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Review

Relationship between Eating and Digestive Symptoms and Respiratory Function in Advanced Duchenne Muscular Dystrophy Patients

Jang Woo Lee[a,d], Hyun Jun Oh[b], Won Ah Choi[b,c,*], Dong Jin Kim[e] and Seong-Woong Kang[b,c,d,*]

[a]*Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea*

[b]*Department of Rehabilitation Medicine and Rehabilitation Institute of Neuromuscular Disease, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea*

[c]*Pulmonary Rehabilitation Center, Gangnam Severance Hospital*

[d]*Yonsei University Graduate School of Medicine, Seoul, Korea*

[e]*Department of Rehabilitation Medicine, SRC Rehabilitation Hospital, Gwangju-si, Gyeonggi-do, Korea*

Abstract.

Background: Duchenne muscular dystrophy (DMD) patients can have various issues that affect their quality of life, including eating and digestive conditions.

Objective: We sought to identify the relationship between respiratory function and various eating and digestion related symptoms in patients with advanced Duchenne muscular dystrophy (DMD).

Methods: Eating and digestive symptoms, including loss of appetite, nausea, vomiting, diarrhea, constipation, swallowing difficulty, mastication difficulty, early satiety, and aspiration, were evaluated among patients with advanced DMD who were nonambulatory and required noninvasive mechanical ventilatory support. In addition, various respiratory function parameters were measured, including forced vital capacity (FVC), maximal insufflation capacity (MIC), peak cough flow (PCF), assisted PCF (APCF), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP). We then analyzed the relationship between gastrointestinal symptoms and respiratory function parameters.

Results: A total of 180 patients (age, 22.3 ± 5.0 years) were included in the analysis. Loss of appetite and early satiety showed no correlation with any of the respiratory function parameters. Constipation was correlated with MEP; swallowing difficulty was correlated with MIC, APCF, MIP and MEP; and mastication difficulty was correlated with FVC, PCF, APCF, MIP, and MEP. Notably, age did not correlate with any gastrointestinal symptoms.

Conclusions: Eating and digestive symptoms are more closely correlated with respiratory function than with age in patients with DMD. We think this correlation is mainly caused by the skeletal muscle strength, which is major determinant of both digestive and respiratory function.

Keywords: Duchenne muscular dystrophy, respiratory function, digestive symptoms, deglutition disorders

*Correspondence to: Seong-Woong Kang and Won Ah Choi, Department of Rehabilitation Medicine, Gangnam Severance Hospital, Rehabilitation Institute of Neuromuscular Disease, Yonsei University College of Medicine 211 Eonjuro, Gangnam-gu, 03722, Seoul, Korea. Tel.: +82 2 2019 3492/ +82 2 2019 3698; Fax: +82 2 3463 7585, E-mail: kswoong@yuhs.ac. (Seong-Woong Kang); E-mail: reedlove37@yuhs.ac. (Won Ah Choi).

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INTRODUCTION

Duchenne muscular dystrophy (DMD), which affects up to 1 in 3,500 live male births, is an X-linked recessive, progressive muscular degenerative disorder [1]. DMD patients show progressive limb muscle weakness, which leads to a loss of ambulatory function in their mid-teens [2]. These patients also have musculoskeletal deformities such as neuromuscular scoliosis and multiple joint contractures [3, 4]. Just a few decades ago, most DMD patients died in their twenties, and respiratory failure and cardiac failure were the leading causes of death [5–7]. However, with improvements in mechanical ventilatory support and the medical management of cardiomyopathy, DMD patients are now living longer than ever before [8, 9] and several new issues have surfaced that had not been considered previously [10]. One of these issues is the development of nutritional conditions [11]. In a previous study, DMD patients suffering from gastrointestinal symptoms, such as dysphagia, choking, heartburn, vomiting, and constipation, were observed against an age-matched healthy cohort [12]. In patients with muscular disease, nutritional support and maintenance of proper nutritional status are critical, given the progressive muscle atrophy and the increased demand of respiration [13]. However, most clinicians tend to be less concerned about eating and digestive symptoms than other complications such as respiratory and cardiac failure, scoliosis, and osteoporosis even with DMD guideline [11] and practical recommendations [14]. Additionally, there is lack of research on the correlation between age and physical functioning with ingestive and gastrointestinal symptoms in advanced DMD patients. In this study, we investigated the relationship between various eating and digestive symptoms and respiratory function parameters in patients with advanced DMD.

METHODS

Subjects

This retrospective observational study included subjects diagnosed with DMD by either genetic analysis or muscle biopsy who were admitted to the Department of Rehabilitation of a single tertiary university hospital between June 2009 and August 2014. All subjects were nonambulatory and required non-invasive mechanical ventilatory support.

The following subjects were excluded from the study: 1) Subjects for whom eating and digestive symptoms or respiratory function could not be properly evaluated due to a cognitive deficit. 2) Subjects who could not tolerate discontinuation of ventilatory support for at least 20 minutes, which is the time required for the respiratory function assessment. This also resulted in an exclusion of patients who needed NIV support even during mealtimes. 3) Tracheostomized patients (these were excluded because the tracheostomy tube interferes with the accurate measurement of respiratory parameters). 4) Subjects who could not maintain a sitting position while eating or who were fed via a gastrostomy or nasogastric tube.

Evaluation of eating and digestive symptoms

Detailed interviews by experienced dietitians were used to assess the presence or absence of subjective eating and digestive symptoms, including loss of appetite, nausea, vomiting, diarrhea, constipation, swallowing difficulty, mastication difficulty, early satiety, and aspiration. Subjects were instructed to report symptoms that occurred during the 3-month period prior to the assessment.

Evaluation of respiratory function

The respiratory function of the patients was evaluated in various respects. The major respiratory pathophysiological cause of neuromuscular restrictive lung diseases such as DMD, is respiratory muscle weakness. Because the strength of the respiratory muscles cannot be evaluated directly, it is assessed indirectly via measurement of maximal inspiratory and expiratory pressure. Forced vital capacity (FVC) is the primary evaluation parameter, as it decreased in restrictive lung diseases and is a major determinant for deciding whether air-stacking exercises should be started and predicting hypocapnia. Respiratory muscle weakness also decreases coughing ability, and decreased cough flow makes it difficult to manage airway secretion and is a major risk factor for respiratory infection [15]. In accordance with our previous research, the various respiratory function parameters that were measured by expert clinicians, included FVC, maximum insufflation capacity (MIC), peak cough flow (PCF), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) [16, 17]. PCF was measured in two different ways: unassisted PCF (UPCF) was assessed by having subjects maximally inhale and then voluntarily cough as strongly as possible; assisted PCF

Table 1
Demographic characteristics of the study group

	Average ± standard deviation ($N = 180$)
Age	22.3 ± 5.0 years
Height	158.4 ± 8.7 cm
Weight	40.6 ± 15.1 kg
Body mass index	16.3 ± 5.6
Left ventricular ejection fraction (%)†	46.0 ± 15.4
Forced vital capacity (%)††	619.8 ± 478.4 mL (15.2 ± 12.7%)
Duration of noninvasive ventilation	11.0 ± 4.2 hours/day
Maximal insufflation capacity	1328 ± 532 mL
Unassisted peak cough flow	107 ± 84 L/min
Assisted peak cough flow	258 ± 91 L/min
Maximal inspiratory pressure (%†)	19.4 ± 13.0 cmH_2O (19.0 ± 14.6%)
Maximal expiratory pressure (%†)	17.8 ± 10.0 cmH_2O (12.0 ± 7.3%)

†Available at 176 patients. ††Ratio for predictive normal value.

(APCF) was assessed with an assistant administering abdominal thrusts while subjects were in the MIC state. Percentages of the normal predicted values were calculated for FVC, MIP, and MEP [18–20]. All respiratory function parameters were measured at least 3 times, and the maximum values were recorded and used in the analysis.

Cardiac evaluation

Additionally, we recorded left ventricular ejection fraction (LVEF), which was evaluated via transthoracic echocardiography at the time of assessment of eating-related symptoms and respiratory function.

Statistical analysis

Statistical analysis was performed using SPSS ver. 23 (IBM Corp., Armonk, NY, USA). Univariate logistic regression was used to analyze the relationship between eating/digestive symptoms and various parameters, including age, pulmonary function, and LVEF. $P < .05$ was considered statistically significant. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB No. 3-2015-0335).

RESULTS

A total of 180 subjects were included in this study. The mean subject age was 22.3 ± 5.0 years (range, 14–40 years). The duration of NIV was 11.0 ± 4.2 hours per day, and in six patients, NIV was discontinued only during mealtime in the day. The LVEF value was 46.0 ± 15.4%; 4 patients were excluded from this analysis, because the examinations on these patients were performed in other hospitals. In total, 87 patients received medications for heart failure at the time of evaluation. Among the other 93 patients who did not take the medication, 12 patients were newly prescribed the medicine and one patient was not able to take the medicine owing to low blood pressure. The demographic characteristics of the subjects are shown in Table 1. Some symptoms, such as nausea, vomiting, diarrhea, and aspiration, were excluded from the analysis because the incidences of these symptoms were quite low. For example, only 1 subject had nausea, 2 subjects had aspiration, and none of the subjects had vomiting or diarrhea.

Loss of appetite and early satiety showed no correlation with respiratory function. Constipation was correlated with MEP; swallowing difficulty was correlated with MIC, APCF, MIP, and MEP; and mastication difficulty was correlated with FVC, PCF, APCF, MIP, and MEP. Notably, both age and LVEF did not correlate with any gastrointestinal symptoms (Table 2). P values and odds ratios with 95% confidential intervals are shown in Table 2. Multiple regression analysis was not conducted because all pulmonary parameters were highly autocorrelated with one another. For example, MIP and MEP are associated with FVC, cough flow, and MIC [21–23]. Moreover, UPCF and APCF are measured when patients are in the FVC and MIC state, respectively.

DISCUSSION

Eating and digestive symptoms can significantly affect the quality of life and nutritional status of patients with advanced DMD. Underlying mechanisms of GI dysfunction in DMD patients are very intricate and multifactorial. Proposed mechanisms

Table 2
Univariate logistic regression between eating & digestive symptoms and age & each cardiac and pulmonary function parameter

		Age	LVEF	FVC	MIC	UPCF	APCF	MIP	MEP
Loss of appetite ($N = 16$)	OR	0.983	0.998	0.993	1.000	0.999	1.001	0.976	0.983
	(95%CI)	(0.884–1.094)	(0.968–1.029)	(0.951–1.036)	(0.999–1.001)	(0.992–1.005)	(0.995–1.007)	(0.994–1.020)	(0.912–1.060)
	p-value	0.759	0.908	0.735	0.712	0.652	0.739	0.287	0.665
Constipation ($N = 33$)	OR	0.973	1.009	0.992	1.000	0.995	0.998	0.997	0.922
	(95%CI)	(0.898–1.054)	(0.986–1.034)	(0.961–1.024)	(0.999–1.001)	(0.991–1.000)	(0.993–1.002)	(0.971–1.024)	(0.860–0.988)
	p-value	0.497	0.431	0.601	0.702	0.050	0.275	0.836	0.021†
Swallowing difficulty ($N = 10$)	OR	1.070	1.020	0.921	0.997	0.997	0.992	0.879	0.815
	(95%CI)	(0.952–1.120)	(0.977–1.064)	(0.850–0.999)	(1.001–1.005)	(0.989–1.004)	(0.985–0.999)	(0.788–0.980)	(0.688–0.965)
	p-value	0.256	0.365	0.047†	0.002††	0.395	0.028	0.020†	0.018†
Mastication difficulty ($N = 41$)	OR	1.027	0.989	0.955	0.999	0.988	0.994	0.960	0.936
	(95%CI)	(0.960–1.100)	(0.966–1.012)	(0.922–0.990)	(0.999–1.000)	(0.983–0.993)	(0.990–0.998)	(0.929–0.993)	(0.882–0.994)
	p-value	0.442	0.349	0.013†	0.054	<0.001††	0.007††	0.018†	0.031†
Early satiety ($N = 32$)	OR	0.959	1.000	0.975	1.000	0.996	0.999	1.015	0.962
	(95%CI)	(0.883–1.042)	(0.978–1.023)	(0.941–1.010)	(0.999–1.000)	(0.991–1.000)	(0.995–1.003)	(0.991–1.040)	(0.907–1.022)
	p-value	0.317	0.988	0.152	0.466	0.069	0.647	0.213	0.216

LVEF; left ventricular ejection fraction, FVC; forced vital capacity, MIC: maximum insufflation capacity, UPCF; unassisted peak cough flow, APCF; assisted peak cough flow, MIP; maximal inspiratory pressure, MEP; maximal expiratory pressure. †*p*-Value<0.05, ††*p*-value<0.01.

include lack of activities; skeletal and smooth muscle dysfunction; abnormalities of the autonomic nervous system; deformities of body structures, such as scoliosis, malocclusion, and macroglossia; NIV; long-term administration of systemic steroids and calcium; and inadequate diet [11, 24–26]. Pulmonary function is also determined by various factors such as respiratory muscle strength, chest wall mobility and compliance, scoliosis, and bulbar function [15, 27]. In addition, pulmonary function-related parameters are measurable and scalable in advanced DMD patients.

Multiple studies have evaluated constipation in DMD patients and several mechanisms have been suggested [26, 28, 29]. The function of stool passing is related to various factors such as psycho-behavioral factors, posture on defecation, consistency of stool, dietary contents, age, and sex [30]. The squatting position increases intra-abdominal pressure during defecation [31] and permits smooth bowel elimination through straightening of the recto-anal angle [32]. Because many DMD patients are unable to assume the squatting position, they may experience defecation difficulty. Further, Boland et al. [33] observed that DMD patients in the second decade of life develop constipation due to smooth muscle degeneration in the gastrointestinal tract. It has also been observed that constipation is closely related to inadequate fiber and water intake. One of the most significant observations of the present study is the relationship between MEP and constipation. Intra-abdominal pressure, which is required for defecation, largely depends on abdominal muscle strength, and abdominal muscle strength is also crucial for generating MEP.

Swallowing difficulty is another symptom that affects patients with advanced DMD [34, 35]. It is a principal cause for decreased oral intake in DMD patients, even among those who do not experience aspiration, and closely associated with bulbar muscle function. MIC and APCF, which are measured when patients are in the MIC state, are also quite affected by bulbar function [22]. It is also possible that inspiratory and expiratory muscle strength, indicated by MIP and MEP respectively, are associated with bulbar muscle function. Therefore, swallowing function should be appraised in DMD patients with reduced respiratory function in order to ensure adequate nutritional support and prevent disease progression.

In this study, we also found that mastication difficulty, which can be caused by weakening of the muscles of mastication, [36] was related to respiratory muscle strength. Symptoms of advanced DMD include facial muscle weakness, which causes chewing difficulty [37]. Therefore, these patients may require alternations in food texture even if they have no difficulty swallowing.

Early satiety is another symptom that affects patients with advanced DMD and is typically due to gastroparesis. In 2005, Borrelli et al. [38] observed a decline in gastric emptying and a higher prevalence of gastric dysrhythmia in a group of ambulatory DMD patients below the age of 7 compared with a control group of healthy children. The researchers suggested that delayed gastric emptying was caused by DMD itself since dystrophin is present in smooth muscle cells, enteric neurons, and interstitial cells of Cajal, all of which influence gastrointestinal motility. However, that study showed no correlation between early satiety and age or between satiety and any of the respiratory function parameters included in the present study.

In this study, we also observed that aspiration was not prevalent among advanced DMD patients. That said, even without aspiration, symptoms such as constipation, swallowing difficulty, mastication difficulty, and early satiety could lead to a decline in oral intake in these patients. Therefore, advanced DMD patients should undergo a detailed nutritional evaluation and receive appropriate nutritional support.

Aging of DMD patients is a major determinant of functional decline, and according to previous studies, objective findings such as videofluoroscopic swallowing study (VFSS) findings, gastric emptying time, colon transit time, and electrogastrography findings were related to patients' age. However, these studies failed to reveal abnormalities related to actual associated symptoms [29, 39] or did not mention any symptoms [38]. Although Pane et al. [40] reported that difficulties in chewing and increase in subsequent meal time were increasingly present with age, and Egli et al. [37] also reported aggravated mastication and orofacial function with age, these studies included young patients aged under 10 years. The result that age was not a determinant of GI-related symptoms in the present study may be caused by inclusion of patients who were relatively older than those included in other previous studies. The patients enrolled in this study were functionally homogenous (non-ambulatory and supported by NIV).

Some GI symptoms may represent heart failure, because heart failure can lead to non-specific symptoms and signs, including loss of appetite, weight gain or loss [41]. However, in this study, no eating-related symptoms were related to LVEF, also.

To the best of our knowledge, this is the first study that assessed the correlation between eating and digestive symptoms and pulmonary function in DMD patients. We think this correlation is mainly caused by the skeletal muscle strength, which is one of the major determinants of various pulmonary function and eating and digestive symptoms evaluated in the present study. However, these parameters and symptoms are determined by very sophisticated mechanisms and the exact relationship is unclear. Thus, further studies, especially those involving adult DMD patients, are required, because the natural history of the disease, based on the increased survival rate, is unclear.

This study has several limitations. First, all subjects in this study were receiving long-term, NIV support, which may have caused aerophagia [42]. Aerophagia in turn could have led to various gastrointestinal symptoms [43]. Second, we assessed the presence or absence of gastrointestinal symptoms rather than the severity of symptoms. Third, we did not evaluate any objective parameters reflecting the eating and digestive disorders, such as colon transit time, nor did we conduct VFSS. Finally, records regarding patient medications or interventions such as enemas were unavailable for this analysis.

In conclusion, eating and digestive symptoms are more closely correlated with respiratory function than with age in advanced DMD patients with reduced respiratory function. Therefore, these patients should be carefully evaluated for the presence of gastrointestinal symptoms.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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