of catecholaminergic neurons in the medullary reticular formation in myotonic dystrophy. Neurology. oct 1998;51(4):1121-4.

42. Baldanzi S, Bevilacqua F, Lorio R, Volpi L, Simoncini C, Petrucci A, et al. Disease awareness in myotonic dystrophy type 1: an observational cross-sectional study.

Orphanet J Rare Dis. 4 avr 2016;11:34.

43. Herzog M, Sucec J, Van Diest I, Van den Bergh O, Chan P-YS, Davenport P, et al. Reduced neural gating of respiratory sensations is associated with increased dyspnoea perception. Eur Respir J. juill 2018;52(1):1800559.

44. von Leupoldt A, Denutte Y. Affective traits, states, and breathlessness. Curr Opin Support Palliat Care. sept 2020;14(3):182-9.

45. O'Donoghue FJ, Borel J-C, Dauvilliers Y, Levy P, Tamisier R, Pépin J-L. Effects of 1-month withdrawal of ventilatory support in hypercapnic myotonic dystrophy type 1. Respirology. oct 2017;22(7):1416-22.

46. Boussaïd G, Lofaso F, Santos DB, Vaugier I, Pottier S, Prigent H, et al. Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: A prospective cohort. Neuromuscul Disord. oct 2016;26(10):666-74.

47. De Mattia E, Lizio A, Falcier E, Sannicolò G, Gualandris M, Rossi G, et al. Screening for early symptoms of respiratory involvement in myotonic dystrophy type 1 using the Respicheck questionnaire. Neuromuscul Disord. avr 2020;30(4):301-9.

Figure 1 : Dyspnea in daily living assessed by the modified Medical research council scale according to Muscular Impairment rating scale, Six-Minute Walk Test and Vital Capacity**.**

Data are expressed as minimum, maximum, median (25^{th} -75^{th} centile).
Abbreviation mMRC: modified Medical Research Council