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Workshop report

207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies: Management and implications for research, 27–29 June 2014, Naarden, The Netherlands

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1. Introduction

Fourteen participants from Italy, France, Germany, The Netherlands, the UK, Canada and the US met in Naarden, The Netherlands, to discuss the diagnostic protocols and management implications of chronic respiratory insufficiency in myotonic dystrophies. The group included six neurologists, three pulmonologists, three rehabilitation specialists, one cardiologist, one geneticist and one neuropsychologist from seven different European centers, one US Center and one Canadian Center, representing a variety of disciplines with experience in the respiratory management of patients with neuromuscular disorders and with experience in myotonic dystrophies. Representatives of patients and patient support groups were also present.

Respiratory problems are among the leading causes of death in adult Myotonic Dystrophy type 1 (DM1) patients (51–76%) [1–4] and usually account for the high rate of mortality in the congenital form of DM1 [5]. Life expectancy is decreased in patients with adult DM1; death, mainly from respiratory involvement, occurs between 50 and 60 years of age, according to the different studies at a mean age of 53 or 59 years old in different studies [2–4]. Myotonic Dystrophy type 2 (DM2) has a similar multiple organ involvement but the frequency and severity are such that a better prognosis is postulated [6]; there are however limited data on respiratory function in these patients. Only a minority of patients with adult DM1 and DM2 seem to receive regular evaluations of pulmonary function on initial assessment, have a pulmonary service referral, are on non-invasive ventilation or receive support for secretion management.

The general aims of the workshop were (i) to review pathophysiology and symptoms of chronic respiratory insufficiency in myotonic dystrophies; (ii) to assess management of respiratory involvement in the EU, US and Canada and agree and report minimum recommendations for screening and for treatment of chronic respiratory insufficiency in myotonic dystrophies including indications for launching of non-invasive ventilation; and (iii) to define areas where further research is needed. In addition, future activities and implications for research were discussed.

During the workshop, all participants contributed to a review and assessment of the published evidence in each area and current practice among the group.

1.1. Session 1: pathophysiology and clinical aspects of respiratory involvement in myotonic dystrophies

(MT Rogers, B Gallais, B Schoser, P Wijkstra, D Duboc).

Myotonic Dystrophies are autosomal dominant disorders characterized by muscle weakness, myotonia and early-onset cataracts. *Multiple organ involvement* is common and there is a broad spectrum of clinical presentations ranging from the congenital forms in DM1 to the older forms of asymptomatic or mildly affected patients with DM1 or DM2. Respiratory involvement is known to occur in these patients and it is broadly more likely the longer since diagnosis and the younger the age of onset, with some correlation with severity and CTG expansion in DM1 [7]. It is the leading cause of (premature) death and a major cause of morbidity, depending on how much it contributes to fatigue and hypersomnolence and on how much apnea or hypopnea disturbs sleep.

While patients with other neuromuscular disorders like amyotrophic lateral sclerosis have overt and rapidly progressing symptoms of dyspnea and orthopnea, in patients with adult DM, having a relatively slowly progressive disorder, respiratory involvement more frequently presents with symptoms, such as fatigue, excessive daytime sleepiness (EDS), sleep disorders [8–12] and reduced cognitive performance, which only

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indirectly point toward pulmonary function abnormalities. In addition there are other causes for fatigue, EDS and reduced cognitive performance in DM1 and 2, resulting in them being less specific indicators of respiratory impairment in these conditions [13].

How *daytime sleepiness and fatigue* in DM1 correlate with respiratory involvement is a complex issue. Daytime sleepiness and impaired sleep are common in patients with adult DM1 [9,12,14–16] representing the 4th most prevalent symptomatic theme among patients with DM1 [17]. Impaired sleep disorders are clearly present in both adults and children and can be present as sleep-related breathing events, periodic limb movements or REM-sleep disturbances [9–11]. Apnea and hypopnea are common in DM1 and have been described in patients with DM2 even in those without EDS [18–20] and these also disturb sleep. In a series of 21 children affected by childhood-onset myotonic dystrophy [21] sleep disturbances were reported in 66% of children with DM1, periodic limb movements and sleep apnea syndromes in 38% and 29% respectively and were more frequently associated with fatigue. Symptoms of daytime sleepiness and fatigue are often overlapping [16,19,22] and progress over time, negatively impacting cognition [23]. Fatigue is present in most patients with DM1 [17,24] and is the second most common symptomatic theme in DM1 while having the greatest impact on patients' lives [17,25]. Patients with EDS have greater pain [26] and worst perception of quality of life (QoL) compared to patients who do not complain of EDS [11,27]. In DM1, EDS is also associated with greater levels of disability, depression and reduced sleep quality [28]. Fatigue is also a predictor of disrupted social participation and EDS is associated with lower employment rates [29]. Fatigue in DM1 [30] may have several facets: it may have a central component, due to central pathways [31,32] or it may relate to functional disability, which is dependent on an individual's coping ability (adaptive fatigue). It may also have an emotional component due to depression, where there is a lack of association between objective and subjective fatigue. Mental fatigability in DM1 may also possibly be related to slowed thinking, poor attention resulting in reduced motor performances but this needs further confirmation. The positive impact of pharmacological treatment with modafinil on patients and parents was also discussed [33].

Central sleep apnea and white matter hyperintense lesions play a role in the progression of chronic respiratory muscle failure. DM1-related EDS is caused by a central dysfunction of sleep regulation and by sleep-related disordered breathing or by sleep fragmentation emphasizing the role of both central and peripheral components [7–13]. Lower scores in attention, vigilance, and executive functioning tests are associated with a higher number of apneic/hypopneic episodes per hour of sleep and with longer total sleep time [13]. The results suggest a role for nighttime breathing problems in the cognitive impairment in DM1 patients. The neurons of the central nervous system, e.g. of the lateral hypothalamus, play integrative and instrumental roles in DMs regarding sleepiness, fatigue, obesity, and ventilation, but studies need to be done to investigate the roles of these neuronal pathways further.

In healthy individuals there is a specific pattern of ventilation, EMG activity and muscle involvement during breathing. Intercostal muscles play a major role during wakefulness and in NREM sleep while the diaphragm becomes the predominant muscle involved during REM sleep [34]. This explains the peripheral component involved in respiratory muscle failure in DMs. More specifically, inspiratory muscle weakness is responsible for the restrictive pattern of lung function, accounting at least in part for chest wall stiffness and for sleep disordered breathing while expiratory muscle weakness is responsible mainly for impairment of cough (or reduced ability to cough) which will both increase the likelihood of developing chest infection and pneumonia and adversely affect recovery from them. Upper airway muscle weakness, oropharyngeal and esophageal muscle weakness cause dysarthria and dysphagia increasing the risk aspiration pneumonia and gastrointestinal reflux [35,36]. The summative effect of these various respiratory system impairments leads to a decrease in PaO_2 and increase in $PaCO_2$, initially during REM sleep. This results in frequent arousals which reduce hours of sleep and impair quality of sleep leading to EDS and sleep deprivation. In turn, this increases periods of REM sleep and causes a depression of respiratory drive which results in severe nocturnal and diurnal hypoventilation and is aggravated by reduced chemosensitivity. Diaphragm weakness comes into play if vital capacity falls by 20% or more from sitting to supine. Maximal Inspiratory Pressure (MIP)/Maximal Expiratory Pressure (MEP), arterial blood gas exchange, sniff and oxycapnography and polysomnography are tests of respiratory function which quantify these different aspects of respiratory function in neuromuscular patients, including DM. Usefulness and reliability of $PtCO_2$ versus $ETCO_2$ and $PaCO_2$ [37] were also discussed, but will need to be addressed further in additional and ongoing studies.

DMs affect the heart and cardiac arrhythmias are common and are the second most frequent cause of death in these patients [3–6]. In general, there is a high prevalence of Obstructive Sleep Apnea Syndrome (OSAS) in cardiovascular patients and, even more specifically, the risks of atrial fibrillation and nocturnal cardiac death are increased in patients with OSAS [38]. In DM patients, there is a relationship between sleep apneas and cardiac arrhythmias [39] and, since sleep apnea can trigger various kinds of brady/tachyarrhythmias, a sleep apnea syndrome should always be searched in case of spontaneous brady/tachyarrhythmia in patients with DM, in order to initiate therapy that may help in preventing recurrences of brady/tachyarrhythmic events. On the other hand, many spontaneous brady/tachyarrhythmias occur without concomitant sleep apnea, related to the abnormal underlying electrophysiological substrate.

1.2. Session 2: management of respiratory insufficiency in different centers

(E Falcier, P Wijkstra, D Orlikoswky, M Philips, A Atalaia, M Boentert, C Gagnon, C Heatwole).

DMs are rare diseases, but are the most frequent muscular dystrophy of adulthood. The accumulated experience of the

group at the workshop represented the care of a large cohort of patients with DM1, including the congenital form, and of patients with DM2 throughout most of Europe, the US and Canada. To reduce inappropriate clinical variation in how patients are assessed, commenced and provided with equipment for home non-invasive ventilation, the group shared diagnostic protocols and management in the different DM clinics.

Dr Falcier, from Milan, Italy presented an overview of 680 patients with DM1, 52 with DM2 and 35 with the congenital form (cDM1) from several Centers in Italy dealing with DM patients. Twenty-one percent of patients with adult DM1, 15% of patients with DM2 and 40% of congenital DM1 are known to be on Non-Invasive Ventilation (NIV). Respiratory assessments vary among the different Centers both with respect to the diagnostic work-up, criteria for NIV, devices prescribed, and follow-up. Details were presented from 71 patients with adult DM1, 7 cDM1 and 9 patients with DM2 regularly followed at the NEMO Center, a dedicated neuromuscular center where neurologists and pulmonologists specializing in neuromuscular disorders work closely together. In the cohort of DM patients studied EDS followed by sleep disturbances was the most frequent symptom. NIV was prescribed in 32 of 71 patients on the basis of the following criteria: nocturnal desaturation (in 87.5% of patients), $HCO_3^- > 30$ mEq/L (in 65%), $paCO_2 > 45$ mmHg (in 52.5%), difference between supine and sitting FVC > 20% (in 30%). Follow-up at the NEMO Center is planned every 4 months if patients are on NIV and every 6 months if respiratory function is normal on first assessment. During follow-up symptoms are reviewed, daytime arterial blood gases are checked, pulmonary function tests performed and night oximetry monitored. Adaptation to NIV occurs during consecutive Day Hospital admissions (at least 5) or during an in-patient stay. Most patients (59.1%) are adapted to servo-assistant devices, followed by presso-volumetric (34.1%) and to Bilevel devices (6.5%).

Dr Wijkstra, from Groningen, The Netherlands described the organization of DM NIV domiciliary care in The Netherlands. There is a growing population on NIV in The Netherlands, accounting for 2617 patients in the country. Of these 86% are taken care of at home. The majority of patients on NIV have central causes and are usually over 60 years of age, the DM population represents 6% of these. Dr Wijkstra presented the organization of the domiciliary Center in Groningen: there are 2 pulmonologists, 15 nurse practitioners, 2 secretaries, and 2 technicians who take care of home ventilation. Specifically nurse practitioners are available by phone 24-hours a day every day of the week. Launching of NIV takes 5–7 days in the pulmonary ward to adapt to the best mask and to the best ventilator; the numbers of hours the patients use the device are increased progressively, settings are adjusted until lung volumes start being recruited. Follow-up occurs at least yearly in the out-patient setting during which arterial blood gases and pulmonary function tests are performed. Home visits by nurse practitioners occur more than once a year and oxycapnography performed.

Dr Orlikowski, from Paris, France presented details from 78 patients with adult DM1 on NIV, representing 30% of patients with neuromuscular disorders followed in France at the Intensive care and Home Ventilation Unit in Garches, France. The majority of patients are independent in activities of daily living and are able to walk unaided. Indications for NIV are based on symptoms of chronic respiratory insufficiency and on functional criteria, including $paCO_2 > 45$ mmHg, $saO_2 < 88\%$ for more than 5 minutes and FVC < 50% of predicted. The majority of patients (94%) have at least 1 symptom of respiratory insufficiency, EDS is a complaint in 73%, effort dyspnea in 69% and sleep disturbances in 55%. The second most frequent indication is nocturnal desaturation (74%) followed by $paCO_2 > 45$ mmHg (73%) and then by CV < 30% of predicted (12%). Dr Orlikowski concludes that the majority are on barometric NIV, and emphasized that compliance is limited: 50% use NIV less than 4 hours during the night and 15% do not use it at all.

Dr Philips, from Nottingham, UK presented data on 364 patients from the UK registry with details on NIV from 148. The majority of patients are between 40 and 49 years of age. No correlation with FVC was noted: there may be patients with low FVC who are not on NIV and others with relatively high FVC who are on NIV. Like the French experience, the majority of patients walk unaided again emphasizing the lack of correlation between severity of respiratory involvement and motor performance. Dr Philips concludes that few centers in the UK have written pathways for respiratory care. Availability of domiciliary chest physiotherapists is also variable among the different centers. There may also be difficulties in obtaining cough-assist devices in some areas.

Dr Atalaia, from Newcastle, UK presented data from the DM Clinic in Newcastle. This covers a large geographic area in northern UK including Newcastle, Middlesborough, Carlisle and Whitehaven. In the same clinic appointment patients are seen by cardiologists, physiotherapists and muscle team doctors or nurses. Data were presented from the Adapted Cardiff DM Clinical Questionnaire including ECG, sitting and supine FVC and FEV1. Patients commence NIV if there is nocturnal hypoventilation with raised CO_2 levels without OSA (26%) or on CPAP if OSA is present (16%). If sleep studies are abnormal or patients have NIV or CPAP intolerance patients are referred to neurologist assessment for modafinil prescription (38%) while 20% of patients with chronic respiratory insufficiency are on no treatment at all.

Dr Boentert from Münster, Germany overviewed the symptoms of respiratory muscle failure pointing out the differences between night-time and daytime symptoms. He also suggested that a potential good screening tool could be the Sleep Disordered Breathing in Neuromuscular Disease Questionnaire (SiNQ-5) that was published by Steier et al. in 2011 [40] but it was agreed that a more thorough validation process is needed before this may be considered a sensitive tool and be translated in different languages to be used widely. He also reviewed pros and cons of respiratory muscle testing and sleep studies and provided the indications for NIV used in Germany based on symptoms and laboratory findings. Specifically, sleep disordered breathing is the most frequent symptom in the German cohort and indications for NIV are

given when alveolar hypoventilation and inspiratory muscle weakness are present and more specifically when $paCO_2 > 45$ mmHg, nocturnal hypercapnia > 50 mmHg, nocturnal hypoventilation $O_2 < 88\%$ for more than 5 minutes, reduced FVC < 50% of predicted and MIP < 60 cmH_2O. However, Dr Boentert concludes that there are no specific guidelines for NIV in DM and that there is a need for a disease specific approach to chronic respiratory insufficiency.

Dr Gagnon described the Canadian experience where patients are mostly followed in specialized neuromuscular clinics. The practice is not uniformed across Canada. The Neuromuscular Clinic in the Saguenay region in Quebec where the highest prevalence worldwide has been documented follow 454 patients with DM1 and none with DM2. Based on previous experiences, there is no regular annual assessment of respiratory function in mildly affected individuals and secretion management varies greatly. In general, if FVC is <35% in the presence of symptoms patients are referred to a pulmonologist. In the London Ontario area, assessment occurs every 2 years and patients are referred to a pulmonologist if FVC is decreased compared to results from a previous visit, if there is a difference in FVC between sitting and supine and if there are symptoms of respiratory insufficiency. Of 120 adult patients with DM1, 20 are on NIV; of 24 patients with DM2 only 2 are on NIV and of the congenital forms who have grown into adults, only 1 is on BiPAP. Rarely patients with the congenital form of DM1 require long-term tracheo with overnight BiPAP. Most children, if they avoid consequences of long-term ventilation, will get off ventilators and tracheostomy. In the London pediatric DM clinic, 1/3 of the kids have an abnormal sleep study and have indications for NIV. However, good mask fit, secretion control and compliance are challenging. In addition, it is the London Ontario Pediatric Clinic's experience that NIV intervention does not really help much with excessive daytime sleepiness in this population. Dr Gagnon presented data from the Neuromuscular Canadian registry: 13% of adult DM1, 6% of DM2, 23% of adult congenital DM1, and 7% of pediatric congenital DM1 patients are on NIV. It is the Alberta Neuromuscular Clinic experience that overall DM1 and DM2 patients have the lowest compliance with NIV and that patients who do better are those in whom the caregiver is an unaffected family member.

Dr Heathwole, from Rochester, NY, USA presented the Rochester experience. The National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy at the University of Rochester includes data from 1028 patients with DM1 from 50 US states and Canada. Surveys using this registry have shown that there is a high prevalence of respiratory problems in DM1 and that these significantly impact patients' lives. Results from the PRISM study [17] regarding pulmonary involvement were emphasized: 'breathing' difficulties were reported in 57.1% of patients with DM1 and in 51.4% of patients with DM2. Morning headaches were a complaint in a third of patients with DM1. Daytime sleepiness was reported by 91.5% of DM1 patients and 71.9% of patients with DM2. 73.7% of patients with DM1 and 88.9% of those with DM2 had an impaired ability to exercise likely in part due to breathing difficulty. Fatigue was a complaint in many patients (90.8% of DM1 and 89.2% of DM2). In clinical practice, physicians should inquire about respiratory symptoms and evaluate for obstructive sleep apnea when appropriate. A careful pulmonary examination should be regularly performed and total and predicted FVC should be checked and monitored from both the sitting and supine positions. Sleep studies are recommended if OSA is suspected and a pulmonology referral should be considered if a patient has symptoms of respiratory muscle failure, if their FVC is <75% of predicted or if they have had a 20% drop in FVC compared to previous FVC assessments.

The workshop members concluded that there is no standardized respiratory diagnostic and management protocol for patients with DM and that there is a need for a disease specific approach. More specifically, there is no consistent system throughout the different countries to assess respiratory function and there are variable resources both in terms of health care workers and equipment. Perhaps little consideration is given to the fact that this is a slowly progressive disorder and that the long term impact and the course of sleep disordered breathing is not known in DM. Natural history data are missing, especially considering CO_2 levels on the long-term in DM and thinking about what the progression of the disorder will be. Regarding the criteria for launching of NIV in patients with DM, there are still many open questions. Several from the group pointed out there may be a need to wait for patients to be aware of symptoms of respiratory muscle failure before NIV is launched. Estimates of sensibility and specificity of the screening tools now available also need to be improved and there needs to be a precise definition of predictors of treatment success.

2. Conclusions

Management of respiratory insufficiency is challenging in DM because of the pathophysiology of the disease, which affects both muscles and central respiratory pathways and patients' cognitive and behavioral characteristics. Although there are no natural history data on the effects of respiratory care on survival and on morbidity in patients with DM, results of ventilation on survival and on better care in other neuromuscular diseases indicate that adequate ventilatory care may improve survival and QoL of patients with DM1 [41–43]. NIV use varies greatly among the different centers, e.g. varying from 20 to 60% in adults with DM1, 20–40% of patients with the congenital form, and 15–20% of patients with DM2. All participants agreed on the need for standard assessments and recommendations for standard of care.

Discussion between the specialists from different countries led to the construction of initial standard protocols which are the necessary preliminary steps for validation processes to follow. Specifically, the workshop led to the creation of: 1) a respiratory symptom check-list to be applied in everyday DM clinic (Table 1); 2) a preliminary version of a screening respiratory protocol to be applied on first assessment during clinic (Figure 1); 3) proposal of criteria for NIV prescription to be used specifically in patients with DM, based on the existing ACI (Consensus Statement from the Agency for Clinical

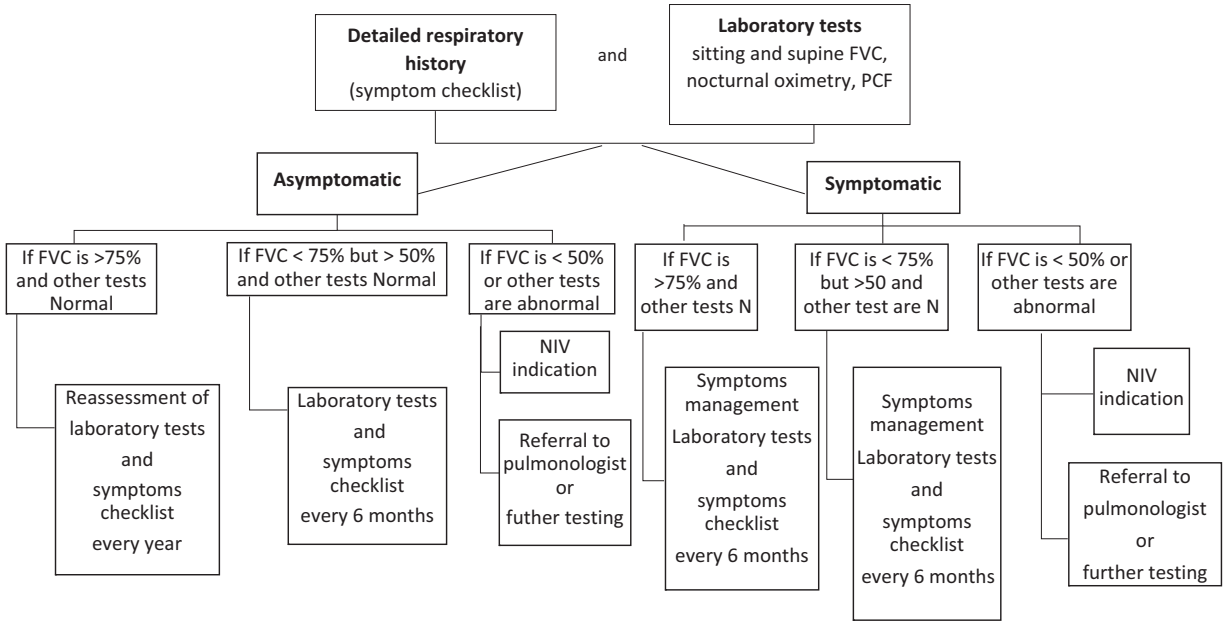

Fig. 1. Protocol for initial respiratory assessment in patients with DM.

Innovation Respiratory Network on Domiciliary Non-Invasive Ventilation in Adult Patients) guidelines for NIV, including recommendations for timing and tests to be performed on follow-up assessments; 4) proposal of a secretion management protocol (Figure 2).

The need for validation of these recommendations and for further research to extend the evidence-base in certain key areas was also highlighted and outline proposals to resolve these deficiencies put forward. All participants agreed on the urge for more natural history data and for specific pathways for emergency care of acute respiratory insufficiency in DM.

2.1. Improving detection and awareness of respiratory symptoms

The group discussed the fact that patients with DM may not be aware of symptoms of respiratory muscle failure and that the

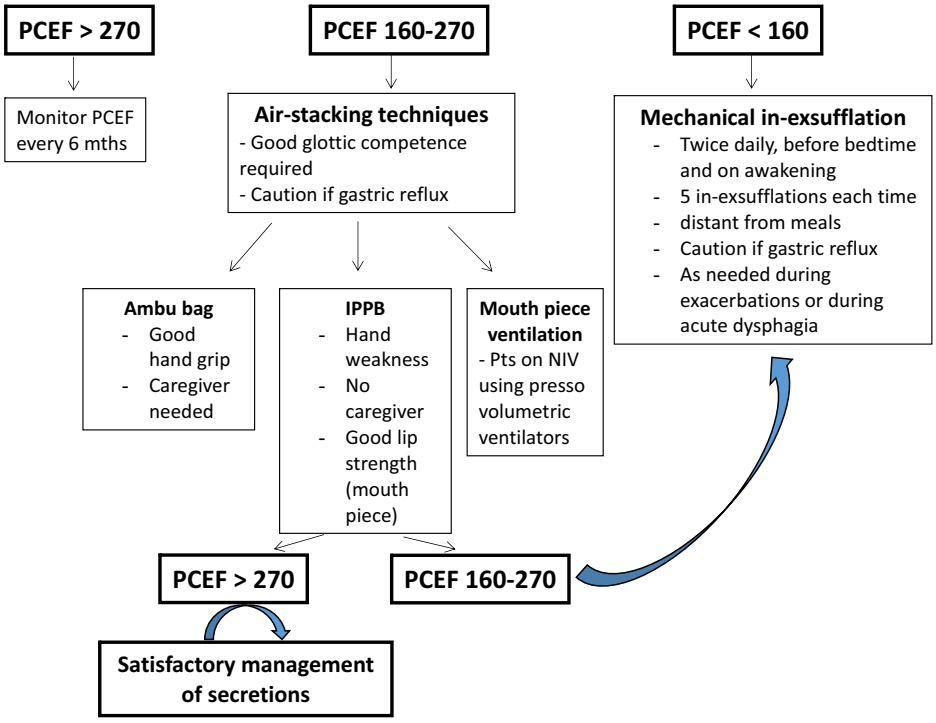

Fig. 2. Secretion management protocol.

way physicians look for these symptoms in this patient population may not be adequate. Caregivers emphasized that symptoms are overlooked and that, even if specifically asked for, patients easily deny having evident symptoms and that if the same question is asked more directly, with practical examples, this can often be more successful in eliciting symptoms. Participants emphasized that central nervous involvement may impede the ability of the person to report his or her symptoms accurately and to be aware of their severity or their impact on his/her daily functioning. Discussion between participants and caregivers on ways to improve detection and awareness concluded that during an initial visit of the patient, a careful and sufficiently long interview with the patient and family about potential symptoms related to pulmonary involvement or sleep-related disordered breathing should be conducted. The interview should include specific questions related to each symptom to help put the patient into concrete situations of his/her daily life. A preliminary symptom checklist was produced by the members and was validated by patient's associations. Symptoms of potential respiratory muscle failure to be addressed during an interview with the patients and if possible spouse or carer to improve reporting of symptoms are: (i) Orthopnea; (ii) Dyspnea with performing ADL; (iii) Poor sleep; (iv) Morning headaches; (v) Apnea; (vi) Decreased cognitive performance; (vii) EDS; (viii) Fatigue; (ix) Treated chest infection since last visit (Table 1).

Participants and carers also agreed that patients with DM require additional time to go through interviews and during visits and assessments, probably due to the slowed cognitive performances and executive dysfunction which are frequently present even in patients with limited motor dysfunction. Physicians seeing patients with DM should be aware of the differences between these patients and others having different neuromuscular conditions. Ideally, they should reserve additional time for appointments and adapt their communication style according to the cognitive and behavioral needs of DM patients.

Table 1
Respiratory involvement symptom check-list. Tick the symptom box if at least one answer per symptom is yes.

Symptom	Yes	No
1) Orthopnea		
a) Do you feel short of breath when you lie down?		
b) Do you need to sleep with more than 1 pillow?		
c) Do you sleep sitting in a chair or arm-chair?		
2) Dyspnea when performing activities of daily living		
a) Do you feel short of breath when you move around the house?		
b) Do you feel short of breath when you wash or dress?		
c) Do you feel short of breath when you talk?		
3) Poor sleep		
a) Do you feel tired when you wake up in the morning?		
b) Do you wake up more than once during the night other than to go to the toilet?		
c) Do you need to get out of bed because of restless legs?		
4) Morning headaches		
a) Do you wake up with a headache in the morning?		
b) Do you feel like your head is heavier in the morning?		
c) Do you feel a pressure in your head when you wake up?		
5) Apneas		
a) Do you wake up short of breath during the night?		
b) Are you told your breathing pauses while you sleep?		
c) Are you told you stop snoring and then suddenly start again while you sleep?		
6) Decreased cognitive performance		
a) Do you feel like your concentration is worse than usual?		
b) Do you find your thinking is slower than usual?		
c) Are you less motivated than usual to do things?		
7) Excessive daytime sleepiness		
a) Do you fall asleep while you eat?		
b) Do you tend to fall asleep while you are driving?		
c) Do you fall asleep while somebody is talking to you?		
8) Fatigue		
a) Do you feel more tired than usual?		
b) Do you feel tired when you wake up after a night's sleep?		
c) Do you feel more tired than expected from what you have done during the day?		
9) Treated chest infection since last visit		
a) Have you had a chest infection that required treatment?		
b) Did you have to use antibiotics for a bad cough?		
c) Have you been admitted to hospital because of a chest infection or because you were short of breath?		

2.2. Recommendations for initial evaluation of pulmonary function: a pulmonary screening protocol for DM

The participants agreed on an algorithm for initial evaluation of pulmonary function for patients with DM. This is based on the assumption that the initial evaluation of pulmonary function is performed by a non-pulmonologist but by the treating physician who may be the general practitioner, the neurologist, or the neuromuscular specialist. Participants agreed on a list of minimal requirements to assess respiratory function and on a list of additional desirable tests to be performed where possible. The minimal assessment includes assessment of symptoms of respiratory muscle failure, respiratory function tests including forced vital capacity (FVC), FEV1, oximetry and Peak Expiratory Cough Flow (PECF). Desirable tests are, in addition, MIP and MEP measurements. The pulmonary function tests outlined below should also be performed, whether patients have symptoms or not, based on the knowledge that the risk of development of progressive respiratory failure should be considered in all subjects with DM1.

Participants reported several potential challenges to properly administer laboratory testing: 1) some severely affected patients have difficulty with lip seal and maximal Sniff Nasal-Inspiratory Pressure (SNIP test) if available may give more reliable readings; 2) some have difficulty understanding instruction so that extra time should be scheduled with these patients; 3) some may not respond to attempts to motivate them so that to give a maximal performance, DM-experienced technicians are desirable; 4) changes in personnel and equipment may lead to decreased standardization in the administration of the tests.

The minimal initial evaluation should include:

– assessment of symptoms of respiratory muscle failure
The interview will be based on the symptoms check-list discussed above.
– pulmonary function tests

These will include:

1) Forced vital capacity (FVC) to be measured sitting and then supine. This is considered abnormal when:
   FVC < 50% of predicted based on the best of 3 measures
   FVC falls by >20% or >500 mL from sitting to supine
2) FEV1 – considered abnormal if <80% of predicted
3) Oximetry – considered abnormal if Oxygen Desaturation Index (ODI) > 15/h.
4) PCEF – considered abnormal if <270 L/min

Referral to a pulmonologist or to a pulmonary service should occur if one or more symptoms of respiratory insufficiency from the symptom check-list are present and if one or more of the tests listed in the minimal requirements list are abnormal. The referral should be done if possible to an institution where there is a sufficient throughput of DM1 patients ensuring optimal management of these patients considering the previous additional challenges described. The pulmonary team will assess the patient further for indication for further management of respiratory involvement including pulmonary health advices, pulmonary rehabilitation and for consideration of non-invasive ventilation.

Additional desirable tests to be performed by a pulmonologist or in a Pulmonary Unit or Service:

– Maximum Inspiratory Pressure (MIP) – considered abnormal if MIP < 60 cmH_2O or SNIP < 40 cmH_2O
– Maximum Expiratory Pressure (MEP) – considered abnormal if MEP < 40 cmH_2O
– Arterial blood gases (ABG) – considered abnormal if $pCO_2 \geq 45$ mmHg (6.0 kPa)

2.3. Recommendations for non-invasive ventilation (NIV) in DM patients

2.3.1. Criteria for launching of NIV

The recommendations are an adaptation of the Consensus Statement from the Agency for Clinical Innovation Respiratory Network on Domiciliary Non-Invasive Ventilation in Adult Patients [44]. This Network consists of seven working groups, including a dedicated group addressing domiciliary non-invasive ventilation.

Generally NIV should be commenced when there is at least one or more of the daytime or nighttime symptoms discussed above suggestive of chronic respiratory insufficiency in combination with:

– Daytime hypercapnia, $PaCO_2 \geq 45$ mmHg (6.0 kPa) *or*
– FVC < 50% of predicted based on the best of 3 measures and MIP < 60 cmH_2O *or*
– Evidence of nocturnal hypoventilation, such as:
  i. A rise in $PaCO_2$ of ≥8 mmHg (1 kPa) between evening and morning ABGs or other accurate CO_2 surrogate
  ii. A rise in $TcCO_2$ or $ETCO_2$ > 50 mmHg (6.7 kPa) for more than 50% of total sleep time
  iii. While not ideal – when a measure of CO_2 is not available – nocturnal oximetry demonstrating sustained oxygen desaturation (SpO_2) ≤ 88% for 5 consecutive minutes or SpO_2 < 90% for >10% of total sleep time

2.3.2. Continuous Positive Airway Pressure (CPAP) versus Bi-Level Positive Airways Pressure (BiPAP)

Respiratory insufficiency can be treated by CPAP or BiPAP. NIV usually refers to BiPAP which assures pressure support during spontaneous breathing reducing respiratory muscle effort during ventilation. CPAP could be an alternative to BiPAP in specific cases when the obstructive component predominates, but respiratory function needs to be closely monitored to allow changes in the type of ventilation support prescribed. If a patient is on CPAP it is necessary to assess blood gases to make sure that nocturnal hypoventilation is adequately taken care of. The panel agreed to prefer BiPAP to start with for most patients considering that nocturnal hypoventilation eventually will occur given the progressive nature of the disease. It was agreed to reserve CPAP in DM if there is only the obstructive component, there are no signs of alveolar hypoventilation and if close follow-up is guaranteed or for those patients in whom BiLevel is not tolerated.

2.3.3. Patient interfaces

Failure of noninvasive ventilation (NIV) has been associated with short-term adverse effects related to the use of masks [45]. This is particularly challenging because of facial and jaw muscle weakness in DM patients and this complicates compliance to NIV whether on CPAP or Bi-Level. The choice of the mask is patient-specific and the performance, comfort and adverse effects have to be weighed each time. Pressure levels again have to be patient specific and especially in patients with DM higher pressure levels reduce comfort and increase adverse effects. Nasal masks are usually preferred by patients with DM although some patients with the total face masks have fewer air leaks and less pain at the nose bridge, although they may complain of greater oronasal dryness and claustrophobia.

2.3.4. Compliance to NIV

Participants addressed the main issue of compliance where they cautioned that given the potential CNS involvement of patients, more time is likely to be necessary for training, adaptation of the instruction and careful training of the spouse or caregivers. Usage throughout all sleep periods should be recommended. Once established on therapy, regular monitoring should be performed; compliance is deemed acceptable if the patients regularly use NIV continuously for more than four hours per night. The more, the better.

Participants discussed the possibility of improving compliance to NIV using home care assistance. Dr Wijkstra pointed out that this is possible in these patients, but adequate monitoring and a solid organization are necessary. The experience at the Groningen Center is based on nurse practitioners being available 24 hours a day, seven days a week. Dr Falcier presented the design of an ongoing trial at the NEMO Center to improve compliance in DM: patients requiring NIV are randomized to standard of care (5–7 day hospital stay after NIV prescription and follow-up 2 months later) or to home-care monitoring. In this case a trained nurse goes to visit patients at

home and checks for compliance by referring to a specific interview addressing potential problems encountered by the patients and by monitoring the number of hours of NIV actually registered on the respirator chip. Preliminary data from this pilot study indicate that aerophagia, gastric discomfort and difficulty initiating sleep are among the main reasons why patients stop using NIV. Specific pharmacological treatment has been required in some patients to induce sleep.

2.3.5. Patient/carer education, training and acclimatization to NIV

Participants including patients' representatives stressed the utmost importance of giving extra consideration to patient and carer training as this was felt to be one of the reasons for poor compliance. The group concluded that, in agreement with ACI recommendations, the following recommendations should be specifically applied:

- Let patients and/or their carers acquire minimum skills and level of knowledge during the process of acclimatization to NIV.
- While training for NIV, make sure you use lay language and that attention is focused.
- Allow time, and specifically allow time for poor visuospatial skills and for executive dysfunction. Make sure you can have another person present. Reduce abstract information and provide specific examples to explain what you are talking about. Keep reasons for the use of NIV symptom focused; limit the use of general information.
- Provide written information as much as possible.
- Acclimatization and education for domiciliary NIV should occur at institutions where there is a sufficient throughput of patients requiring long term NIV.
- Make sure the patient and carer are aware of whom to contact for medical and technical difficulties.

2.3.6. Follow-up after NIV implementation

The participants acknowledged that there is no scientific evidence regarding an optimal procedure for follow-up after NIV implementation. They also recognized that practice might vary greatly according to national policies, organization of care and insurance policies. However, they propose the following procedures until more evidence is available.

- Patients can be reviewed after 4 weeks following the commencement of NIV to determine the clinical response to therapy. After initiation of NIV, clinical review should occur within the first 2–3 months to assess symptoms, technical problems, ventilator settings, compliance and success. The number of hours a patient uses NIV should be carefully monitored and checked on the respiratory chip device. Further clinical reviews should be performed by a Sleep Physician/Respiratory Physician every 6–12 months, again assessing symptoms, compliance, technical problems, lung function, oximetry and further investigations (including ABGs and overnight oximetry or PSG) as required.
- At any time, when there are indications of unsatisfactory results like the recurrence of clinical symptoms or awake blood gases deteriorate despite clinical stability (e.g. absence of recent pulmonary infection) and adequate compliance, then inadequate ventilation must be suspected and objective evaluation during sleep must be undertaken.
- Assessment of nocturnal CO_2 and saturation.

If results are abnormal, a polysomnography should be performed.

2.3.7. Outcomes of NIV implementation

Participants discussed several outcomes that need to be assessed before and after NIV implementation, specifically:

- Improvement of symptoms related to the symptom checklist
- Improvement of laboratory tests such as:
  - awake ABG
  - nocturnal SpO_2

All participants agreed that further evidence need to be available about outcome measurement properties and applicability in clinical setting before making formal recommendations.

2.4. Secretion management in DM

Secretion management is an important aspect of pulmonary health in DM1 but limited data are available in this patient population [46–52]. Data on various neuromuscular disorders such as ALS, Duchenne Muscular Dystrophy and Spinal Muscular Atrophy type 1 patients suggest that in-exsufflation assistance reduces the risk of infection, the duration of the exacerbations, the risks of reintubation and the number of hospital admissions due to acute respiratory failure [50,53–55]. Secretion management, both for in-patients and especially for out-patients, may occur in several ways: using MI-E, performing air-stacking exercises with or without an Ambu bag using IPPB (intermittent positive pressure breathing) or mouthpiece ventilation with presso-volumetric ventilator [50–52]. This is usually taken care of by physiotherapist specialized in pulmonary rehabilitation or by pulmonologists. Drug therapy with amytriptiline for example can help by reducing secretions. The NEMO Neuromuscular Center (M Iatomasi) presented preliminary data on the use of the cough assist machine and on secretion clearance in 69 patients. One third of patients (13/69) required cough-assistance based on clinical examination and on results from the peak expiratory cough flow test which is routinely done during the initial neuromuscular respiratory assessment at the NEMO Clinic. The majority of patients requiring cough-assistance devices were females or patients having reduced volumes (FVC = 64% of predicted) and this was irrespective of age, BMI, and motor impairment.

Participants approved the following criteria for secretion management, in agreement with ACI recommendations:

- a peak cough flow of at least 160 L/min is necessary to manage secretions effectively.
- Patients with a baseline PCF < 270 L/min should have access to manual assisted cough or mechanical cough in-exsufflation techniques. This is especially important

considering that these values are likely to decrease to <160 L/min during chest infections, increasing the likelihood of pneumonia and respiratory failure.
- Training of insufflation should commence when FVC is ≤2 L or is ≤50% predicted.
- Techniques of insufflation, manual assisted coughing and mechanical in-exsufflation require substantial acclimatization and should be trained when the patient is well and ideally prior to an acute infective requirement.

Participants discussed the potential problems associated with secretion management and first of all they pointed out difficulties with adherence to instructions. Other issues addressed were those related to the correct use of the facial device due to facial and jaw muscle weakness and gastric discomfort. During insufflation the lower esophageal sphincter may be dilated causing gastric dilation. The group also discussed the need to couple pulmonary function tests and cough assessments to swallowing studies. Finally, participants agreed that secretion management should be assessed regularly in DM1 and specific outcomes need to be defined for these patients.

2.5. Other considerations

2.5.1. Vaccination and antibiotic treatment

As recommended by an international panel, patients should receive regular vaccination against influenza and pneumococcus [56]. This is also in agreement with published guidelines from the Italian Muscle Association [57]. Of note, low gammaglobulinemia, which is typically found in these patients, is not associated with increased risk of infection [58].

2.5.2. Overweight and lack of regular physical exercise

More than 50% of patients with DM1 may be overweight or obese [59].There is good evidence that being overweight and obese is detrimental in pulmonary diseases and sleep related disordered breathing [60–62], and it is likely that losing weight may help patients with their pulmonary symptoms.

Patients with DM1 tend to exercise less than national health guidelines. Lack of exercise may influence their general respiratory health. Patients should be advised to exercise as often as permitted by their condition in line with the Cochrane recommendations on exercise for people with neuromuscular disorders [63].

2.5.3. Acute respiratory insufficiency emergency care plan

Acute respiratory insufficiency may occur during a chest infection. If a chest infection is suspected, early and aggressive antibiotic treatment should be started to reduce the risk of bacterial super-infection and the source of the pathogen should be looked for. Recommendations are to look for early respiratory insufficiency in DM and to consider that the clinical picture and especially ventilation may rapidly deteriorate during a chest infection in these patients. Mucolytics should not be prescribed if peak cough flow is <160 L/min because of an increased risk of obstructing airways. Oxygen should not be used in acute respiratory muscle failure if not in addition to ventilator support. Oxygen alone has a higher risk to reduce bulbar respiratory drive and increase CO_2 levels worsening the respiratory insufficiency itself [64]. Dr Philips and Ms Bowler from the Myotonic Dystrophy Support Group presented the Emergency Care Card which is being used in the UK. Few centers have written pathways in this sense and there is concern about how these plans are put into action. Emergency care usually goes through a different system from that of neuromuscular emergency services. Specific neuromuscular knowledge is often not available in the emergency and is not sought in the first 24 hours and flagging may be necessary. Participants agreed on the need for a patient-held standardized acute respiratory insufficiency emergency care plan. This could occur by implementing the existing UK Emergency Care Card and by defining a program to disseminate knowledge on respiratory involvement in DM.

Acute respiratory muscle failure may also occur peri-operatively. It is not unusual that patients have been diagnosed with chronic respiratory insufficiency but have no respiratory recommendations, are not on NIV and have no clear indications for secretion management. If surgery is needed, either planned or in an emergency setting, these patients are at higher risk for developing acute respiratory muscle failure. Participants agreed that there is a need for written protocols and for links to perioperative respiratory care including use of NIV and other specific respiratory pathways including secretion management protocols as discussed above.

2.5.4. Future activities and implications for research

Ongoing results from the Dyvine study (NCT01225614), a randomized controlled open label study in France estimating the efficiency and the tolerance of the early introduction of NIV in DM1 adults and from the Rochester US study (NCT01406873) on the effects of mexiletine on respiratory function, will be important to clarify issues discussed during the workshop. Results from the home care program for NIV monitoring which is being conducted at the NEMO Center will also provide additional information on whether home care may improve NIV compliance in patients with DM. Thinking about trial readiness, participants agreed that given the importance of respiratory involvement in DM, any treatment option must consider the impact this may have on respiratory symptoms and outcomes. Participants therefore agreed there is a need to define specific patient-reported outcomes to be used in clinical trials, and in particular it was agreed that it is necessary to approve and validate measures of fatigue, sleep quality, tolerability of NIV and impact of symptoms on patients' lives and that these PROMS need to be available in all languages for the different countries.

Participants

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