Nutritional status, swallowing disorders and respiratory prognosis in adult Duchenne muscular dystrophy patients

Abdallah FAYSSOIL (1, 2, 3, 4), MD PhD, **Cendrine CHAFFAUT** (5), PhD; **Helene PRIGENT** (2, 4, 6), MD PhD, **Pascal LAFORET** (2, 4, 7), MD PhD, **Bernard CLAIR** (1, 2), MD, **David ORLIKOWSKI** (1, 2, 4), MD PhD, **Adam OGNA** (1), MD, **Sylvie CHEVRET** (5), MD PhD, **Paris MENG** (1), MD , **Djillali ANNANE** (1, 2, 4), MD PhD; **Frederic LOFASO** (2, 4, 6), MD PhD, **Pascal CRENN** (2, 4, 8), MD PhD.

1) Service de Médecine intensive et Réanimation/Unité de ventilation à domicile. Hôpital Raymond Poincaré, APHP, Université Paris Saclay/UFR Simone Veil-Santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
2) CRMR des maladies neuromusculaires Nord-Est-Ile de France. Hôpital Raymond Poincaré, APHP, Université Paris Saclay/UFR Simone Veil-Santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
3) Service de cardiologie, Centre de référence des cardiomyopathies et des troubles du rythme cardiaque héréditaires ou rares, Hôpital Ambroise Paré, AP-HP, Université Paris Saclay/UFR Simone Veil-Santé-Université de Versailles Saint Quentin en Yvelines, Boulogne-Billancourt, France
4) Centre d'Investigation clinique (CIC) 1429 INSERM. Hôpital Raymond Poincaré, APHP, Université Paris Saclay/UFR Simone Veil-Santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
5) Service de Biostatistiques et Information Médicale (SBIM). Hôpital Saint Louis, APHP, Université Paris, Paris, France
6) Service de Physiologie - Explorations fonctionnelles. Hôpital Raymond Poincaré, APHP, Université Paris Saclay/UFR Simone Veil-Santé -Université de Versailles Saint Quentin en Yvelines, Garches, France
7) Service de Neurologie/Hôpital Raymond Poincaré, APHP, Université Paris Saclay/ UFR Simone Veil-Santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
8) Unité de Nutrition clinique transversale, Hôpital Raymond Poincaré, APHP Université Paris Saclay/UFR Simone Veil-Santé-Université de Versailles Saint Quentin en Yvelines, Garches, France

Corresponding Author
Pr. Pascal CRENN, MD PhD
E-mail:pascal.crenn@aphp.fr
Tel 33 (1) 47 10 76 40

Abbreviations:
BMI: body mass index; HMV: home mechanical ventilation; DMD: Duchenne muscular dystrophy; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; PCF: peak cough flow

Key words: albumin; malnutrition; Duchenne muscular dystrophy; prognosis; home mechanical ventilation

Word count: 2782 words

Abstract

Malnutrition and swallowing disorders are common in Duchenne muscular dystrophy (DMD) patients. We assessed, in adult DMD with HMV (home mechanical ventilation) and cough assist device, its prevalence and the relationships with respiratory muscle strength and long-term respiratory prognosis. We reviewed the patients (n=117, age 18 to 39 years (median 24)), followed in a reference center, from 2006 to 2015, to obtain clinical baseline, nutritional status, vital capacity (VC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP). Median body mass index was low (15.6). Prevalence of malnutrition, swallowing disorders and gastrostomy were respectively 62, 34 and 11%. BMI and serum albumin level were significantly associated with MIP, MEP and VC. The 1/5-years cumulative incidences of respiratory events (pulmonary sepsis and acute respiratory distress) were respectively 20.7/44.5%. Using univariate analysis, predictive factors for respiratory events were swallowing disorders (p=0.001), transthyretinemia (p=0.034), MIP (p=0.039) and MEP (p=0.03) but not BMI or albuminemia. Using multivariate analysis, only swallowing disorders remained significantly associated with respiratory events (OR=4.2, IC95% 1.31-12.2, p=0.01). If prevalence of malnutrition and swallowing disorders are high in adult DMD on HMV, and respiratory muscles strength associated with serum albumin level and BMI, respiratory prognosis is mainly related to swallowing disorders.

1 Introduction

Duchenne muscular dystrophy (DMD) is a rare inherited myogenic disorder due to mutations in the dystrophin gene on chromosome Xp21.1, affecting male patients. Respiratory muscles weakness as well as dilated cardiomyopathy are frequent in this disease (1, 2, 3). Respiratory impairment exposes patients to pneumonia, acute respiratory failure and mortality (3, 4, and 5). Currently, with home mechanical ventilation (HMV) and cough assist devices, survival has improved in adult DMD (6, 7, and 8). However, nutritional status is a common clinical challenge in patients with chronic respiratory insufficiency, particularly in adult DMD patients, due to disability, macroglossia, dysphagia and swallowing disorders (9, 10, 11, 12, 13, and 14). Albumin level has been reported to be associated with respiratory function and is a reliable prognostic factor in hospitalized patients (15, 16).

Robust evidence-based nutrition research specific to DMD is lacking. Particularly, little is known about nutritional status, its relationship with respiratory function and long-term respiratory morbidity in DMD in the area of HMV. We designed this study to determine the prevalence of malnutrition, the prevalence of swallowing disorders, the association between nutritional status and respiratory muscle strength and the long-term respiratory morbidity in adult DMD patients on HMV.

2 Methods

2.1 Study design

We retrospectively reviewed the charts of all adult DMD patients followed at Raymond Poincare University Hospital (University Paris Saclay, Garches, France), a tertiary neuromuscular center (CRMR: *centre de référence des maladies rares* i.e. rare disease reference center), from 2006 to 2015. From the adult DMD population with genetically proven DMD (17), we included patients who have chronic respiratory insufficiency treated by non-invasive HMV. The **figure 1** represents the flow chart of patients.

The initial visit in the unit, which includes a cardiac and respiratory functional assessment and a nutritional assessment (BMI, serum albumin and transthyretin levels), was the baseline for the present study. From the medical records, for each patient, we collected clinical baseline, presence of swallowing disorders -by video endoscopic evaluation of deglutition function and Pharyngeal Residue Severity Rating Scale score (18), presence of gastrostomy (percutaneous endoscopic gastrostomy or radiologically inserted gastrostomy), body mass index (BMI) calculation, serum prealbumin (transthyretin), serum albumin and C-reactive protein (CRP). In addition, pulmonary forced vital capacity (VC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), peak cough flow (PCF) and respiratory outcomes data were collected. As markers of efficiency of HMV, from the routinely performed daytime arterial or arterialized capillary blood gases, we recorded diurnal carbon dioxide tension (pCO_2) and bicarbonates. In addition, we recorded the results of nocturnal oximetry, performed with a Covidien Nellcor oximeter (percentage of sleep time with oxygen saturation SaO_2 <90%).

We noted the following parameters as acute respiratory events during the follow-up for this study: pulmonary sepsis, acute respiratory distress, pneumothorax, atelectasis, and onset of tracheostomy procedure for invasive ventilation during follow up. The study was performed in compliance with the ethical principles formulated in the declaration of Helsinki and was approved by the *Comité de Protection des Personnes* and the *Commission Nationale de l'Informatique et des Libertés.* The study was registered on Clinical.Trials.gov (NCT02501083).

2.2 Malnutrition and severe malnutrition definition

Patients were classified at the baseline in the group malnutrition in case of BMI<20 and/or serum albumin<35 g/dl. Patients were classified in the group severe malnutrition in case of BMI<18.5 and/or albumin <30 g/dl. For BMI as phenotypic criteria, we used the recent GLIM (Global Leadership Initiative on Malnutrition) criteria’s (19). The criteria reduced muscle mass was not available due to absence of measurement by a validated technic of body composition but all patients had severe reduction of muscle function, due to the myopathy, and the criteria of sarcopenia was not considered for the diagnosis of malnutrition. All patients had CRP in the normal range at the baseline. All patients had the GLIM etiologic criteria, *i.e.* DMD.

2.3 Respiratory function and respiratory muscle strength

At baseline, pulmonary function tests were performed according to the ATS/ERS recommendations (20, 21), using a *Vmax 229 Sensormedics System* (*Yorba Linda, USA*) in the upright position. Forced pulmonary vital capacity (VC) was also measured in supine position. Measurements are expressed as percent of predicted values.

Maximal sniff nasal inspiratory pressure (Psnip) and maximal inspiratory pressure (MIP) were measured from functional residual capacity (FRC) in the upright position. Maximal expiratory pressure (MEP) was measured at total lung capacity (TLC). For each technique, the best value was recorded (21). MIP and MEP were also expressed in percentage of estimated lower limit (21). Peak-cough-flow (PCF) was measured with an appropriately fitted facemask (*Leadal Medical, Limonest, France*) instead of a mouthpiece, placed around the mouth to allow mouth opening and reduce cheek compliance. Care was taken to avoid leaks around the mask. Patients were asked to cough as hard as possible, and the highest PCF obtained from three cough maneuvers, within 10% of the maximal value, was recorded. PCF cut-off values of 270 L/min and 160 L/min were used to indicate cough disorders, as they are considered as indicative of, respectively, respiratory failure risk during respiratory tract infection and inability to clear airway successfully(22).

MIP was measured using a flanged mouthpiece with the manoeuvres repeated at least three times or until two identical readings were obtained. Once the operator was satisfied, the maximum value of three manoeuvres that varied by less than 20% was recorded (23).

2.4 Statistical analysis

Continuous variables were described by median ± interquartile range (IQR) and compared by Wilcoxon Rank Sum test. Dichotomous or categorical variables were described by number of subjects and percentage and compared by Fisher's exact test. The associations between respiratory continuous parameters were explored by the nonparametric Spearman's correlation coefficient. Univariate and multivariate logistic models allowed to estimate the strength of association based on the odd ratio (OR). Statistical analysis was performed using R® (http://www.R-project.org/). A $p < 0.05$ was considered as statistically significant.

3 Results

3.1 Patient characteristics and prevalence of malnutrition at baseline

A total of 117 male patients were included in the study. Age ranged from 18 years to 39 years with a median of 24. All patients were wheel chair bound. Median age of ambulation loss was 10 years. Median BMI was 15.6 [12.2– 20.6] and swallowing disorders were present in 34% of patients. Five patients were overweighed (BMI between 25 and 30 kg/m²) and one patient was obese (BMI at 32). Gastrostomy was present in 11% (n=13) of patients. Prevalence of malnutrition and severe malnutrition were respectively 62% and 42%. It is to note that only 16% had transthyretinemia below normal range (<0.2 mg/dL) and 9% albuminemia below normal range (<35 g/L). CRP values were in the normal range, so there were no patients with chronic inflammation. Left ventricular ejection fraction (LVEF) was reduced with a median at 47% [40– 55]. Ninety % of patients were treated with Angiotensin converting enzyme (ACE) inhibitors and beta-blockers were prescribed in 52% of patients. Patients were not on steroids in this cohort. HMV was efficient with a median diurnal PCO_2 at 5.4 kPa, without nocturnal desaturation. Baseline characteristics of the population are detailed in **table 1.**

3.2 Respiratory function and respiratory muscle strength

Included patients had severe restrictive respiratory function with a median VC of 10.5 % [7 –17] of predicted value. Respiratory muscle strength was severely affected with median MIP at 15 cmH_2O [10 – 25] and median MEP at 12 cm H_2O [8 – 20] (**table 1**). The PCF was severely reduced with a median at 145 L/min [105 – 171].

3.3 Association between nutritional parameters and respiratory muscle strength

We found a significant association between serum albumin concentration and MIP (r=0.43 p<0.0001) and between serum albumin concentration and MEP (r=0.36, p=0.00045) (**figures 2** and **3**). The PCF was not associated with serum albumin (p=0.08). The VC was significantly associated with serum albumin (r=0.29, p=0.003). VC, MIP and MEP were also associated with BMI. The **table 2** summarizes the association between nutritional parameters and respiratory function.

3.4 Cumulative incidence of respiratory events and prognosis

The one–year and 5-years cumulative incidence of respiratory events were respectively 20.7% [IC95%: 13.3 – 28.2] and 44.5% [IC95%: 34.6 – 54.3] (**figure 4,** Kaplan-Meier method). Among events, pulmonary sepsis was the most frequent (56 patients, 48%) as well as acute respiratory distress (39 patients, 33%) and atelectasis (10.8%). Pneumothorax occurred in five patients. Invasive ventilation (ventilation using tracheostomy) was necessary in seven patients during the follow up**. The figure 5 (**Kaplan-Meier method with log rank test**)** represents the respiratory event-free survival in patients with swallowing disorders *vs.* patients without swallowing disorders. During the follow-up, no patients were lost of view but 35 patients (29.9%) deceased. Among documented death, 40% were related to respiratory diseases and 60% were related to cardiac diseases.

Additional gastrostomy was performed in eight patients during follow up, because of severe malnutrition and/or swallowing disorders.

Using univariate analysis, predictive factors for respiratory events were swallowing disorders (p=0.001), serum transthyretin concentration (p=0.034), serum albumin concentration (p=0.057), MIP (p=0.039) and MEP (p=0.030), but not presence of malnutrition even severe, BMI or serum albumin concentration (**table 3**). Using multivariate analysis, only swallowing disorders were associated with respiratory events (OR= 4.2 IC95% 1.31-12.2, p=0.01).

4 Discussion

This study provides insights on nutritional status (BMI, serum albumin and transthyretin concentrations) and long term respiratory morbidity in adult DMD patients on HMV. The main findings of this study, with a large cohort of patients (n=117), not on steroids, is that: a) malnutrition (undernutrition) is frequent in adult DMD with a prevalence reaching 62% but is not *per se* a predictive factor of respiratory events, b) respiratory muscle strength (evaluated by MIP and MEP) is associated with serum albumin concentration and BMI, c) prevalence of swallowing disorders (evaluated by presence of pharyngeal residues, defined as pre-swallow secretions and post-swallow food residue in the pharynx not entirely cleared by a swallow, as a clinical predictor of prandial aspiration) is high, reaching 34%, and d) respiratory morbidity is high, particularly in patients with swallowing disorders.

Upper airway muscles impairments have been reported in other neuromuscular disorders, particularly in amyotrophic lateral sclerosis (ALS) and affect prognosis (24). Our data regarding prevalence of malnutrition in adult DMD are similar to others studies reported in the pediatric literature, *i.e.* 54% at about 18 years of age in the study by Willig *et al* (14). Conversely, to young DMD patients who experienced high prevalence of obesity (22), adult DMD disclosed weight loss and malnutrition (14) with its specific risks such as decubitus bedsores. In this cohort, only one adult DMD patient was obese and an overweight status was present in only 5 adult DMD patients.

In DMD, the presence of chronic respiratory failure in late stage may increase energy expenditure, but is not the case in all situations (25). Malnutrition may result from a reduction of food intake and/or an increase of energy expenditure. In DMD, weight loss is caused mainly by a negative energy and protein balance, in relation to a reduction in dietary intake. In DMD, reduced food intake is in relation with oral muscles weakness and dysphagia, swallowing disorders, reduced chewing, prolonged mealtime and respiratory muscle weakness (26). It is important to note that diagnosis of malnutrition is not easy in adult DMD. In this study, in the absence of body composition measurement and with a disease-related severe impairment of muscle function, we used the GLIM criteria (19) with additional data, like serum albumin as a prognostic indicator.

Prevalence of swallowing disorders, in adult DMD, is high, *i.e.*, 34% in this study. Usually, the swallow process is characterized by a brief apnea followed by expiration, delaying the next respiratory cycle (26). In DMD, this cycle is altered and Terzi *et al* (27), in a study that evaluated the swallowing-breathing interaction, reported frequent occurrences of inspiratory effort immediately after swallowing which may increase the risk of aspiration, particularly in case of post-swallowing pharyngeal residue. HMV and cough assist devices have improved respiratory care and prognosis of patients with DMD (6, 7, 8). However, the presence of swallowing disorders remains a major predictive factor for mortality (28) and morbidity, as underlined by our data (OR=4.2 for acute respiratory events). This emphasizes the need for a multidisciplinary approach, including not only a respiratory care management, but also a nutritional status and caloric intake evaluations with a dietician and a particular focus on swallowing disorders assessment with a swallowing therapist.

Since gastrostomy (endoscopic or radiologic) is indicated in DMD patients with swallowing disorders leading to infectious swallowing lung disease and malnutrition, according to the *DMD Care Considerations Working Group* (29), earlier gastrostomy may be discussed in selected DMD patients. The family and care team should consider gastrostomy tube placement to be a necessary and positive intervention when progressive weakness interferes with self-feeding and swallowing. Indications for gastrostomy tube placement include severe malnutrition that is unresponsive to interventions to improve oral caloric intake, diagnosis of severe swallowing disorders, and inability to maintain adequate hydration. Assessment of the benefits of gastrostomy tube feeding should be discussed in the context of respiratory, cardiac, and anesthetic risks (29). Enteral feeding by gastrostomy has been shown to improve nutritional status in adult DMD (30) and mechanical ventilation may improve swallowing function in patients with neuromuscular disorders (31). Malnutrition may also alter immunologic responses. This feature increases the risk of pulmonary sepsis (32). It is of note that in this study the prevalence of gastrostomy appears to be low (21 under 117 patients *i.e.* 18%), due to the technical difficulties and delay of potential acceptance by patients and its family or care team.

This study highlights the significant relationship between malnutrition and respiratory function status. Indeed, significant association was found between serum albumin and respiratory muscle strength. In addition, in DMD, the BMI has been reported to be associated with respiratory function (33) and the regional lean mass is reduced and associated with decreased strength (34). We found a significant association between nutritional parameters, namely albumin, prealbumin (transthyretin) and BMI and respiratory muscles strengths (MIP and MEP). In addition, malnutrition may affect diaphragm thickness and function (35). Like a vicious circle, respiratory muscle failure may lead to a reduction of oral intake that inversely affects respiratory muscle strength. Recently, a group from Korea reported relationship between the presence of eating disorders and the decrease of respiratory muscle strength in DMD (36).

Nevertheless, our study has some limits. We do not have data for these patients on the possible reduction in weight and oral intake (of different cause like dysphagia, swallowing disorders, macroglossia…) in the months before starting HMV and during the follow-up. This methodological aspect may misestimate nutritional status in DMD. We previously shown that food intake of theses adult DMD patients on HMV was 1.2+/-0.4 greater than their resting energy expenditure (25). Body composition may provide specific nutritional status evaluation of patients. Indeed, adult patients with DMD disclosed reduction in fat-free mass (bio-impedancemetry) and reduced resting energy expenditure (indirect calorimetry) (25). In DMD, body composition is characterized by a reduction of lean body mass and an increase of intramuscular fat mass (37). In fact, patients with advanced forms of Duchenne muscular dystrophy have balanced energy intakes and resting energy expenditure (25). In addition, serum albuminemia as well as BMI may underestimate nutritional status in DMD at the difference of body composition (38, 39). As albumin discloses a long half time and reflects an index of chronic malnutrition; it can in fact be considered as a reliable global prognosis biomarker. It is important to note that in this study most, with the exception of 9 to 16%, of patients had serum albumin -and transthyretin- in the normal usual range. This raises the question of the relevance of these protein biomarkers in DMD, a situation with a severe sarcopenia, as it is well known in anorexia nervosa for example. Finally, this study was mono-centric, but it is a rare disease followed in a tertiary reference center (CRMR: *centre de référence des maladies rares* i.e. rare disease reference center), and retrospective and the results may be hampered by the recruitment specificities of a specialized unit.

5 Perspectives

DMD is a neuromuscular disorder with disability that affects not only the skeletal muscle system but also the respiratory muscles and the swallowing function. These results highlight the need for a multi-collaborative association in the management of these patients. Regular screening for swallowing disorders is necessary with in addition a very regular nutritional status evaluation. It is possible that an analysis of body composition with a well-validated technique in this situation brings more prognosis information for these adult patients.

6 Conclusion

Prevalence of malnutrition and swallowing disorders are significantly high, respectively 62% and 34%, in adult DMD on HMV. Respiratory prognosis is affected mainly by swallowing disorders. Respiratory muscles strength is associated with albumin level and BMI. These results emphasize the importance of regular nutritional and dietetic assessments for DMD patients.

Acknowledgments

Grants and funding: no

Authorship:

Abdallah FAYSSOIL: study design, practical performance, data collection, preparation of manuscript

Cendrine CHAFFAUT data analysis

Helene PRIGENT practical performance, critical review of manuscript

Pascal LAFORET practical performance, critical review of manuscript

Bernard CLAIR practical performance

David ORLIKOWSKI practical performance, critical review of manuscript

Adam OGNA practical performance

Sylvie CHEVRET data analysis

Paris MENG practical performance

Djillali ANNANE study design, critical review of manuscript

Frederic LOFASO study design, practical performance, critical review of manuscript

Pascal CRENN: study design, preparation of manuscript, critical review of manuscript, final form of the manuscript.

Conflict of interest statement: no conflict of interest

References

1) Nigro G, Comi LI, Politano L, Bain RJ. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. Int J Cardiol. 1990 Mar;26(3):271-7.
2) Rideau Y, Gatin G, Bach J, Gines G. Prolongation of life in Duchenne's muscular dystrophy. Acta Neurol (Napoli). 1983 Apr;5(2):118-24.
3) Nagai T. Prognostic evaluation of congestive heart failure in patients with Duchenne muscular dystrophy—retrospective study using non-invasive cardiac function tests. Jpn Circ J. 1989 May;53(5):406-15.
4) Benditt JO, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease. Am J Respir Crit Care Med. 2013 May 15;187(10):1046-55.
5) Khirani S, Ramirez A, Aubertin G, Boulé M, Chemouny C, Forin V, Fauroux B. Respiratory muscle decline in Duchenne muscular dystrophy. Pediatr Pulmonol. 2014 May;49(5):473-81.
6) Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002 Dec;12(10):926-9.
7) Simonds AK, Muntoni F, Heather S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. Thorax. 1998 Nov;53(11):949-52
8) Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2014 Dec 13;12:CD001941.
9) Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999 Dec;160(6):1856-61
10) Ambrosino N, Clini E. Long-term mechanical ventilation and nutrition. Respir Med. 2004 May;98(5):413-20
11) Davis J, Samuels E, Mullins L. Nutrition Considerations in Duchenne Muscular Dystrophy. Nutr Clin Pract. 2015 Aug;30(4):511-21.
12) Allen KS, Mehta I, Cavallazzi R. When does nutrition impact respiratory function? Curr Gastroenterol Rep. 2013 Jun;15(6):327.
13) Dureuil B, Matuszczak Y. Alteration in nutritional status and diaphragm muscle function. Reprod Nutr Dev. 1998 Mar-Apr;38(2):175-80.
14) Willig TN, Carlier L, Legrand M, Rivière H, Navarro J. Nutritional assessment in Duchenne muscular dystrophy. Dev Med Child Neurol. 1993 Dec;35(12):1074-82
15) Herrmann FR, Safran C, Levkoff SE, Minaker KL. Serum albumin level on admission as a predictor of death, length of stay, and readmission. Arch Intern Med. 1992 Jan;152(1):125-30.
16) Park SY, Chung JS, Kim SH, Kim YW, Ryu H, Kim DH. The safety and prognostic factors for mortality in extremely elderly patients undergoing an emergency operation. Surg Today. 2016 Feb;46(2):241-7.
17) Fayssoil A, Ben Yaou R, Ogna A, Chaffaut C, Leturcq F, Nardi O, et al. Left bundle branch block in Duchenne muscular dystrophy: Prevalence, genetic relationship and prognosis.PLoS One. 2018 Jan 5;13(1):e0190518.
18) Neubauer PD, Hersey DP, Leder SB. Pharyngeal Residue Severity Rating Scales Based on Fiberoptic Endoscopic Evaluation of Swallowing: A Systematic Review. Dysphagia. 2016 Jun;31(3):352-9
19) Cerderholm T et al. GLIM criteria for the diagnosis of malnutrition. A consensus report from the global clinical nutrition community. Clin Nutr 2018 https://doi.org/10.1016/j.clnu.2018.08.002
20) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of lung function testing: the authors' replies to readers' comments. The European respiratory journal 2010;36(6):1496–1498. 10.1183/09031936.00130010
21) American Thoracic Society; European Respiratory Society. ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:528–547.
22) Saure C, Caminiti C, Weglinski J, de Castro Perez F, Monges S. Energy expenditure, body composition, and prevalence of metabolic disorders in patients with Duchenne muscular dystrophy. Diabetes Metab Syndr. 2018 Apr - Jun;12(2):81-85
23) Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984: 39(7): 535-538)
24) Westeneng HJ, Debray TPA, Visser AE, van Eijk RPA, Rooney JPK, Calvo A, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol. 2018 May;17(5):423-433.
25) Gonzalez-Bermejo J, Lofaso F, Falaize L, Lejaille M, Raphaël JC, Similowski T, et al. Resting energy expenditure in Duchenne patients using home mechanical ventilation. Eur Respir J. 2005 Apr;25(4):682-7
26) Toussaint M, Davidson Z, Bouvoie V, Evenepoel N, Haan J, Soudon P. Dysphagia in Duchenne muscular dystrophy: practical recommendations to guide management. Disabil Rehabil. 2016 Oct;38(20):2052-62

27) Terzi N, Orlikowski D, Aegerter P, Lejaille M, Ruquet M, Zalcman G, et al. Breathing-swallowing interaction in neuromuscular patients: a physiological evaluation. Am J Respir Crit Care Med. 2007 Feb 1;175(3):269-76
28) Boussaïd G, Lofaso F, Santos DB, Vaugier I, Pottier S, Prigent H, et al. Impact of invasive ventilation on survival when non-invasive ventilation is ineffective in patients with Duchenne muscular dystrophy: A prospective cohort. Respir Med. 2016 Jun;115:26-32.
29) Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018 Mar;17(3):251-267
30) Martigne L, Seguy D, Pellegrini N, et al. Efficacy and tolerance of gastrostomy feeding in Duchenne muscular dystrophy. Clin Nutr. 2010;29:60–64.
31) Garguilo M, Lejaille M, Vaugier I, Orlikowski D, Terzi N, Lofaso F, et al. Noninvasive Mechanical Ventilation Improves Breathing-Swallowing Interaction of Ventilator Dependent Neuromuscular Patients: A Prospective Crossover Study. PLoS One. 2016 Mar 3;11(3):e0148673.
32) Pane M, Vasta I, Messina S, Sorleti D, Aloysius A, Sciarra F, et al. Feeding problems and weight gain in Duchenne muscular dystrophy. Eur J Paediatr Neurol. 2006 Sep-Nov;10(5-6):231-6
33) Chew K, Carey K, Ho G, Mallitt KA, Widger J, Farrar M. The relationship of body habitus and respiratory function in Duchenne muscular dystrophy.Respir Med. 2016 Oct;119:35-40
34) Skalsky AJ, Han JJ, Abresch RT, Shin CS, McDonald CM. Assessment of regional body composition with dual-energy X-ray absorptiometry in Duchenne muscular dystrophy: correlation of regional lean mass and quantitative strength. Muscle Nerve. 2009 May;39(5):647-51.
35) Arora NS, Rochester DF. Effect of body weight and muscularity on human diaphragm muscle mass, thickness, and area. J Appl Physiol Respir Environ Exerc Physiol. 1982 Jan;52(1):64-70.
36) Lee JW, Oh HJ, Choi WA, Kim DJ, Kang SW. Relationship between Eating and Digestive Symptoms and Respiratory Function in Advanced Duchenne Muscular Dystrophy Patients J Neuromuscul Dis. 2020;7(2):101-107.
37) Leroy-Willig A, Willig TN, Henry-Feugeas MC, Frouin V, Marinier E, Boulier A, et al. Body composition determined with MR in patients with Duchenne muscular dystrophy, spinal muscular atrophy, and normal subjects. Magn Reson Imaging. 1997;15(7):737-44.
38) Kyle UG, Morabia A, Slosman DO, Mensi N, Unger P, Pichard C. Contribution of body composition to nutritional assessment at hospital admission in 995 patients: a controlled population study. Br J Nutr. 2001 Dec;86(6):725-31.
39) Pessolano FA, Súarez AA, Monteiro SG, Mesa L, Dubrovsky A, Roncoroni AJ, et al. Nutritional assessment of patients with neuromuscular diseases. Am J Phys Med Rehabil. 2003 Mar;82(3):182-5.

TABLES

Parameters	N (%) or median [IQR]
Age (y)	24 [21 ; 28]
Weight (kg)	41 [32 ;56.5]
BMI (kg/m²)	15.6 [12.2; 20.6]
Malnutrition	73(62%)
Severe malnutrition	49(42%)
Swallowing disorders	37 (34%)
Gastrostomy	13(11%)
Transthyretin concentration (mg/dl)	0.24 [0.2; 0.27]
Serum albumin concentration (g/dl)	41[39; 43]
CRP (mg/l)	3.6 [1.9; 8]
VC (% predicted)	10.5 [7; 17]
MIP (cmH_2O)	15 [10; 25]
MEP (cmH_2O)	12[8; 20]
PCF (l/min)	147 [105 – 171]
Bicarb(mmol/l)	26 [23.75 – 28.8]
Diurnal PCO2 (kPa)	5.4 [4.67 – 6.12]
Nocturnal satO2<90% (%)	0 [0 – 1]

Table 1: Characteristics of the studied HMV DMD population (n=117) at baseline

HMV: home mechanical ventilation; BMI: body mass index; CRP: C reactive protein
VC: pulmonary vital capacity; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure;
PCF=peak cough flow; Bicarb=bicarbonates; PCO_2: diurnal carbon dioxide tension
y=years, SaO_2: oxygen saturation

	VC (%)	MIP (cmH20)	MEP (cmH20)
Serum albumin concentration	p=0.003 r=0.29	p<0.0001 r=0.43	p=0.00045 r=0.36
Transthyretin concentration	P=0.001 r=0.33	P=0.003 r=0.33	P=0.26
BMI	P=0.009 r=0.27	P=0.001 r=0.35	P=0.001 r= 0.35

Table 2: Relationship between nutritional and respiratory function parameters at baseline in the 117 HMV DMD patients

VC: pulmonary vital capacity (predicted value)

MIP: maximal inspiratory pressure

MEP: maximal expiratory pressure

BMI: body mass index

r= Spearman coefficient correlation

Parameters	**No respiratory events (N= 59)**	**Respiratory events (N=58)**	**P value**	**OR (95%IC)**
Age (y)	24[22; 27.5]	25 [21; 28.7]	0.49	1.02(0.96-1.10)
Weight (kg)	42.5 [35.5; 59]	39.5 [32; 53]	0.13	0.98(0.96-1.01)
BMI (kg/m²)	15.9 [13.2; 21.3]	15.2 [12; 20]	0.30	0.96(0.89-1.04)
Malnutrition	35(59%)	38(65.5%)	0.49	1.3 (0.62-2.76)
Severe malnutrition	24(41%)	25(43%)	0.79	1.1 (0.53-2.3)
Serum albumin (g/l)	42[39; 44]	40 [38; 42]	0.057	0.91(0.82-1.00)
Transthyretin (mg/dl)	0.25[0.22; 0.28]	0.23[0.2; 0.26]	0.034	0.00(0.00-0.48)
CRP (mg/l)	3.2 [2; 5.4]	4.7 [1.7; 10.3]	0.67	1.01(0.96-1.06)
Swallowing disorders	10(18.5%)	27 (49%)	0.001	4.24 (1.78-10.1)
Gastrostomy	6 (10%)	7 (12%)	0.80	1.17(0.33-4.13)
Tracheostomy	24 (41%)	32(55%)	0.14	1.74(0.84-3.64)
VC (%predicted)	13 [8; 21.5]	10 [6; 16]	0.07	0.97(0.93-1.00)
MIP (cmH_2O)	18 [10; 27]	12 [7; 20]	0.039	0.96(0.93-1.00)
MEP (cmH_2O)	13.5 [9; 21.5]	11 [8; 17]	0.030	0.95(0.90-0.99)
PCF (l/s)	2.49[1.75; 2.96]	2.38[1.84; 2.67]	0.58	0.81(0.39-1.69)
Bicarb (mmol/l)	26[24.25; 28.6]	26 [23.6; 29.1]	0.79	1.01(0.92-1.12)
PCO_2 (kPa)	5.45 [4.7– 6.18]	5.34 [4.33 – 6.06]	0.27	0.82(0.58-1.16)
Nocturnal $SatO_2$<90%	0.2 [0 – 1]	0 [0 – 1]	0.31	1.04(0.97-1.12)

Table 3: Parameters associated with respiratory events in the follow-up of the cohort of 117 HMV DMD patients

Values are expressed as median [interquartile range] or N, number (proportion).

BMI: body mass index; CRP: C –reactive protein; DMD: Duchenne muscular dystrophy

VC: pulmonary vital capacity; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure;

HMV: home mechanical ventilation; PCF: peak cough flow; Bicarb=bicarbonates

PCO_2: diurnal carbon dioxide tension; $SatO_2$, oxygen saturation

FIGURES

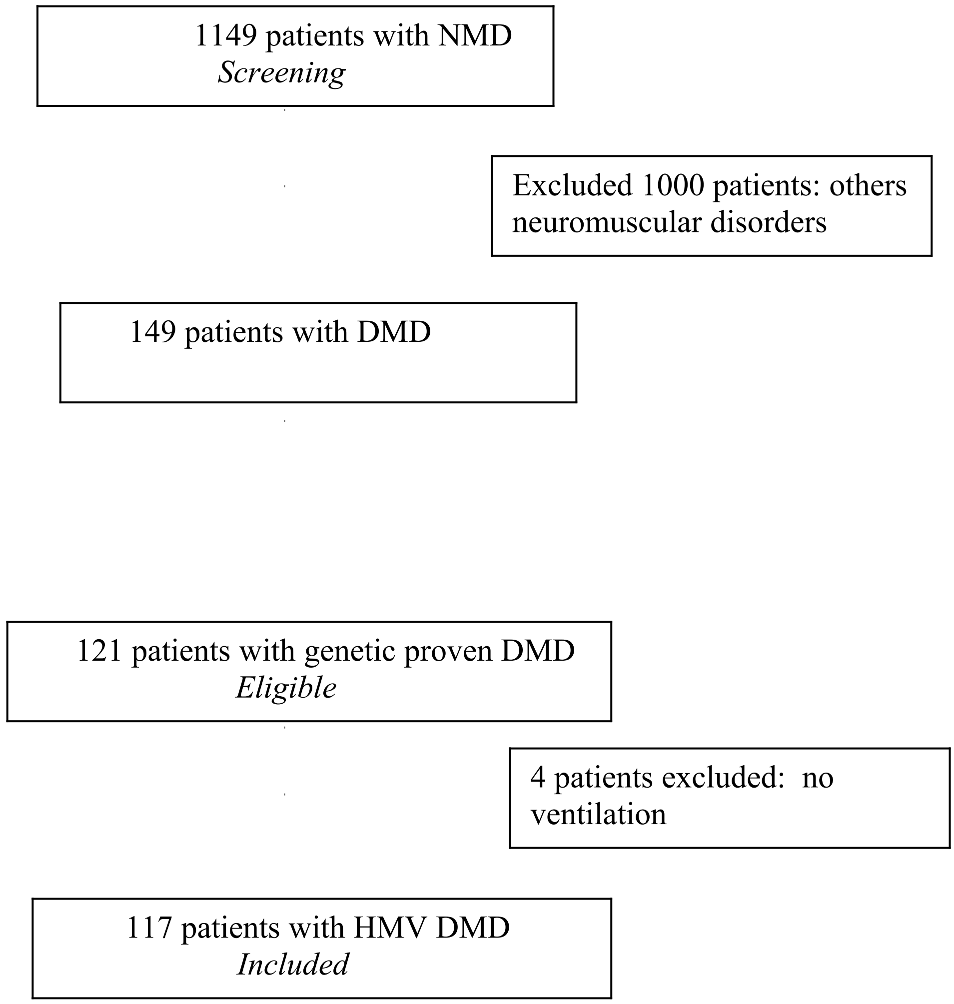

Figure 1: Flow chart Diagram

HMV: home mechanical ventilation

NMD: neuromuscular disorders

DMD: Duchenne muscular dystrophy

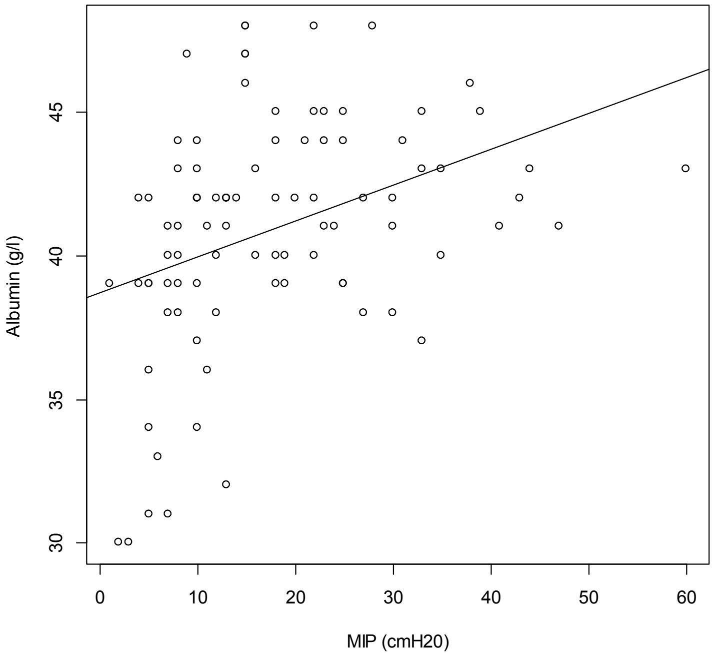

Figure 2: *Relationship between serum albumin (g/l) and MIP (cm$H_2$0) at baseline in the population of HMV DMD (n=117)*

Spearman test

r=0.43 (p<0.0001)

MIP=maximal inspiratory pressure

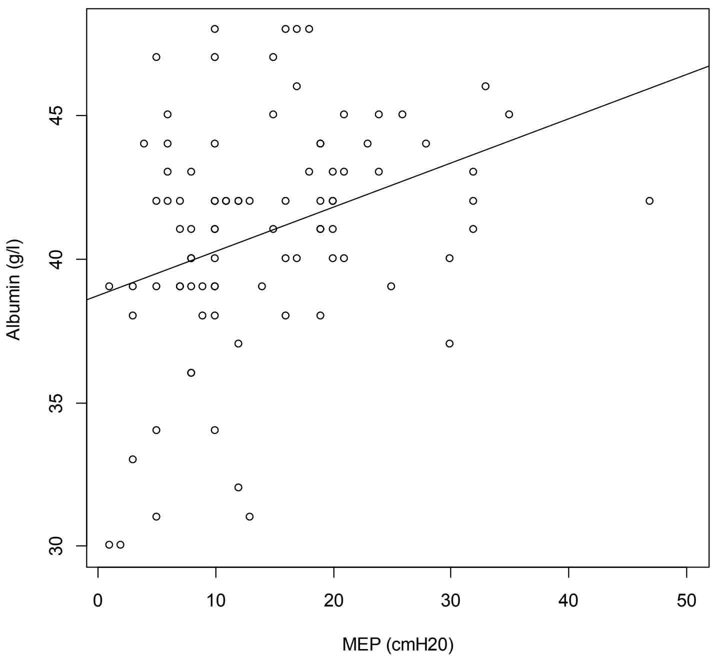

Figure 3: *Relationship between serum albumin (g/l) and MEP (cm$H_2$0) at baseline in the population of HMV DMD (n=117)*

Spearman test

r=0.36 (p=0.00045)

MEP=maximal expiratory pressure

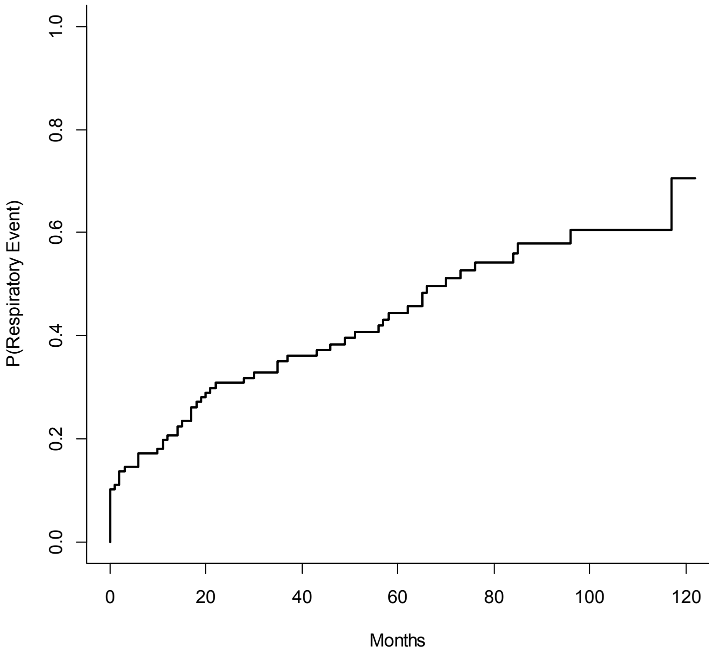

Figure 4: Cumulative incidence of respiratory events in the 117 DMD patients on HMV

DMD: Duchenne muscular dystrophy
HMV: home mechanical ventilation

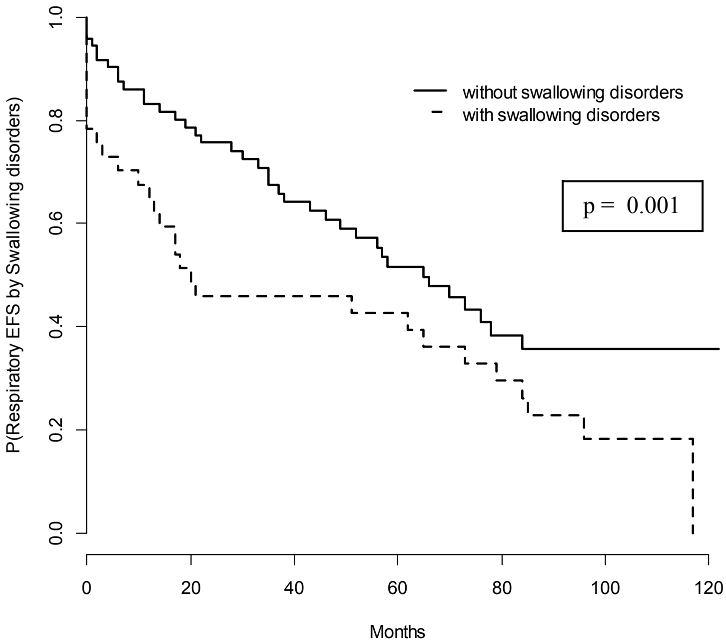

Figure 5: Event-free survival (EFS) in Duchenne muscular dystrophy (DMD) patients with swallowing disorders (n=37) *vs* DMD patients without swallowing disorders (n=80)