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Respiratory function and therapeutic expectations in DMD: families experience and perspective

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Conflict of interest
Study participants did not receive any form of compensation.
All the authors are involved in several studies in Duchenne muscular dystrophy (Sarepta, Santhera, PTC, Pfizer, Italfarmaco, Roche). EM has participated to advisory boards from the same companies.

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Objective. The aim of this study was to use a structured questionnaire in a large cohort of Duchenne Muscular Dystrophy (DMD) patients to assess caregivers and patients views on respiratory function and to establish if their responses were related to the patients' age or level of functional impairment.

Methods. Questionnaires were administered to caregivers in 205 DMD patients of age between 3 and 36 years (115 ambulant, 90 non-ambulant), and to 64 DMD patients (3 ambulant, 61 non-ambulant) older than 18 years, subdivided into groups according to age, FVC, ambulatory and ventilatory status.

Results. Some differences were found in relation to FVC % values ($p = 0.014$), ambulatory ($p = 0.043$) and ventilatory status ($p = 0.014$). Nearly half of the caregivers expected deterioration over the next years, with the perspective of deterioration more often reported by caregivers of non-ambulant ($p = 0.018$) and ventilated patients ($p = 0.004$). Caregivers appeared to be aware of the relevance of respiratory function on quality of life (84%) showing willingness to enter possible clinical trials if these were aiming to stabilize the progression of respiratory function with a very high number of positive responses across the spectrum of age, FVC, ambulatory and ventilatory status. The boys older than 18 years showed similar results.

Conclusions. Our study showed that the concern for respiratory function increases with age and with the reduction of FVC or the need for ventilation, but the need for intervention was acknowledged across the whole spectrum of age and functional status.

Key words: Duchenne muscular dystrophy, respiratory, quality of life, patient reported outcome measures

Introduction

Over the last few years, there has been increasing attention to the natural history of respiratory function in Duchenne Muscular dystrophy

(DMD). It has become increasingly obvious that after the age of 10 years percent predicted Forced Vital Capacity (% FVC) show progressively reduced values [1-3]. Steroid naïve DMD patients have an earlier onset of deterioration, approximately 2 years before steroid treated patients, but in both groups, once established, the rate of progression is similar [1-3].

The changes are relatively regular and, with increasing age, the decrease in % FVC reaches values that are generally associated with nocturnal hypoventilation and subsequent need for noninvasive ventilation (NIV), initially restricted to nighttime and, later on in life, increasingly used also during the day [4]. This data has been particularly useful at the time of designing or interpreting the results of clinical trials targeting respiratory function as primary or secondary measures [5-8].

While several studies have explored patient and caregivers' perspective about quality of life, care burden or motor aspects [9], less has been investigated in relation to clinical relevance of respiratory function at different ages [10-12].

As recently suggested by the United States Food and Drug Administration (FDA) the use of patient reported scales should be strongly encouraged to include the patient and caregivers perspective to determine the relevance of observed functional changes [13].

Assessing the relevance of respiratory function in DMD at different ages, including patients in the first decade can however be more challenging than when assessing motor function. While clinical signs of motor deterioration are increasingly present in the first decade, especially after the age of 7 years, overt signs of respiratory impairment often become obvious only in the second part of the second decade 14. As a constant decrease in % FVC and more generally a progressive respiratory impairment already start by the age of 10 years [1,3,14], it would be of interest to understand if and how DMD patients and their families are already concerned about the early changes in % FVC and, more generally, how their level of concern varies at different ages and in relation to different functional respiratory levels.

The aim of this study has been to investigate caregivers/patients' views on respiratory function using a structured questionnaire investigating different aspects of respiratory function, including rate of infections or use of antibiotics. More specifically we wished to assess their relevance as meaningful indicators of the progression of the disease and whether the level of responses changes according to age or functional based on their FVC % values and forced expiratory volume (FEV) scores. We also wished to assess caregivers/patients' expectations regarding clinical trials targeting primarily or secondarily respiratory function.

Materials and methods

This is a multicentric study conducted in Italy in three centers (Nemo Center, Policlinico Gemelli, Catholic University, Rome; Nemo Center, University of Messina; Nemo Center, Milan).

The study was approved by the Ethical Committees of all the participating centers. Parents/caregivers of participants (minor/children) and patients above age of 18 were asked to sign a dedicated consent form that also includes consent for sharing academic data and for publication.

A face to face or telephone interview based on a structured questionnaire was administered to caregivers of DMD patients, irrespective of the patients' age. Patients older than 18 years used a self-reported version of the questionnaire. Telephone interviews were conducted only if patients had been seen within the previous 3 months and the results of their respiratory assessments were available. A trained clinician conducted the in-person interviews and telephone interviews using the same semi-structured data collection sheet.

A number of questions were asked to investigate specific respiratory aspects and caregivers/patients' view on possible changes over the next 5 years and the impact of respiratory function on quality of life. In the second part caregivers/patients were asked about their expectations regarding the possibility to enter clinical trials focusing on respiratory function by investigating what would be the minimal change in respiratory function (slowing deterioration, stability, improvement) that would justify the participation into a clinical trial. The interviews lasted 10-15 min on average.

Table I reports details on the questions asked in both the caregivers and self-reported questionnaire.

FVC

From the age of 6 years all DMD patients are routinely asked to perform, depending on their compliance, FVC. FVC was assessed by qualified and certified evaluators according to a standard protocol, which reflects, established international guidelines for lung function testing (American Thoracic Society, European Respiratory Society). The patients were appropriately instructed on the use of the spirometer before the FVC assessments were initiated. In cases where the patient could not perform a mouth seal reliably with the clinic-based Spirometer, a scuba mouthpiece or a facemask should be used. In agreement with natural history studies, reporting % predicted FVC, we will also focus on this measure as this is more comparable with previous studies [1-3].

For all respiratory assessments, the patient was requested to repeat each test 3 to 5 times and the highest value was used.

Table I. Question asked in the caregivers and self-reported questionnaire.

Caregivers /self-reported questionnaire	
Question 1:	How many respiratory infections did your child have/*did you have*, over the past last year?
Question 2:	How many times did your child/*did you* need to take antibiotics for respiratory problems, over the last year?
Question 3:	How do you expect your child's/*your* breathing capacity will change over the next 5 years, according to the evolution of the disease and growth?
Question 4:	Could an improvement in your child's /*your* respiratory function have a positive effect on him quality of life?
Question 5:	Would you consider enrolling/*to be enrolled* in a clinical trial with drugs targeting respiratory function?
Question 6:	What reason would convince you to consider enrolling/*to be enrolled* in a clinical trial with drugs targeting respiratory function?
Question 7:	Would you consider enrolling/*to be enrolled* in a clinical trial with drugs that could reduce the number of respiratory infections?

Key to legend: Words in italic reports the self-reported version of the questionnaire.

Statistical analysis

Descriptive analysis, with absolute and percentage frequencies, was performed to establish the range of responses in relation to the different age, ventilation assistance, motor and respiratory functional levels. Responses between groups were compared for significant difference using the Chi-square test. A p-value of < 0.05 was considered significant.

Results

Caregivers' questionnaires

Questionnaires from the main caregiver for 205 DMD patients (115 ambulant and 90 non ambulant) of age between 3 and 36 years were collected (mean 13.48 ± 6.06 SD). With a few exceptions the main caregiver was the mother.

Caregivers' questionnaires were subdivided in 5 groups according to the age of the patients: group 1 included 18 patients aged 3.0-6.9 years. In this group FVC was recorded only in the 9 patients older than 6 years with a mean % FVC of 81.89%; group 2 included 50 patients aged 7.0-10.9 years. FVC could be reliably recorded in 48/50, with a mean % FVC of 84.75%; group 3 included 55 patients aged 11.0-13.9 years. FVC could be reliably recorded in 53/55, with a mean % FVC of 82.08%; group 4 included 42 patients aged 14.0-17.9. FVC could be reliably recorded in 40/42, with a mean % FVC of 57.73%; group 5 included 40 patients 18 years and above. FVC could be reliably recorded in 34/40, with a mean % FVC of 27.42%.

In the 184 patients who were able to perform FVC, 73/184 (39.7%) had FVC% ≥ 80%; 46 (25%) had FVC% between 60-80%; 16 (8.7%) had FVC% between 50-60%; 10 (5.4%) had FVC % between 40-50%; another 10 (5.4%) had FVC% between 30-40%; 7 (4.0%) had FVC% between 20-30% and in 22 (11.9%) had FVC% below 20%. In 8 patients (4.3%), who were too weak and more severely impaired, their FVC was too low to be reliably recorded and was arbitrarily labelled as below 10%. Another 13 patients who were reported as unable to perform FVC, 9 because too young and 4 due to the presence of behavioral or cognitive problems.

Thirty-two of the 205 patients (15.6%) used NIV.

Question 1: number of respiratory infections

Over 88% reported no infections (65.9%) or only one infection (22.4%). Two infections were reported in 8.8% and more than 2 in 3%. The number of infections did not change significantly in relation to age, but some differences were found in relation to FVC% values ($p = 0.014$). There was also a difference according to ambulatory and ventilatory status with more infections found in non-ambulant vs ambulant patients ($p = 0.043$) and in ventilated versus non ventilated patients ($p = 0.014$).

Question 2: number of antibiotics

Over 90 % reported no antibiotics (73.7%) or only one (20%). Two antibiotics were reported in 3.9% and more than 2 in 2.5%. The number of antibiotics did not change significantly in relation to age, ambulatory status or FVC % values, but there was a difference according to ventilatory status with more antibiotics reported in ventilated versus non ventilated patients ($p = 0.001$).

Question 3: possible respiratory changes over the next 5 years

Nearly 48% anticipated a stable course with no major changes, 47.8% a deterioration and 4.4% an improvement. The expectations did not change in relation to age or FVC% but some differences were found in relation to ambulatory and ventilatory status, with the perspective of a deterioration more often reported in non-ambulant vs ambulant patients ($p = 0.018$) and in ventilated *versus* non ventilated patients ($p = 0.004$).

Question 4: effect of respiratory function on quality of life

Nearly 84% felt that an improvement in respiratory function would result in an improvement in quality of life while 2.9% replied no and 13.2 % reported that they did not have a clear opinion about it. The distribution of responses did not change significantly in relation to age, FVC %, ambulatory and ventilatory status.

Table II and Figure 1 show details of the distribution of the responses for questions 1-4.

Question 5: enrolling in a clinical trial with drugs targeting respiratory function

Nearly 71% of the caregivers would consider enrolling in a clinical trial targeting respiratory function, 2% replied they wouldn't and 27.3% replied that they did not have a clear opinion about it as this would depend on a number of variables such as possible side effects, trial burden, etc.

The distribution of responses changed in relation to age ($p = 0.012$), FVC % values ($p = 0.037$) and ventilatory status ($p = 0.044$). There was no difference in relation to ambulatory status.

Question 6: reasons to consider enrolling in a trial targeting respiratory function

Nearly 87% of the caregivers replied that they would consider participation if the treatment would aim to at least slow down deterioration; an additional 3.4% replied that would consider it if the treatment would aim to stop deterioration, and an additional 3.5% if there was the possibility of an improvement. Approximately 5% did not have a clear opinion and 1 % would not consider entering in a trial. The distribution of responses did not change significantly in relation to age, FVC %, ambulatory and ventilatory status.

Question 7: enrolling in a clinical trial that could reduce the number of respiratory infections

Over 72% replied that they would consider participation, 8.3% replied they wouldn't and 19.5% replied that this would depend on a number of variables such as possible side effects, burden of the trial etc. The distribution of responses did not change significantly in relation to age, FVC %, ambulatory and ventilatory status.

Table III and Figure 2 show details of the distribution of the responses for questions 5-7.

Table II. Caregivers' responses distribution (N, %) by age and FVC% subgroups for questions 1 to 4.

		Age (years)						FVC%							
		3-7 (n:18)	7-10 (n:50)	10-14 (n:55)	14-18 (n:42)	> 18 (n:40)	All (n:205)	< 20% (n:22)	20-30% (n:7)	30-40% (n:10)	40-50% (n:10)	50-60% (n:16)	60-80% (n:46)	> 80% (n:73)	All (n:184)
QUESTION 1	0	11 (61.1%)	36 (72.0%)	43 (78.2%)	23 (54.8%)	22 (55.0%)	135 (65.9%)	10 (45.5%)	3 (42.5%)	7 (70.0%)	7 (70.0%)	11 (68.8%)	34 (73.9%)	54 (74.0%)	126 (68.5%)
	1	7 (38,9%)	10 (20.0%)	7 (12.7%)	11 (26.6%)	11 (27.5%)	46 (22.4%)	9 (40.9%)	1 (14.3%)	2 (20.0%)	1 (10.0%)	2 (12.5%)	8 (17.4%)	15 (20.5%)	38 (20.7%)
	2	0 (0,0%)	3 (6.0%)	3 (5.5%)	6 (14.3%)	6 (15.0%)	18 (8.8%)	2 (9.1%)	2 (28.6%)	1 (10.0%)	2 (20.0%)	3 (18.8%)	3 (6.5%)	3 (4.1%)	16 (8.7%)
	3	0 (0.0%)	1 (2.0%)	1 (1.8%)	1 (2.4%)	1 (2.5%)	4 (2.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	1 (1.4%)	3 (1.6%)
	> 3	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (2.4%)	0 (0.0%)	2 (1.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
QUESTION 2	0	11 (61.1%)	40 (80.0%)	45 (81.8%)	29 (69.0%)	26 (65.0%)	151 (73.7%)	12 (54.5%)	3 (42.9%)	9 (90.0%)	9 (90.0%)	14 (87.5%)	37 (80.4%)	57 (78.1%)	141 (76.6%)
	1	7 (38.9%)	8 (16.0%)	8 (14.5%)	8 (19.0%)	10 (25.0%)	41 (20.0%)	7 (31.8%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	2 (12.5%)	7 (15.2%)	16 (21.9%)	34 (18.5%)
	2	0 (0.0%)	1 (2.0%)	1 (1.8%)	4 (9.5%)	2 (5.0%)	8 (3.9%)	2 (9.1%)	1 (14.3%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	2 (4.3%)	0 (0.0%)	7 (3.8%)
	3	0 (0.0%)	1 (2.0%)	1 (1.8%)	0 (0.0%)	2 (5.0%)	4 (2.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
	>3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (5.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
QUESTION 3	Improving	1 (5.6%)	3 (6.0%)	2 (3.6%)	1 (2.4%)	2 (5.0%)	9 (4.4%)	1 (4.5%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)	3 (4.1%)	7 (3.8%)
	No change	12 (66.7%)	32 (64.0%)	24 (43.6%)	16 (38.1%)	14 (35.0%)	98 (47.8%)	7 (31.8%)	2 (28.6%)	6 (60.0%)	6 (60.6%)	4 (25.0%)	24 (52.2%)	38 (52.1%)	87 (47.3%)
	Worsening	5 (27.8%)	15 (30.0%)	29 (52.7%)	25 (59.5%)	24 (60.0%)	98 (47.8%)	14 (63.6%)	5 (71.4%)	3 (30.0%)	4 (40.0%)	10 (62.5%)	22 (47.8%)	32 (43.8%)	90 (48.9%)
QUESTION 4	No	0 (0.0%)	1 (2.0%)	3 (5.5%)	1 (2.4%)	1 (2.5%)	6 (2.9%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	4 (5.5%)	6 (3.3%)
	Don't know	4 (22.2%)	12 (24.0%)	8 (14.5%)	1 (2.4%)	2 (5.0%)	27 (13.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	2 (12.5%)	5 (10.9%)	16 (21.9%)	24 (13.0%)
	Yes	14 (77.8%)	37 (74.0%)	44 (80.0%)	40 (95.2%)	37 (92.5%)	172 (83.9%)	21 (95.5%)	7 (100%)	10 (100%)	9 (90.0%)	13 (81.3%)	41 (89.1%)	53 (72.6%)	154 (83.7%)

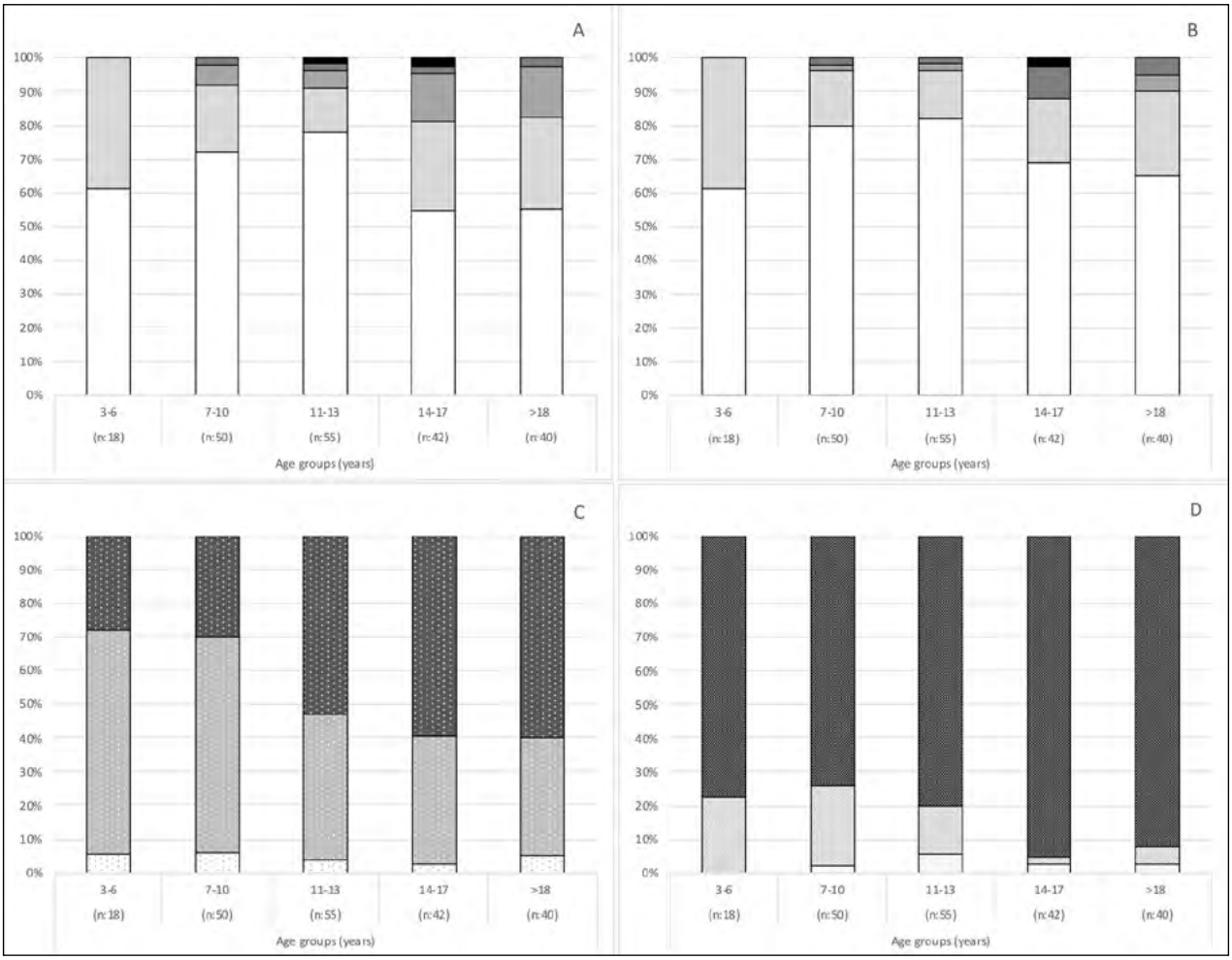

Figure 1. Caregivers' responses distribution by age for questions 1 to 4. (A) Question 1, (B) Question 2, (C) Question 3, (D) Question 4. Key to panels A&B: White= 0; Light grey= 1; Dark grey= 2; Light Black= 3; Black=> 3. Key to panel C: Dotted white= Improvement; Dotted light grey= No change; Dotted black= Worsening. Key to panel D: White texture= No; Light grey texture = I don't know; Black texture= Yes

Self-reported questionnaires in patients older than 18 years

Questionnaires from 64 DMD patients older than 18 years (3 ambulant and 61 non ambulant) were available. These included 45 patients for whom caregivers' questionnaires were also available. Seven patients could not perform FVC because too weak (n:4) or had a tracheostomy (n:3), the remaining 57 were able to perform FVC. Only 2/57 (3.5%) had FVC% ≥ 80; 4 (7%) had FVC% between 60-80, 2 (3.5%) between 50 and 60, 7 (12.3%) between 40 and 50; 8 (14%) between 30 and 40; 4 (7%) between 20-30 and the remaining 30 (52.6%) below 20. Forty-four of the 64 patients (68.7%) used NIV.

Question 1: number of respiratory infections

Over 88 % reported either no infections (59.4%) or only one infection (26.6%). Two infections were reported in 10.9% and more than 2 infections in 3.1%. The number of infections did not change significantly according to ventilatory status, but some differences were found in relation to FVC % values ($p = 0.021$).

Question 2: number of antibiotics

Over 80% reported no (71.9%) or only one (17.2%) antibiotics. Some differences were found in relation to ventilatory status and according to FVC % values ($p = 0.041$).

Question 3: possible respiratory changes over the next 5 years

Nearly 38% anticipated a stable course with no major changes, 53.1% a deterioration and 9.4% an improve-

Table III. Caregivers' responses distribution (N, %) by age and FVC% subgroups for questions 5 to 7.

		Age groups (years)						FVC%							
		3-7 (n:18)	7-10 (n:50)	10-14 (n:55)	14-18 (n:42)	> 18 (n:40)	All (n:205)	< 20% (n:22)	20-30% (n:7)	30-40% (n:10)	40-50% (n:10)	50-60% (n:16)	60-80% (n:46)	> 80% (n:73)	All (n:184)
QUESTION 5	No	2 (11.1%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (2.5%)	4 (2.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	1 (1.4%)	3 (1.6%)
	Don't know	5 (27.8%)	21 (42.0%)	16 (29.1%)	8 (19.0%)	6 (15.0%)	56 (27.3%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	8 (50.0%)	11 (23.9%)	29 (39.7%)	51 (27.7%)
	yes	11 (61.1%)	29 (58.0%)	38 (69.1%)	34 (81.0%)	33 (82.5%)	145 (70.7%)	19 (86.4%)	7 (100%)	10 (100%)	9 (90-0%)	8 (50.0%)	34 (73.9%)	43 (58.9%)	130 (70.7%)
QUESTION 6A	No	1 (5.6%)	0 (0.0%)	1 (1.8%)	1 (2.4%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	2 (1.1%)
	Don't know	2 (11.1%)	6 (12.0%)	8 (14.5%)	3 (7.1%)	5 (12.5%)	24 (11.7%)	2 (9.1%)	1 (14.3%)	0 (0.0%)	1 (10.0%)	6 (37.5%)	5 (10.9%)	7 (9.6%)	22 (12.0%)
	yes	15 (83.3%)	44 (88.0%)	46 (83.6%)	38 (90.5%)	35 (87.5%)	178 (86.8%)	20 (90.9%)	6 (85.7%)	10 (100%)	9 (90.0%)	10 (62.5%)	41 (89.1%)	64 (87.7%)	160 (87.0%)
QUESTION 6B	No	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 0.5%)
	Don't know	2 (11.1%)	3 (6.0%)	5 (9.1%)	4 (9.5%)	5 (12.5%)	19 (9.3%)	2 (9.1%)	1 (14.3%)	1 (10.0%)	1 (10.0%)	4 (25.0%)	4 (8.7%)	4 (5.5%)	17 (9.2%)
	yes	15 (83.3%)	47 (94.0%)	50 (90.9%)	38 (90.5%)	35 (87.5%)	185 (90.2%)	20 (90.9%)	6 (85.7%)	9 (90.0%)	9 (90.0%)	12 (75.0%)	42 (91.3%)	68 (93.2%)	166 (90.2%)
QUESTION 6C	No	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.5%)
	Don't know	1 (5.6%)	3 (6.0%)	2 (3.6%)	2 (4.8%)	4 (10.0%)	12 (5.9%)	1 (4.5%)	1 (14.3%)	0 (0.0%)	1 810.0%)	2 (12.5%)	1 (2.2%)	4 (5.5%)	10 (5.4%)
	yes	16 (88.9%)	47 (94.0%)	53 (96.4%)	40 (95.2%)	36 (90.0%)	192 (93.7%)	21 (95.5%)	6 (85.7%)	10 (100%)	9 (90.0%)	14 (87.5%)	45 (97.8%)	68 (93.2%)	173 (94.0%)
QUESTION 7	No	2 (11.1%)	4 (8.0%)	6 (10.9%)	3 (7.1%)	2 (5.0%)	17 (8.3%)	4 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (4.3%)	9 (12.3%)	16 (8.7%)
	Don't know	4 (22.2%)	14 (28.0%)	12 (21.8%)	5 (11.9%)	5 (12.5%)	40 (19.5%)	2 (9.1%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	4 (25.0%)	9 (19.6%)	21 (28.8%)	37 (20.1%)
	yes	12 (66.7%)	32 (64.0%)	37 (67.3%)	34 (81.0%)	33 (82.5%)	148 (72.2%)	16 (72.7%)	6 (85.7%)	10 (100%)	10 (100%)	11 (68.8%)	35 (76.1%)	43 (58.9%)	131 (71.2%)

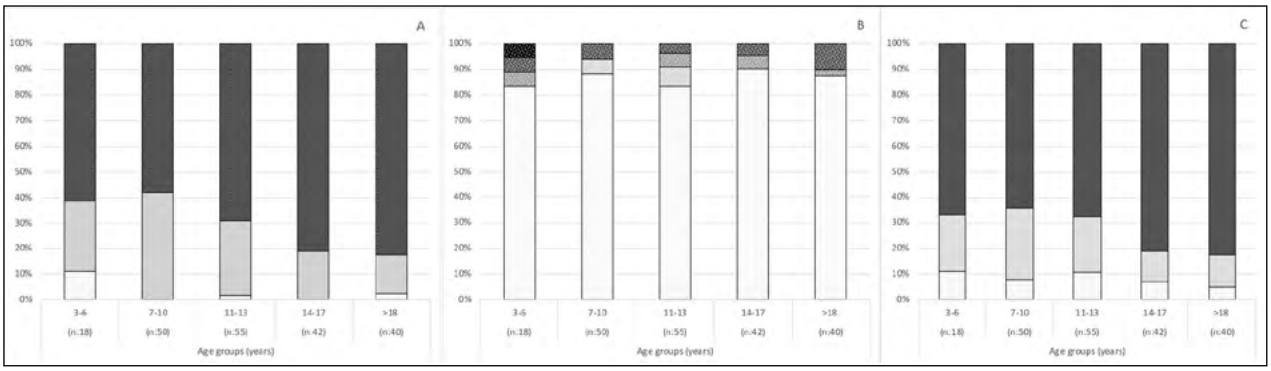

Figure 2. Caregivers' responses distribution by age for questions 5 to 7. (A) Question 5, (B) Question 6, (C) Question 7. Key to panels A&C: White texture= No; Light grey texture= I don't know; Black texture= Yes. Key to panel B: Dotted white= At least slow down; Dotted light grey= At least slow down; Dotted dark grey= At least improve, Dotted light black= I don't know, Dotted black= No.

ment. The distribution of responses did not show significant changes in relation to FVC and ventilatory status.

Question 4: effect of respiratory function on quality of life

Nearly 80% replied yes, 6.3% felt that this would not produce an improvement in Quality of life and 14.1% replied that they did not have a clear opinion about it. Some differences were only found in relation to ventilatory status ($p = 0.028$).

Question 5: enrolling in a clinical trial with drugs targeting respiratory function

Over 70% of patients replied that they would consid-

er participation, 7.8% replied they wouldn't and 20.3% replied that they had not a clear idea. The distribution of responses did not show significant changes in relation to FVC and ventilatory status.

Question 6: reasons to consider enrolling in a trial targeting respiratory function

Nearly 70 % of patients replied that they would consider participation if the treatment targeted to at least slow down deterioration; an additional 17.2% replied that would consider it if the treatment would aim to stop deterioration, and an additional 7.8% if there was the possibility of an improvement. Approximately 5% did not have a clear opinion and 1.6 % would not consider entering in a trial. The distribution of responses did not show significant changes according to FVC or ambulatory status, but some differences were found in relation to ventilatory status ($p = 0.023$).

Question 7: enrolling in a clinical trial that could reduce the number of respiratory infections

Nearly 60 % of patients replied that they would consider participation, 7.8% replied they wouldn't and 32.8% replied that they did not have a clear opinion about it as this would depend on a number of variables such as possible side effects, burden of the trial etc. The distribution of responses did not show significant changes in relation to FVC or ventilatory status.

Discussion

The advent of clinical trials specifically targeting respiratory function or including FVC and other respiratory indexes as secondary measures [5, 6, 8,15] has highlighted the need for better understanding of the progression of respiratory impairment in DMD children. While in the last few years several papers have reported longitudinal natural history data on FVC and FEV, showing concordance on the age when FVC and FEV decline and on their rate of progression [1-3], less has been reported about patient reported outcome measures or, more generally, on the patients' and caregivers' perspective on respiratory function, with the exception of some studies mainly focusing on ventilated patients [10]. One of the aims of our questionnaire was to investigate the awareness of clinical signs in caregivers of DMD patients with a wide range of age and respiratory impairment from very young patients to older adults with severe respiratory impairment. The questionnaire included a first part evaluating the frequency of infections and antibiotics and general questions on the expectations on respiratory function over time and its effect on their quality of life and a second part assessing the willingness of the caregivers to have their children enrolled in studies targeting respiratory function. We were interested in recording what was the general perception from the families and to establish if their responses were related to the patients' age or level of functional impairment, expressed by different parameters FVC, ventilatory and ambulatory status.

When asked to report the number of infections, we found that the overall number of infections was relatively low, with no infections or only one infection in 65.9%. There was an increased number of infections in patients with the lowest FVC and a difference between ambulant and non-ambulant and between ventilated and non-ventilated. The number of patients with frequent infections was however relatively low even in the non-ambulant ventilated patients with very low FVC, probably related to the implementation of care recommendations suggesting the use of vaccinations, In-Exufflator and other recommendations [4]. The number of antibiotics was similar and only slightly lower than the reported number of infections, this suggesting a low number of reported minor infections not requiring antibiotics.

It is of interest that even though in 41.4% of the cases the age of the patients was over 10 years, that is the age when respiratory tests start showing a mild but progressive decline, nearly half of the responders did not foresee a deterioration over the next 5 years. The perspective of deterioration, found in less than half of the patients, was more often reported by caregivers of non-ambulant and ventilated patients or in those with very reduced % FVC. These results suggest that even if caregivers are informed of a possible respiratory impairment in their children as part of the progression of the disease, the progressive deterioration starting at the end of the first decade is in some cases underestimated. This is probably due to the fact that in the first phase respiratory decline is often not associated with any overt clinical respiratory sign, unlike motor difficulties that are obvious since the time of diagnosis. In ambulant patients, loss of ambulation is seen as the major life changing event and is probably the biggest cause of concern, overshadowing other aspects that do not require immediate intervention. Caregivers however appear to be aware of the relevance of respiratory function as demonstrated by their responses on the effect on quality of life and by their willingness to enter possible clinical trials targeting respiratory function. Less that 3% felt that an improvement in respiratory function would not results in an improvement in their quality of life, with a very high number of positive responses (84%) across the spectrum of age, FVC, ambulatory and ventilatory status. In our study we did not use structured assessments to measure quality of life but it is of interest that these results are consistent with previous findings also reporting Quality of life in ventilated patients [10,11].

Similarly, there were a very high percentage (70%) of caregivers considering having their children enrolled in clinical trials targeting respiratory function. The relatively high percentage of caregivers who responded that they did not have a clear idea, was mainly related to the need to have more details about the possible trials, including the severity of possible side effects. It is of interest that despite the results of question 3, with a significant proportion of caregivers reporting a stabilization over the next 5 years, nearly 87% of the caregivers felt that they would consider participating in a clinical trial if, in the absence of significant side effects, the intervention would even only slow down the rate of deterioration. There was a much smaller percentage of patients with no clear idea, mainly in the younger groups with more preserved FVC, but this percentage decreased, with an increase of positive responses to over 90 and nearly 95% if the prospect was stabilization or improvement, therefore including nearly the totality of caregivers, irrespective of age and functional status.

When we asked the DMD patients older than 18 years to fill the same questions of the questionnaire using a self-reported procedure, we observed that the responses were often similar but not identical to the responses recorded by caregivers of patients in the same age group. A correlation between caregivers and patients however was not entirely possible as some adult patients came to clinic not accompanied by their caregivers and in some cases the questionnaire was given only to the caregivers if the patient had moderate or severe cognitive or behavioural problems. The main difference between patients and caregivers was on the question exploring their willingness to participate in a clinical trial. The percentage of patients who would consider a clinical trial if the expectations was slowing down deterioration was overall high but lower in patients than in in caregivers. The percentage increased when the expected result was stabilization.

One of the limitations of this study is that we did not systematically collect economic status or schooling in the caregivers and in the patients. Although we did exclude patients with severe behavioral or cognitive problems, at the time of collecting the questionnaires we felt that patients were often emotionally or cognitively less mature than their age and this may have contributed to their reduced awareness of the severity of their respiratory impairment or on their expectations.

Conclusions

Even with these limitations, our study provides the views of caregivers and older patients on respiratory function in relation to different variables such as age or functional status and is an ideal complement to the recent studies reporting respiratory functional data. Not surprisingly the concern on respiratory function increases with age and with the reduction of % FVC or the need for ventilation but the need for intervention was acknowledged across the whole spectrum of age and functional status. Further studies also using other respiratory measure and more structured assessments of quality of life may help to better define the correlation between these aspects.

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