

Physical development and pulmonary function in children and adolescents treated at two cystic fibrosis treatment centres in Poland

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Abstract

Introduction: Delayed physical development, delayed puberty and malnutrition are common in children suffering from cystic fibrosis

Material and methods: Physical development and respiratory function were assessed in 33 children and adolescents with cystic fibrosis treated at two cystic fibrosis treatment centres in Poland.

Results: Mean body height and body weight were significantly lower in the study group than in the reference population. Eighteen percent of the patients had severe developmental problems, and had body heights that were more than two standard deviations below the mean for the reference population. Over 60% of the patients were malnourished, and a third of these were severely malnourished. Mean leg length was considerably lower in the study group than in the reference population. The children with cystic fibrosis had infantile body proportions. Chest depth was higher and chest width was lower in the study group than in the reference population. Predicted FVC, predicted FEV₁ and predicted FEF₂₅₋₇₅ were lower in the study group than in the reference population. There was a strong positive correlation between nutritional status and predicted FEV₁. On the other hand, there was no clear correlation between the type of CFTR gene mutation or infection caused by *Pseudomonas aeruginosa* and predicted FEV₁.

Conclusions: A full-scale study is underway to determine the effect of the type of CFTR gene mutation and infection caused by *P. aeruginosa* on pulmonary function in children with cystic fibrosis treated at specialized care facilities in Poland.

Key words: children, cystic fibrosis, growth, body proportions, spirometric measurements.

Introduction

Cystic fibrosis is diagnosed in about one in every 2,500 live births in Poland [1]. The disease is caused by a mutation in the cystic fibrosis trans-membrane conductance regulator (CFTR) gene, which is located on chromosome 7. More than one thousand different mutations of this gene have been found [2]. The most common mutation is Δ_{508} , which is present in almost 70% of the cases reported [3]. Patients who are homozygous for this mutation generally have a more severe form of the disease characterized by greater impairment of pulmonary function and a shorter life expectancy [4, 5].

Delayed physical development, delayed puberty and malnutrition are common in children suffering from cystic fibrosis, and are important

prognostic markers of the course of the disease and the life expectancy of the patient. In a study on patients with cystic fibrosis in the United States, the probability of death was at least three times higher in patients in the lowest fifth percentile with respect to body weight than in the tallest patients [6]. In another study, there was a strong positive correlation between weight deficit and the probability of death. Regardless of the state of the respiratory system, malnutrition is an essential prognostic marker of the course of the disease and the life expectancy of the patient [7].

Malnutrition in patients with cystic fibrosis has a complex aetiology that can be described as a vicious cycle. Children with cystic fibrosis require 30 to 50% more calories per day than their healthy peers [8, 9].

Respiratory dysfunction is the main factor that determines the quality and length of life in patients with cystic fibrosis [10-12]. More than 95% of deaths in these patients are caused by chronic purulent obstructive lung disease [13].

In functional studies of the respiratory system, the degree of airway obstruction can be estimated by measuring the predicted forced expiratory volume in one second (FEV₁). In patients with cystic fibrosis, predicted FEV₁ depends on several factors, including age, sex and body height. Previous studies also indicate that predicted FEV₁ may also be affected by nutritional status, the type of CFTR gene mutation, and the presence of respiratory tract infection caused by *Pseudomonas aeruginosa* [4, 14-16].

The aim of this pilot study was to assess physical development and respiratory function in children and adolescents with cystic fibrosis treated at two cystic fibrosis treatment centres in Poland, and to determine whether pulmonary function in these patients was affected by nutritional status, the type of CFTR gene mutation and infection caused by *P. aeruginosa*.

Material and methods

A pilot study was carried out on twenty boys and thirteen girls treated for cystic fibrosis during the spring of 2006 at the Institute of Mother and Child in Warsaw and the Pulmonary Medicine and Allergy Centre in Karpacz, Poland. The mean age of the subjects was 14.0 ± 6.7 years, with a minimum of 6.2 years, and a maximum of 18.5 years.

In all patients, the diagnosis was confirmed by positive sweat tests. The mean age of diagnosis was about 2.5 years, with a minimum of one month, and a maximum of twelve years.

The children in this study were treated in accordance with the guidelines published by the Polish Working Group for Cystic Fibrosis [17]. According to these guidelines, the quality of life and

the longevity of patients with cystic fibrosis are to be improved by centralized medical care. The treatment protocol should include the following elements:

- individually tailored high calorie diets and pancreatic enzyme supplements, which are especially important when absorption in the gastro-intestinal tract is reduced; in the present study, all of the patients were on special diets. 88% had exocrine pancreatic insufficiency and were receiving pancreatic enzyme supplementation;
- effective, timely and targeted antibiotic therapy, especially of respiratory infections; 18% of the patients were receiving antibiotic treatment to control pulmonary infection caused by *P. aeruginosa*; infection was diagnosed by sputum culture, and appropriate antibiotics were selected on the basis of sensitivity testing; among the antibiotics prescribed were Colomycin, tobramycin, azlocillin, ciprofloxacin, ceftazidime and colistin, either alone or in combination; antibiotics were administered orally, intravenously or by aerosol inhalation, depending on the nature of the drug;
- physical therapy to increase stamina, mobility, respiratory competence, and growth in muscle and bone growth; all of the patients were receiving appropriate physical therapy at the time of this study; and
- regular follow-up visits to monitor growth and respiratory parameters; the children in this study came for follow-up visits every three or 6 months.

Physical development and pulmonary function were evaluated by collecting anthropometric and spirometric data on admission and during follow-up visits. All of the subjects and their legal guardians consented to the study.

Anthropometric measurements were performed in accordance with the procedures described by Martin and Knusmann [18]. The following data were collected: body height, body weight, leg length, trunk length, chest depth and chest width. Height was measured with an anthropometer accurate to 1.0 mm. Weight was measured with a scale accurate to 0.1 kg. Chest measurements were made with bow calipers accurate to 1.0 mm.

The following ratios were also calculated: trunk length to body height, leg length to body height, and chest depth to chest width. The body mass index was also calculated.

Anthropometric measurements were recorded in terms of standard deviations away from the age-specific and sex-specific reference means for the general population of Poland as determined by a survey that is widely recognized as valid for research purposes [19]. Normality was analyzed using the Shapiro-Wilk test. Differences between

the mean values for the patients and the reference group and between boys and girls were tested using Student's *t*-test.

Nutritional status was assessed by calculating Cole's nutritional status index (CNSI) in accordance with the following formula [20]:

$$\text{CNSI} = \left[\frac{\text{body weight} \times (\text{standard body length})^2}{\text{standard body weight} \times (\text{body length})^2} \right] \times 100$$

Nutritional status was recorded on the basis of the score as follows:

- > 110: over-nutrition;
- 90-110: normal nutrition;
- 85-90: slight malnutrition;
- 75-85: moderate malnutrition; and
- <75: severe malnutrition.

None of the subjects were diagnosed with other conditions that could affect nutritional status, such as CF diabetes or gastro-intestinal reflux.

Spirometric measurements were performed during routine check-up visits at three to six month intervals. Data recorded included forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and forced expiratory flow (FEF₂₅₋₇₅). All spirometric parameters were measured using an MES JAEGGER 100 spirometer in accordance with the procedures recommended by the Polish Phthisio-pneumological Society [21]. All results were recorded as percentages of the predicted values, standardized for height and sex [22, 23].

Molecular DNA studies had been previously carried out on all patients in order to determine the type of CFTR gene mutation. The studies were carried out at the Medical Genetics Laboratory of the Institute for Mother and Child at the time the patients were admitted.

The effect of nutritional status on pulmonary function was determined using Pearson's linear correlation. The effect of standardized body weight, CFTR gene mutation type, and infection caused by *P. aeruginosa* on the percent of predicted FEV₁ was assessed using the multiple regression method. Results were considered statistically significant at *p* < 0.05. All calculations were carried out using the STATISTICA 7.0 software package.

Results

The results for the anthropometric measurements are presented in Table I. Mean body height was lower in the study group than in the reference population. Eighteen percent of the patients had severe developmental problems, and had body heights that were more than two standard deviations below the mean for the reference population.

Mean body weight and body mass index were also significantly lower in the study group than in

Table I. Anthropometric measurements expressed in terms of standard deviations away from the mean values for the general population of Poland

	Mean	Standard deviation	Value <i>p</i>
Body height	-0.87	1.35	< 0.01
Body weight	-1.02	1.00	< 0.001
Body mass index	-0.87	0.86	< 0.01
Leg length	-1.39	1.75	< 0.001
Ratio of leg length to body height	-1.64	1.88	< 0.001
Trunk length	0.83	1.77	< 0.05
Ratio of trunk length to body height	1.85	1.81	< 0.001
Chest depth	0.90	1.21	< 0.01
Chest width	-0.62	1.50	< 0.05
Ratio of chest depth to chest width	1.62	1.65	< 0.001

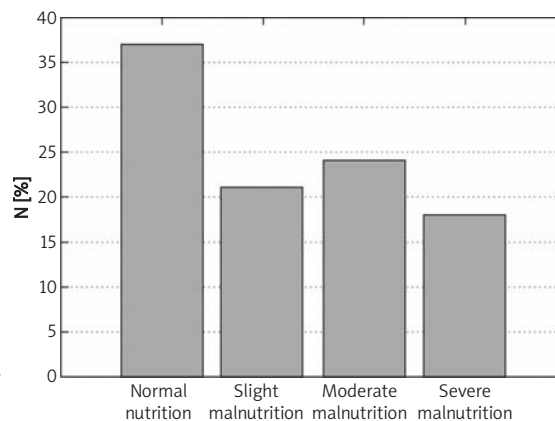


Figure 1.

the reference population. Over 60% of the patients were malnourished, and a third of these were severely malnourished. None of the patients were overweight (Figure 1).

Mean leg length was considerably lower in the study group than in the reference population, as was the ratio of leg length to body height. On the other hand, mean trunk length was higher than in the reference population, as was the ratio of trunk length to body height. Chest depth was higher and chest width was lower in the study group than in the reference population. The ratio of chest depth to chest width was therefore considerably higher than in the reference population.

There were no statistically significant differences between boys and girls in any of the anthropometric measures (data not shown).

Table II. Percent of predicted forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and forced expiratory flow (FEF₂₅₋₇₅), standardized for age and sex

	Mean	SD	Range
Percent of predicted FVC	77.5	26.8	22-137
Percent of predicted FEV ₁	72.3	28.8	25-132
Percent of predicted FEF ₂₅₋₇₅	55.7	39.7	70-150

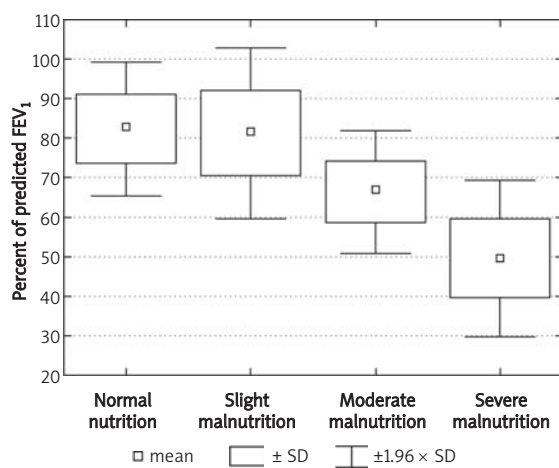


Figure 2.

Table III. Results of the multiple regression analysis

	Beta	B	t	Value p
Standardized body weight	0.54	15.32	3.70	0.0009
Type of CFTR mutation	-0.18	-6.90	1.32	0.1954
Infection caused by <i>P. aeruginosa</i>	0.21	11.75	1.48	0.1503

The results for the spirometric measurements are presented in Table II. Percent of predicted FVC, percent of predicted FEV₁, and percent of predicted FEF₂₅₋₇₅ were lower in the study group than in the reference population. Percent of predicted FEV₁ was highest in those patients who were normally nourished or only slightly malnourished, and lowest in those patients who were severely malnourished (Figure 2). There was a strong positive correlation between percent of predicted FEV₁ and Cole's nutritional status index ($r^2 = 0.49, p < 0.01$).

In terms of the type of mutation identified, the patients could be divided into three groups. Fifty five percent of the patients were homozygous for the mutation Δ_{508} . Twenty seven percent had Δ_{508} and another mutation such as R334W or R117H.

Eighteen percent had mutations other than Δ_{508} such as 3849+10kbC→T/3849+10kbC→T or 3849+10kbC→T/3659delC.

The results of the multiple regression are presented in Table III. There was a strong positive correlation between standardized body weight and percent of predicted FEV₁ (corrected $R^2 = 0.43$). On the other hand, there was no clear correlation between the type of CFTR gene mutation or infection caused by *P. aeruginosa* and percent of predicted FEV₁.

Discussion

The results of this study confirm the results of previous studies in Poland and elsewhere in which body height and body weight were lower in patients with cystic fibrosis than in the general population [11-13, 24-28].

Based on studies carried out in Denmark and Australia, physical development and nutritional status in patients with cystic fibrosis are significantly improved when the patients are treated in specialized cystic fibrosis treatment centres. In some cases, growth parameters can even approach the values reported for the general population [29, 30]. Proper assessment of physical development and nutritional status and effectively targeted treatment to correct developmental deficiencies are essential for mitigating the symptoms of cystic fibrosis and prolonging the lifespan of the patient.

The children in this study were treated in accordance with the guidelines published by the Polish Working Group for Cystic Fibrosis, according to which the treatment protocol should include individually tailored high calorie diets and pancreatic enzyme supplements [17]. Nevertheless, over sixty percent of the children in this study were malnourished, and a third of these were severely malnourished. This suggests that their parents failed to strictly adhere to the recommended guidelines.

Failure to adhere to the treatment plan is a major problem in children from families with a low socio-economic status. Children with cystic fibrosis from poorer families are more likely to be malnourished, and, as a result, are more likely to suffer from growth retardation, pulmonary insufficiency and reduced lifespan [31]. Malnutrition in these children may be due to the additional cost of providing a special diet, which may strain or exceed the financial resources of the family. On the other hand, it may also be due to the fact that the parents do not possess the knowledge and sophistication required to correctly and consistently implement the treatment plan, including the special diet.

In this pilot study, parental compliance to nutritional guidelines was not monitored, and the

socio-economic status of the patients' families was not taken into account. However, these factors will be included in the full-scale study that is currently underway.

The patients in this study had significantly different body proportions than the reference population. They were considerably shorter, mainly because they had much shorter legs than their healthy peers. In normal individuals, leg length increases rapidly during the adolescent growth spurt. In patients with cystic fibrosis, however, this process is delayed by about ten months, and the annual increase in height is about one centimetre less than in healthy adolescents [32, 33]. The children with cystic fibrosis had infantile body proportions. Their legs were short and their trunks were long in comparison to their height. Infantile body proportions have also been found in abused children and in children who have undergone premature puberty [34, 35]. In the subjects in this study, chest depth was relatively high compared to chest width. This had also been observed in a previous study on children with cystic fibrosis, in which abnormalities in chest structure persisted in spite of treatment [27].

In the patients in this study, predicted FEV₁ was significantly lower than in the general population. This agrees well with the results of previous studies [14, 15, 36].

There was also a strong correlation between nutritional status and FEV₁, which is also consistent with previous reports [13, 16, 24]. In one study on children with cystic fibrosis between three and 6 years old, nutritional status was strongly correlated with respiratory function. The authors concluded that adherence to proper nutritional practices from early childhood on can significantly improve respiratory function [24]. In another study, proper and timely nutritional intervention slowed down the loss of respiratory function as estimated on the basis of the percent of predicted FEV₁ [13].

Preserving respiratory competence is a high priority in treating children with cystic fibrosis because impaired respiratory function can increase morbidity and mortality. In one study, the probability that a child with cystic fibrosis would survive the next two years fell to 50% if the percent of predicted FEV₁ fell below 30% [37]. In another study, the annual rate at which the percent of predicted FEV₁ declined was found to be a reliable prognostic indicator [36].

Over the past fifty years, considerable progress has been made in arresting the loss of respiratory function in children with cystic fibrosis. In one study, the annual rate at which the percent of predicted FEV₁ declined was considerably lower in children born in the 1990s than in children born in the 1960s [15].

In the present study, there was no correlation between the type of CFTR gene mutation and FEV₁. In previous studies, the rate at which respiratory function is lost was particularly high in patients who were homozygous or heterozygous for the mutation Δ_{508} [4, 5].

Furthermore, there was no correlation between infection caused by *P. aeruginosa* and FEV₁. In other studies on children with cystic fibrosis, the annual rate at which the percent of predicted FEV₁ declined was elevated in patients who had respiratory tract infections caused by *P. aeruginosa* [15, 16].

These inconsistencies may be due to the small sample size of the patients in this pilot study. A full-scale study is underway to determine the effect of the type of CFTR gene mutation and infection caused by *P. aeruginosa* on pulmonary function in children with cystic fibrosis treated at specialized care facilities in Poland.

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