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Adherence to inhalation therapy and quality of life in children with cystic fibrosis: a cross-sectional study

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ABSTRACT

Introduction: Inhalation therapy is a crucial part of the cystic fibrosis (CF) treatment regimen. Drugs that assist in mucociliary clearance and inhaled antibiotics are used by most patients.

Methods: This is a cross-sectional study where patients with CF and their caregivers answered questionnaires regarding their adherence to inhalation therapy and QoL. Demographic, spirometric, and bacteriological data, as well as S-K scores and hospitalization frequencies were also collected.

Results: We included 66 patients in this study; participants had a mean age of 12.3 years and Z-scores of -1.4 for forced expiratory volume in 1 second and 48.6 for body mass index. Patients were divided into 2 groups according to their self-reported adherence to inhalation therapy: high adherence (n = 46) and moderate/low adherence (n = 20). When comparing both groups, there was no statistically significant differences in age, sex, family income, and S-K score ($p > 0.05$). The high-adherence group had had shorter hospitalization periods in the previous year ($p = 0.016$) and presented better scores in the following domains of the QoL questionnaire: emotion ($p = 0.006$), eating ($p = 0.041$), treatment burden ($p = 0.001$), health perception ($p = 0.001$), and social ($p = 0.046$).

Conclusions: A low self-reported adherence to inhalation therapy recommendations was associated with longer hospitalizations in the previous year and with a decrease in QoL in pediatric patients with CF.

Keywords: *Cystic fibrosis; adherence; nebulization; quality of life*

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INTRODUCTION

Cystic fibrosis (CF) is a complex autosomal recessive genetic disease; it is potentially lethal and more common in the White population. A change in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is a chloride channel, causes an electrolyte imbalance and results in structural lung damage, chronic pulmonary infection by drug-resistant microorganisms, and malnutrition, with debilitating symptoms and frequent hospitalizations that require intensive treatment[1].

The mean average age of patients with CF has increased significantly in recent decades owing to early diagnosis and appropriate therapy provided by specialized multidisciplinary centers[2]. The therapeutic regimen is extensive and includes antibiotic therapy, airway hygiene, physical exercise, mucolytic agents, bronchodilator and anti-inflammatory medications, nutritional support, and oxygen supplementation[3,4]. The development of CFTR-modulating drugs has shifted the focus of CF treatment strategies: Instead of only treating the consequences of organic damage, these medications will allow the correction and restoration of protein function. However, this kind of treatment is not

yet suitable for all individuals with CF and does not replace the symptomatic treatment[1,5].

Inhalation therapy is crucial in the treatment of CF. Drugs that assist in mucociliary clearance and inhaled antibiotics are used in most patients[2]. Mucolytics present benefits in lung function, quality of life (QoL), and respiratory exacerbations, while inhaled antibiotics can delay the deterioration of lung function in patients that are chronically infected with *P. aeruginosa*[3]. However, inhalation therapy requires great involvement of the patient and his or her family, with a daily routine that demands time and dedication. The barriers to treatment adherence are multifactorial, involving aspects related to disease severity, education, as well as emotional and behavioral characteristics of parents and children[6]. In the pediatric population, the difficulty in establishing treatment routines faced by the parents or guardians and the use of trial and error methods represent obstacles to treatment adherence; anticipatory guidance from the multidisciplinary team can facilitate disease management[7,8].

The present study aims to assess the self-reported adherence to inhalation therapy in children with CF, in addition to the associations between adherence and lung function, clinical score, and QoL.

METHODS

This cross-sectional study was conducted with patients with CF that were followed by the Pediatric Pulmonology Team at Hospital de Clínicas de Porto Alegre (HCPA). The study sample consisted of children and adolescents diagnosed with CF[3] and aged between 6 and 17 years.

Sample selection was performed consecutively, considering all patients in follow-up visits who met the inclusion criteria. Individuals in stable clinical conditions for at least 30 days without hospitalization or changes in the maintenance therapy regimen were included in the study. Individuals with neurological disorders who had difficulties in answering the questionnaires were excluded. Our research was approved by the Ethics Committee of HCPA under protocol number 14-0157, and informed consent was obtained from the parents or guardians of the patients.

After accepting to participate in our study, the children answered an initial questionnaire along with their guardians. This questionnaire was developed by the authors and inquired about their adherence to inhalation therapy with objective questions regarding the previous 2 weeks, such as: How many days per week and how many times per day inhalation therapy was usually performed? Subsequently, the Cystic Fibrosis Questionnaire (CFQ) was applied; this questionnaire was developed for individuals with CF and validated for Brazilian Portuguese[9]. Both questionnaires were applied by a researcher not linked to the hospital's CF team. The team's physical therapist answered the same questions and recorded the inhalation therapy recommendations for each participant, according to the prescription issued by the care team.

A general data collection form was also applied, including the following information: sex, age, age at diagnosis, body mass index (BMI), sputum bacteriology, lung function data, days of hospitalization, number of hospitalizations in the previous year, and Shwachman-Kulczycki (S-K) score[10].

Spirometry was performed at the Pulmonary Physiology Unit of the Pulmonology Service at HCPA, with the patient in a sitting position and using a model v4.31a spirometer (Jaeger, Würzburg, Germany) in accordance with Brazilian guidelines for technical acceptability[11]. Results of forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and FEV_1/FVC were recorded. The parameters were also expressed in Z-scores[12].

Statistical Analyses

Data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Patients were classified into 2 groups according to the self-reported adherence to inhalation therapy in the last 2 weeks: high adherence (performed the treatment recommended by the physiotherapist and rarely missed any sessions), moderate/low adherence (often or always missed the sessions recommended by the physiotherapist).

Quantitative data were presented as means and standard deviations (SDs). Categorical data were expressed in frequencies and proportions of the studied population. Continuous variables were compared using a Student's t-test for independent samples. Ordinal or continuous variables that did not present normal distributions were compared using the Mann-Whitney-Wilcoxon U test. Qualitative data were analyzed using the chi-squared test, and when necessary, a Yates' correction or Fisher's exact test were used. The agreement between the recommendations made by the care team and the reports of patients regarding inhalation therapy was evaluated using the kappa agreement coefficient.

All statistical tests used were two-tailed and considered a significance level of $p < 0.05$. The sample size was calculated considering the proportion between the high-adherence group and the moderate/low-adherence group. For an expected proportion of moderate/low adherence of 0.40 and using a total range of 0.25 with a 95% confidence level, the appropriate sample size would be 59 patients.

RESULTS

During the study period, the HCPA Pediatric Pulmonology Team followed 72 individuals aged 6 to 17 years. Two patients did not meet the inclusion criteria for pulmonary exacerbation, requiring hospitalization, and 4 patients did not attend consultations during the study period. Therefore, 66 individuals with a mean age of 12.3 (SD, 3.2) years were included in this study, of which 55% were heterozygous for the F508del mutation, 26% were homozygous for the F508del mutation, and 19% had no identified mutations.

According to their self-reported adherence, 46 individuals were classified with high adherence (69%) and 20 individuals with moderate/low adherence (31%). Table 1 describes the general characteristics of individuals with CF according to the self-reported adherence to inhalation therapy. There was no difference between groups regarding pulmonary function, BMI, microbiological cultures, S-K score, and family income ($p > 0.05$). However, individuals with greater adherence to the inhalation therapy had fewer days of hospitalization in the previous year ($p < 0.05$).

Table 2 shows characteristics related to QoL according to the CFQ. Individuals with greater adherence to inhalation therapy had higher QoL scores in the emotion, eating, treatment burden, social, and health perception domains ($p < 0.05$).

Table 1: General characteristics of pediatric patients with cystic fibrosis according to self-reported adherence to inhalation therapy.

Variable	***High adherence n = 46***	***Moderate/low adherence n = 20***	***P value***
Age (years), mean ± SD	11.8 ± 2.8	13.15 ± 3.8	0.138
Gender (male / female)	22/24	9/11	--
Diagnostic age (years), median (II)	0.25 (1)	0.34 (2)	0.919
Family income, n (%)			0.691
< 3 salaries	26 (56.5%)	9 (45%)	
3 – 5 salaries	9 (19.5%)	4 (20%)	
> 5 salaries	11 (24%)	7 (35%)	
BMI (Z-score), mean ± SD	50.7 ± 24.0	43.3 ± 26.8	0.292
Total S-K (points), mean ± SD	77.9 ± 13.9	74.7 ± 13.2	0.390
FVC (Z-score), mean ± SD	-0.8 ± 1.7	-1.2 ± 1.7	0.321
FEV_1 (Z-score), mean ± SD	-1.2 ± 1.8	-1.8 ± 1.7	0.184
SpO_2 %	97.9 ± 1.7	97.8 ± 1.7	0.813
Length of hospital stay (days), median (II)	0 (17)	17 (20)	**0.016**
Hospitalizations in the last year, median (II)	0 (1)	1 (1)	0.486
Bacteriology, n (%)			
MSSA	26 (56.5)	14 (70)	0.336
MRSA	7 (15.2)	0 (0)	0.069
P. aeruginosa	23 (50)	13 (65)	0.197
B. cepacia	5 (10.8)	8 (40)	0.345

SD = standard deviation, II = interquartile range, BMI = body mass index, SK = Shwachman-Kulczycki score, FVC = forced vital capacity, FEV1 = forced expiratory volume in the first second, SpO_2 = peripheral oxygen saturation, MRSA = *Methicillin-resistant Staphylococcus aureus*, MSSA = *Methicillin susceptible Staphylococcus aureus.*

Table 2: Quality of life score in pediatric patients with cystic fibrosis according to adherence to inhalation therapy.

Variable	***High adherence n= 46***	***Moderate/low adherence n=20***	***P value***
QoL score (points), mean ± SD			
Physical	81.43 ± 18.7	74.6 ± 19.2	0.238
Emotion	80.8 ± 13.8	68 ± 16.3	**0.006**
Nutrition	86.6 ± 20.1	72.5 ± 26.5	**0.041**
Treatment burden	78.6 ± 18.7	54 ± 25.4	**0.001**
Social	77.2 ± 17.3	65.9 ± 20.1	**0.046**
Body image	85.4 ± 20.2	79.2 ± 27.1	0.364
Digestion	83.1 ± 21	83.7 ± 27.4	0.942
Respiratory	73.7 ± 18.7	64 ± 21.7	0.108
Social role	86.3 ± 18.7	77 ± 18.2	0.296
Weight	81.8 ± 31.1	62.5 ± 37.5	0.237
Vitality	80.3 ± 19.1	66.6 ± 8.9	0.079
Health perception	88.8 ± 15.7	63.8 ± 11.5	**0.001**

SD = standard deviation, QoL = quality of life.

Table 3 shows the coefficient of agreement between the care team's recommendations and the patients' reports of inhalation therapy.

Table 3: Agreement coefficient between care team recommendations and treatment performed by individuals with cystic fibrosis for inhalation therapy variables.

Variable	*Kappa*	*Agreement*	*P value*
Saline solution 0.9% (yes / no)	0.481	Moderada	< 0.001
Hypertonic saline 7% (yes / no)	0.676	Forte	< 0.001
Dornase alfa (yes / no)	0.484	Moderada	< 0.001
Inhalations (times a day)	0.317	Razoável	< 0.001
Inhaled Tobramycin (yes / no)	0.721	Forte	< 0.001
Inhaled colistin (yes / no)	0.818	Quase perfeita	< 0.001
Antibiotics (times a day)	0.607	Forte	< 0.001
Beta 2 short-acting agonist (yes / no)	0.687	Forte	< 0.001

DISCUSSION

Sixty-six individuals followed by the HCPA Pediatric Pulmonology Team participated in this study; our objective was to assess the self-reported adherence to inhalation therapy in a pediatric CF population. Out of these patients, 69% reported a high adherence to inhalation therapy, while approximately 31% acknowledged not regularly following treatment recommendations. Individuals who followed the inhalation therapy recommendations obtained better QoL scores and spent fewer days in the hospital in the previous year when compared to those with a moderate/low adherence.

In this study, 31% of the individuals reported not regularly following treatment recommendations. This result may be even higher when considering that our questionnaire assessed the patient's self-report, thus possibly overestimating treatment adherence[13-15]. In subjective assessments such as questionnaires, interviews, or diaries used with patients, parents, or healthcare professionals, data are easily collected but carry a potential information bias, resulting in a low reliability of results and an overestimation of adherence. Objective assessments for this case could include serum levels of medications, capsule counting, or medication dispensing records[13,14].

The correct use of inhaled medications is associated with better disease control, reducing pulmonary exacerbations and improving lung function[16,17]. In the present study, individuals with moderate/low adherence to inhalation therapy had more days of hospitalization in the previous year; this outcome indicated more severe exacerbations in this group. Low adherence to treatment in individuals with CF is associated with longer hospital stays, higher costs of respiratory exacerbations, increased numbers of hospitalizations and pulmonary exacerbations requiring intravenous antibiotics, and lower baseline lung function[8,18,19]. In this study, the pulmonary function of individuals with CF remained within the normal range, with no difference between groups according to their adherence to inhalation therapy. Our results may present differences in more severely affected individuals, considering that these patients seem to follow treatment routines more rigorously[20,21].

In the present study, the high-adherence group presented significantly higher scores when compared to the moderate/low-adherence group in the following QoL domains: emotion ($p = 0.006$), eating ($p = 0.041$), treatment burden ($p < 0.001$), social ($p = 0.046$), and health perception ($p < 0.001$). Generally, QoL is not one of the main outcomes assessed by studies that assess treatment adherence[8,16,17]. However, the use of inhaled medications, when compared to a placebo group, has been shown to improve QoL[22].

In this study, the agreement between treatment recommendations by the care team and the treatment reported by the individual was substantial for inhaled tobramycin (kappa = 0.721, $p < 0.001$), almost perfect for inhaled colistin (kappa = 0.818, $p < 0.001$), and moderate for dornase alfa (kappa = 0.484, $p < 0.001$). On the other hand, the agreement was only fair for the number of nebulizer sessions per day (kappa = 0.317, $p < 0.001$). A perfect adherence cannot be realistically expected in view of the complexity of CF care, especially considering the time burden of the treatment regimen[23].

As limitations of this study, we highlight that there are currently no validated questionnaires for assessing inhalation therapy in this population. The subjective, easy-to-apply questionnaire used in this study could overestimate the adherence perceived by the health care team. Furthermore, temporal interventions were impossible due to the cross-sectional design of our study, which did not allow us to make inferences over time. Nevertheless, structured and detailed

questionnaires regarding the CF treatment regimen are inexpensive and can be quickly applied in outpatient consultations in the absence of complementary objective data on treatment adherence.

In conclusion, we observed a self-reported high adherence to inhalation therapy in 69% of the studied individuals, and a moderate/low adherence in 31% of the patients. Individuals with moderate/low adherence to inhalation therapy had longer hospital stays in the previous year and reduced QoL. Behavioral interventions that improve treatment adherence and identify factors related to nonadherence should be considered in future studies.

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Conflict of interest statement

The authors declare no conflicts of interest.

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