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Quality of life in long term ventilated adult patients with Duchenne muscular dystrophy

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Abstract

The aim of this study was to evaluate quality of life (QoL) and its possible determinants in patients affected by Duchenne muscular dystrophy (DMD) in late stages of their disease, when non-invasive ventilation (NIV) is already established. Forty-eight DMD patients who were treated by NIV were enrolled. QoL was assessed by the Individualized Neuromuscular Quality of Life (INQoL) questionnaire. By this questionnaire, different aspects of QoL were assessed on a scale from 0 (best) to 100 (worst). In addition, motor and respiratory function tests were performed. Dysautonomia symptoms, sleep quality, sleepiness, anxiety, and depression were evaluated by validated questionnaires. The global INQoL score was 42.8 ± 19, reflecting a moderately altered QoL. The physical health domain was heavily impaired while the psychosocial domain was only mildly affected. Independence had the highest scores (81.1 ± 21.2), proving to be the most affected item. On multivariate analysis, maximal inspiratory pressure and Pittsburgh Sleep Quality Index, but not daily duration of NIV therapy, predicted global INQoL score. Respiratory impairment and sleep quality were independent predictors of poor QoL in DMD patients under NIV. Sleep quality in DMD is often disregarded, while it should be carefully addressed to ensure a better QoL.
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1. Introduction

Duchenne muscular dystrophy (DMD) is one of the most common neuromuscular diseases. It determines a progressive impairment of muscular function that can lead to inability to move, respiratory failure and death [1–3]. Although improvement in disease management and therapeutic advancements have significantly increased life expectancy [4,5], the progression of the disease and of the functional impairment is not arrested by the present treatment modalities. In older DMD patients, symptoms due to skeletal muscles impairment are prominent, and the severe deterioration of respiratory muscles function causes frequent lung infections and reduces ability to cough [6]. Sleep quality, either assessed subjectively by the patients or evaluated objectively on EEG recordings, can become poor, due to reduction of spontaneous motility and to nuisance associated with application of non-invasive ventilation (NIV), and may associate with excessive sleepiness [7,8]. Dysautonomic manifestations can arise, due to increase in sympathetic tone and decrease in parasympathetic modulation [9]. Not unexpectedly, the psychological status often worsens, and fatigue, sleepiness, anxiety and depression may become highly prevalent [10].

Most of the studies aimed to evaluate quality of life (QoL) in DMD have been performed in young patients [11]. Studies that addressed QoL in adult DMD mostly used the SF36 questionnaire [12], which is not specific for neuromuscular diseases, can show a floor effect for the physical functioning [13] and may be even less sensitive in advanced stages of the disease.

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The Individualized Neuromuscular Quality of Life questionnaire (INQoL) is a muscle disease-specific questionnaire that was developed in a heterogeneous group of patients affected by congenital and inflammatory myopathies and muscular dystrophies, including subjects who had progressed to respiratory failure [14,15]. The INQoL has been recently validated in the Italian language [16]. It is recommended in the assessment of QoL in muscle disease because of its ability to capture physical limitation that are specifically relevant to the muscle condition.

The aim of the present study was to evaluate QoL in adult long-term ventilated patients with DMD using the INQoL questionnaire and to determine its relationship with motor and respiratory dysfunction, sleep quality, psychological status and symptoms of autonomic impairment.

2. Patients and methods

2.1. Patients

We recruited consecutive adult patients (≥18 years old) with diagnosis of DMD who came to the center for prevention and treatment of respiratory complications of neuromuscular diseases of Cervello hospital between 2015 and 2017 for a follow-up evaluation. Inclusion criteria were the following: (1) a genetic test or a muscle biopsy demonstrating absence of the dystrophin protein; (2) NIV treatment started at least 3 months earlier. Setting of NIV was established based on nocturnal full polysomnographic data and blood gases determinations in the early morning.

Body weight and length were measured, and body mass index (BMI) was calculated. Patients' evaluation included polysomnography, respiratory function assessment and administration of multiple questionnaires. Questionnaires were self-administered, with the help of a trained interviewer (R.D.), if needed. All items of the questionnaires were completed without missing data. Compliance to NIV was evaluated by software data download.

The study was approved by the local ethics committee (Palermo 2, verb n. 14, prot. amm.vo 325, AOR 05.10.2016) and all patients gave informed consent.

2.2. Protocol

2.2.1. QoL assessment

QoL was evaluated by the INQoL. It consists of 45 questions that pertain to three different domains. The first domain is physical health, and is subdivided in four sections exploring the impact of common symptoms of muscle dysfunction, i.e. weakness, locking, pain and fatigue; the second domain, areas of life, includes three sections that concern the impact of activities, independence, and body image; the third domain, psycho-social health, includes one section about relationships and one section about emotions. One additional section that regards effects and expectations of treatment was not used in this study since it is not taken into account to calculate the global INQoL score. Participants respond to each question using a seven-point Likert scale. The final score for each section is presented as percentage of the maximum detrimental impact, with a higher percentage indicating greater symptom impact or worse QoL. Global INQoL score is calculated according to Vincent et al. [14].

Although the INQoL was developed in patients with various muscular diseases, no one of them was affected by DMD [14,16]. Therefore, we tested its reliability in our group of DMD patients with the evaluation of its internal consistency and test-retest reproducibility within 3 weeks.

2.3. Functional respiratory and muscular assessment

Pulmonary function was evaluated by spirometry and arterial blood gases. Spirometry was performed in a sitting position with a flow meter attached to a flanged rubber mouthpiece with the nose occluded. Technical procedures, acceptability and reproducibility criteria, interpretative values, standardization and equipment were in accordance with American Thoracic Society/ European Respiratory Society recommendations and modified criteria [17–19]. Arterial blood gases were measured early in the morning in the supine position during NIV administration.

Respiratory muscle strength was assessed by maximal static inspiratory pressure (MIP), maximal expiratory pressure (MEP) and sniff nasal inspiratory pressure (SNIP). Prior to each test, participants were given detailed instructions and a demonstration of the procedures by the examiner. MIP was measured following maximal inspiration from residual volume. MEP was obtained through maximal expiration from total lung capacity. The highest value obtained from at least five attempts was considered, with three acceptable manoeuvres [20]. SNIP was evaluated according to standard methodology. The test was performed with one nostril occluded by a nasal plug, while the other one remained unobstructed [21].

Upper extremity function was assessed by the Brooke Upper Extremity scale [22]. The grades of the Brooke scale range from 1 (best) to 6 (worst).

2.4. Symptoms assessment

Subjective sleepiness was evaluated by the Epworth sleepiness scale (ESS). It consists of eight items, each of which is relevant to a common situation of daily life. Patients are instructed to rate their likelihood of dozing in each situation on a scale from 0 (no chance of dozing) to 3 (strong chance of dozing). A total score >10 is considered representative of excessive daytime sleepiness [23].

Anxiety and depression were evaluated by the 14-item Hospital Anxiety and Depression Scale (HADS), which includes one subscale for anxiety and one for depression. Total score in each subscale may range from 0 to 21. Scores <7 identify negative cases, 8 to 10 mild, 11 to 14 moderate, and 15 to 21 severe cases [24].

Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI) questionnaire that assesses sleep quality and quantity over a month-long period. It consists of 19 questions answered by the patient and of five questions that should be answered by bed-mates or roommates. The last questions are used only for clinical information, but not in the scoring. The 19 questions are categorized into seven components that are graded on a scale from 0 (worst) to 3 (best). Subjects with a global PSQI score >5 are considered poor sleepers [25].

Autonomic symptoms were evaluated by the Composite Autonomic Symptom Score 31 (Compass 31). It is an instrument for self-assessment which includes 6 domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor). The total score from the six subscales may range from 0 to 100, with higher values indicating worse impairment [26]. Normal values were extrapolated from healthy controls [27].

2.5. Statistical analysis

Data are presented as mean ± standard deviation, or median (interquartile range). The Kolmogorov-Smirnov test was used to test the data for normal distribution.

Internal consistency of the INQoL was determined by Cronbach's a-coefficient. A coefficient >0.70 was taken as acceptable and satisfactory. Test-retest reproducibility was assessed by intraclass correlation coefficient (ICC). An ICC >70 indicated sufficient test-retest reproducibility.

Unpaired *t*-test and U-Mann-Whitney test were used for comparisons between normally and non-normally distributed data, respectively. Correlations were analyzed using Pearson's correlation coefficient. To identify potential independent predictors of global INQoL, a stepwise regression model was used. In this regression, all variables that were correlated with the global INQoL with a p value <0.10 were entered.

$P < 0.05$ was considered significant. Statistical analysis was performed using a commercial software package (IBM SPSS version 22).

3. Results

Fifty-four patients accepted to participate to this study. Spirometry and measurement of maximal respiratory pressures were not feasible in four DMD patients due to ventilator dependency or insufficient cooperation. In addition, two patients were not able to complete the questionnaires. The final sample included 48 patients, aged 29.1 ± 7.1 years (range 19–44), with a BMI of 19.9 ± 5.9 kg/m^2, all of which were wheelchair dependent. All patients were taking B-blockers and most of them ACE-inhibitors. Eighty-three% of patients used NIV for more than 12 h/day (Table 1).

The Cronbach's a-coefficient of the INQoL showed good reliability (0.83 [95% confidence interval 0.75–0.89]). It was increased by removing the item "relationship" from the total scale, but removal would increase alpha only by 0.007. ICC indicated good reproducibility (0.97 [95% confidence interval 0.95–0.98]).

Table 1
Therapeutic regimen.

	% of subjects
Pharmacological therapy	
B-blockers	100
ACE inhibitors	89.6
Antidepressants	12.5
Anxiolytics	2.1
Use of mechanical devices	
NIV ≤ 12 h/day	16.7
NIV >12 h/day	83.3
Cough assist	100

NIV, non invasive-ventilation.

Table 2
INQoL scores.

Domain	Section	
Physical Health (symptoms)	Weakness	61.6 ± 30.6
	Locking	27.8 ± 20.5
	Pain	43.9 ± 27.2
	Fatigue	32.9 ± 31.9
Areas of life	Activities	65.1 ± 26.7
	Independence	81.1 ± 21.2
	Body image	41.2 ± 28.8
Psychosocial	Relationships	30.5 ± 29.1
	Emotions	31.9 ± 25.8
Global		42.8 ± 19.2

Data are expressed as mean ± SD. Values range between 0 and 100, with higher values indicating worse scores.

Table 3
Functional assessment.

Respiratory and motor function variables	mean ± SD
FVC (% predicted)	20.9 ± 15.5
MIP (% predicted)	28.7 ± 18.6
MEP (% predicted)	18.2 ± 11.5
SNIP (cm H_2O)	21.1 ± 10.1
PCF (L/min)	139.4 ± 71.5
pH	7.40 ± 0.0
PaO_2 (mmHg)	94.7 ± 20.8
$PaCO_2$ (mmHg)	42.4 ± 7.4
$HCO3^-$ (mmol/L)	26.4 ± 3.6
BE (mmol/L)	2.1 [0.2–3.7]
Brooke UES	5.4 ± 0.5

Data are expressed as mean ± SD or median [IQR]. FVC, forced vital capacity; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; SNIP, sniff nasal inspiratory pressure; PCF, peak cough flow; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure; $HCO3^-$, bicarbonate; BE, base excess; Brooke UES, Brooke Upper Extremity Functional Scale.

Scores obtained at the INQoL are shown in Table 2. Independence was the most affected section. Lower scores were obtained in the psychosocial health than in the other domains.

Polysomnographic data are shown in Supplemental Table A1. Supplemental Table A2 shows that there were no correlations between polysomnographic data and INQoL; however, sleep stages durations were correlated with PSQI.

Results of functional assessment are reported in Table 3. Most respiratory function scores showed severe alterations, but arterial blood gases were close to normal, demonstrating

Table 4
Symptoms and psychological status assessment.

Questionnaires	mean±SD	% subjects with abnormal scores
PSQI	6.1 ± 2.9	56.2
ESS	3.5 ± 2.2	0
HADS- Anxiety	5.0 ± 3.2	20.8
HADS - Depression	3.6 ± 2.5	10.4
Compass 31	12.1 ± 8.8	56.2

PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; Compass 31, Composite Autonomic Symptom Score.

that NIV treatment was effective. Scores of the Brooke scale demonstrated severe impairment, as expected.

Scores relevant to symptoms and psychological status are shown in Table 4. On average, the patients reported mean normal scores for sleepiness, anxiety and depression whereas they had abnormal scores for sleep quality. Mean Compass 31 score was only slightly elevated.

Table 5 shows univariate correlations of the variables under study with each section of the INQoL, as well as with the global INQoL score. Respiratory and muscular function ratings were correlated to sections of the physical domain. NIV use was correlated to areas of life sections. Sleep quality was correlated to sections belonging to all domains. Sleepiness, anxiety, depression and degree of autonomic dysfunction showed few, if any, correlations with INQoL sections. The global INQoL was correlated to variables relevant to respiratory and muscular function, to duration of NIV use and to PSQI. Correlations between all the other variables and the global INQoL were not significant, with p values >0.10.

Table 6 shows results of a multiple regression with the global INQoL score as dependent variable. We identified MIP and PSQI as independent predictors of INQoL.

Table 6
Multiple regression for predictors of global INQoL score.

Independent variables	B	SE	t	p-value
MIP (% predicted)	−0.37	0.13	−2.9	0.005
PSQI	0.35	0.84	2.8	0.007

Adjusted $R^2 = 0.29$; $F(2, 45) = 10.6$; $p = 0.0001$.
MIP, maximum inspiratory pressure; PSQI, Pittsburgh Sleep Quality Index.

4. Discussion

In this study, we evaluated QoL in patients with an advanced stage of DMD using for the first time the INQoL, a questionnaire created for patients with muscular disorders, and analyzed its relation with functional impairment and symptoms burden of the patients. In our sample, we demonstrated that this questionnaire has a good degree of internal consistency and a high test-retest reproducibility, which suggests that it may be a useful tool for patients with DMD. The global score of the INQoL was high, which was indicative of a poor QoL, mainly due to high scores in the domains of physical health and areas of life, whereas the psychosocial domain was much less affected. Loss of independence was the most important concern. Respiratory and muscular dysfunction, as well as subjective sleep quality, which were severely impaired, were significantly correlated with several aspects of QoL, whereas symptoms of sleepiness, psychological distress or autonomic dysfunction, which were not prominent, were at most marginally related to it.

4.1. Role of respiratory function

To our knowledge, only two studies evaluated the relationship between respiratory function and QoL in muscular dystrophies. In the first one, the authors did not find any relation between respiratory function and QoL

Table 5
Univariate correlations of age, functional and symptoms ratings with INQoL.

	Physical domain				Areas of life domain			Psychosocial domain		Global
	Weakness	Locking	Pain	Fatigue	Activity	Independence	Body image	Relation	Emotion	
Age (years)	**0.36**	**0.36**	**0.44**	**0.38**	0.28	**0.29**	0.02	0.23	0.24	**0.38**
FVC (% predicted)	**−0.41**	**−0.39**	−0.21	−0.20	**−0.37**	**−0.31**	**−0.38**	**−0.33**	−0.18	**−0.43**
MIP (% predicted)	**−0.35**	**−0.37**	**−0.38**	−0.27	**−0.31**	−0.18	−0.15	**−0.30**	−0.22	**−0.44**
MEP (% predicted)	**−0.33**	**−0.30**	−0.21	−0.20	−0.27	−0.26	−0.12	−0.16	−0.23	**−0.29**
SNIP (cmH_20)	−0.18	**−0.31**	−0.09	−0.17	−0.18	−0.20	−0.13	−0.07	−0.12	−0.23
PCF (L/min)	−0.10	−0.26	−0.12	−0.23	−0.17	−0.21	−0.01	−0.17	−0.19	−0.18
NIV (≤ / > 12 h)	0.28	0.21	0.17	0.22	**0.50**	**0.45**	0.17	0.18	0.15	**0.38**
Brooke UES	**0.29**	**0.38**	**0.29**	**0.32**	**0.32**	**0.34**	0.07	0.22	0.10	**0.35**
PSQI	**0.34**	0.22	**0.49**	**0.44**	**0.37**	0.26	**0.38**	0.22	**0.42**	**0.43**
ESS	0.08	0.18	0.15	0.05	0.21	0.04	0.21	0.24	0.01	0.11
HADS - Anxiety	0.08	0.07	0.09	0.02	0.23	0.18	**0.38**	0.10	**0.30**	0.22
HADS - Depression	0.09	0.19	0.22	0.09	0.05	0.01	**0.31**	0.22	0.09	0.23
Compass 31	0.14	0.09	0.14	0.16	0.28	0.15	0.09	0.01	0.08	0.19

FVC, forced vital capacity; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; SNIP, sniff nasal inspiratory pressure; PCF, peak cough flow; NIV, non-invasive ventilation; Brooke, Upper Extremity Functional Scale; PSQI, Pittsburgh sleep quality index; ESS, Epworth sleepiness scale; HADS, Hospital Anxiety and Depression Scale; Compass 31, Composite Autonomic Symptom Score 31.
Bold characters indicate significant correlations.

in their DMD patients [28]. However, those patients were much younger than ours, which may account for a milder respiratory impairment and a limited impact of respiratory function on QoL; besides, only a minority of patients used NIV nearly continuously over 24 h. In the second study, by contrast, Ahlstrom et al. found that QoL was significantly related to FVC in 76 individuals affected by muscular dystrophy (not specifically DMD) who were 16 to 64 years old [29]. In DMD, age is related to lung volume decline and ventilation inhomogeneity [30]. The latter, together with cough insufficiency, is significantly associated with upper airway microbial colonization, high risk of pulmonary infections and acute respiratory failure [31,32]. As showed by a recent study, DMD patients and their caregivers consider the preservation of pulmonary function, with maintenance of an effective cough and reduction of risk of airway infections, an important treatment goal [33]. Indeed, the relation between QoL and respiratory function observed in this study may reflect respiratory challenges faced by DMD patients with advanced age. In both previous studies, the respiratory function parameter that was used for statistical correlations with QoL was FVC. In addition to FVC, we used other parameters that are related to respiratory function in muscular diseases and, among them, MIP emerged as the only independent predictor of the global INQoL. The reason for the closer MIP, than FVC, relationship with QoL is not clear. MIP has been recognized as an important outcome measure in neuromuscular disease [34]. In DMD, before NIV introduction, MIP showed a slower decline with age in comparison to FVC [35], which may reflect a worse impairment of the diaphragm than of other respiratory muscles [36]. FVC, but not MIP, is highly dependent on chest wall compliance and expiratory muscles activity [36], which are severely impaired in DMD . In fact, in our patients MIP tended to be less impaired than FVC, and to have a wider range of values. Possibly, the occurrence of some values closer to normal and the wider range of values could be one explanation for the better MIP than FVC correlation with INQoL.

SNIP was less often correlated to INQoL sections than MIP, and was not correlated to its global score. In fact, it has been reported that SNIP is not reliable in DMD, due to failure of the nostrils to collapse at low inspiratory pressures [37,38].

The relationships between respiratory function parameters and several QoL aspects in DMD suggests that any means that improve respiratory function would also improve patients' well-being. As a tool improving pulmonary function and reducing proneness to airway infections, NIV would be expected to ameliorate QoL in DMD. Actually, that has been demonstrated in previous studies [39]. In our patients, duration of daily NIV application did not affect the global INQoL but was associated with a higher score in some of its sections, i.e. independence and body image. This result does not question conclusions of previous studies but highlights that some usually underestimated aspects of QoL may be negatively affected by it. It may be possible to attenuate the impact of NIV on these aspects. The patients of this study were ventilated with devices whose battery life was <24 h. In a study performed to evaluate patients' opinions and expectations about long-term NIV, the extension of battery life of mechanical ventilators emerged as an important issue to be improved in order to increase independence [40]. Possibly, using ventilators with longer battery life, the correlation between duration of ventilator use and areas of life sections of the INQoL would have not been found. Moreover, the use of mouthpiece ventilation, which may improve body image, could be implemented. It can represent a valuable treatment for some patients but is still underused, in part because of limitations in the available equipment [41].

4.2. Role of sleep quality

Sleep quality was the second significant independent predictor of the global INQoL. Previous studies demonstrated that sleep quality is poor in DMD [42,43]. Need to be turned during sleep [44], residual respiratory disorders during NIV [45], poor patient-ventilator coordination [8,46] may contribute to poor sleep quality. In this study, sleep quality turned out one of the most important possible determinants of QoL in relatively old DMD patients. Quality of sleep is often considered as a minor issue in the management of DMD patients. Instead, our findings suggest that more attention should be paid to improve sleep in these patients in order to ensure them a better QoL. Interestingly, despite poor sleep quality, nobody complained of sleepiness, which may be related to chronic sympathetic activation [47].

4.3. Quality of life: psychosocial aspects

In our patients, the psychosocial was the least affected among the INQoL domains. The low percentage of patients with significant anxiety or depression may account for the low scores in the psychosocial domain. A similarly uncommon occurrence of anxiety and depression in DMD was reported by Pangalila et al. who, however, found significant correlations between severity of these symptoms and QoL evaluated by the SF-36 and the WHOQ questionnaires [43]. Good support and care may have warranted a good psychological state in our patients and maintained the psychosocial domain of QoL unaffected, as already observed in other studies [48].

4.4. Role of age

Age was correlated to sections of the physical domain of the INQoL and to the global INQoL score at univariate, but not at multivariate analysis. The relationship of age in the global INQoL was likely mediated by worsening respiratory function, as commonly occurs in the age range we examined (19–44 years). In fact, in our sample age of the patients and was negatively correlated with both FVC and MIP (data not shown). After considering respiratory variables, no independent effect of age on global INQoL could be observed.

This correlation may not be valid in young patients at the time of NIV initiation. However, this aspect was not explored because it was beyond purposes of this article.

4.5. Strengths and limitations

This study has some strengths and limitations. One strength is that we took advantage of a questionnaire created specifically for neuromuscular diseases, and demonstrated that it has a good reliability and reproducibility in DMD. Additionally, the sample of patients we studied can be considered large, proportionally to the low prevalence of their disease. The data we collected could be generalized to neuromuscular patients with similar characteristics that receive the same level of healthcare. A limitation of the study is that we collected only cross-sectional data so that the correlations we found may not reflect a cause-effect relationship.

5. Conclusions

Some features commonly present in the advanced stages of DMD, when NIV treatment is established, could significantly impact on QoL. They include respiratory dysfunction and poor sleep quality. Our result underscore that a parameter better reflecting global respiratory muscle function, like MIP, may be a more appropriate object of attention than FVC in the management of older patients with DMD, at least when improvement of QoL is the main target. Exploring factors affecting sleep quality of DMD patients may help to develop adequate measures to improve QoL by means of an improvement in sleep quality.

CRediT authorship contribution statement

Grazia Crescimanno: Conceptualization, Investigation, Methodology, Writing - original draft. **Francesca Greco:** Data curation. **Rosaria D'Alia:** Data curation. **Luigi Messina:** Formal analysis. **Oreste Marrone:** Supervision, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.06.599.

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