

ORIGINAL ARTICLE

Growth and nutritional status in children and adolescents with cystic fibrosis

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Abstract

Background: Growth retardation, delayed puberty and malnutrition are frequently observed in children suffering from cystic fibrosis.

Aim: The aim of this study was to estimate growth and nutritional status in children with cystic fibrosis on the basis of body proportions and body mass index.

Subjects and methods: Anthropometric data were collected from the medical histories of 62 patients treated in three cystic fibrosis treatment centers in Poland. Anthropometric parameters were expressed in terms of standard deviations away from age-specific and sex-specific reference means reported for the population of Poland. Two-way analysis of variance was used to determine whether the type of cystic fibrosis transmembrane conductance regulator (CFTR) mutation is correlated with age at the time of diagnosis and with body proportions.

Results: The type of mutation was significantly correlated with height, weight and transverse chest width. Growth retardation was greater in subjects diagnosed before they were 3 years old than in subjects diagnosed later. The children had infantile body proportions. Their legs were short and their trunks were long in comparison to their height. Almost 40% of the subjects suffered from malnourishment.

Conclusion: Further study is needed to determine how growth in children with cystic fibrosis is affected by clinical practice and socio-economic factors.

Keywords: *Children, cystic fibrosis, growth failure*

Introduction

Cystic fibrosis is one of the most common genetic metabolic disorders, and can lead to premature death. In Poland, the incidence of cystic fibrosis is 1 in 2500 live births (Bożkowska et al. 1971).

Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The gene product serves as a chloride channel, and also regulates other ion channels in the cell (Hubert 2005). More than 1000 mutations of the CFTR gene have been reported. The most common is $\Delta 508$, which accounts for almost 70% of observed cases (Sinaasappel et al. 2002).

CFTR gene mutations have been divided into five classes on the basis of how the mutation affects the function of the gene product. The classification of CFTR mutations has contributed to a better recognition the effect of genotype on the course of the disease (Hubert 2005).

Children with cystic fibrosis grow slower and enter puberty later than their peers (Shepherd 2002; Stallings et al. 2005). Growth rate is an important indicator of the course of the disease and the lifespan of the patient. Children with cystic fibrosis also frequently suffer from malnutrition. Nutritional status is an important prognostic marker, regardless of the level of respiratory function in the patient. Weight loss significantly increases the risk of death in patients with CF (Sharma et al. 2001). Height is also correlated with longevity. In a study on 19 000 patients treated in cystic fibrosis care centers in the USA, the risk of death in the shortest 5% of patients was more than three times that in the tallest 5% (Beker et al. 2001).

Although significant progress has been made in treating cystic fibrosis, patients with cystic fibrosis still grow slower than their healthy peers (Morison et al. 1997; Lai et al. 1999; Laursen et al. 1999). On the other hand, studies in Denmark and Australia have shown that intensive care in medical centers specialized in treating cystic fibrosis significantly improves growth rate and nutritional status (Nir et al. 1996; Collins et al. 1999).

In Poland, patients with cystic fibrosis suffer from marked height and weight deficiency (Walkowiak 1998; Szczepanik et al. 2000; Pogorzelski et al. 2001; Kosińska et al. 2005). In studies on growth in children with cystic fibrosis, the parameters most often investigated have been height, weight, body mass index, and skinfold thickness. Some studies also have also taken chest structure into account. There have not yet been any studies on how cystic fibrosis affects other body proportions in children (Kurniewicz-Witczakowa et al. 1976; Kosińska et al. 2005).

The aim of this study was to assess growth rate, nutritional status, and body proportions in children with cystic fibrosis.

Materials and methods

Anthropometric data were collected from the medical histories of 30 girls and 32 boys diagnosed and treated in three major cystic fibrosis treatment centers in Poland in 2005 and 2006. The centers are in Warsaw, Karpacz, and Rabka. The number of patients represents about 6% of the number of new cases reported in Poland each year, and is therefore an adequate sample for the purposes of this study.

Mean age was 11.5 years, with a minimum of 1.2 years and a maximum of 19.5 years. In all patients, cystic fibrosis was confirmed by positive sweat tests. All of the subjects and their legal guardians consented to the study.

Anthropometric parameters were measured by trained staff during follow-up visits. All parameters were measured in accordance with the procedures described by Martin and Saller (1957–1959). The following anthropometric parameters were recorded: height, weight, trunk length, leg length, shoulder width, hip width, chest width and chest depth.

Height was measured with an anthropometer accurate to one millimeter. Weight was recorded to the nearest one-tenth of a kilogram. Widths were measured with large bow calipers accurate to one millimeter. All parameters were measured in accordance with the procedures described by Martin and Saller (1957–1959).

The following ratios were also calculated: trunk length to body height; leg length to body height; chest depth to chest width; and hip width to shoulder width.

Body mass index (BMI) was used as an indicator of relative weight, and was calculated by dividing the body mass in kilograms by the square of the body height in meters.

Nutritional status was recorded in terms of BMI percentiles in accordance with the guidelines published by Cole et al. (2000), Mei et al. (2002), and Zhang and Lai (2004). BMI was calculated by dividing the body mass in kilograms by the square of the body height in meters. Patients below the 50th percentile were considered to be underweight, and patients over the 85th percentile were considered to be overweight. The reported age at onset of menarche was recorded with an accuracy of 1 month.

Anthropometric parameters were expressed in terms of standard deviations away from age-specific and sex-specific reference means for the population of Poland reported in Palczewska and Niedźwiedzka (2001). Normality of distributions was analyzed using the Shapiro–Wilk test.

All comparisons between the subjects and the reference population were statistically elaborated separately for girls and boys using two-way analysis of variance, followed by means separation using Student's *t*-test at $p < 0.05$. All calculations were carried out using the Statistica 6.0 software package.

Results

Anthropometric parameters in the subjects in this study were significantly different from those in the reference population (Table I).

Height was lower in the subjects than in the reference population (SDS = -0.92). Leg length was also lower (SDS = -1.98). On the other hand, trunk length was higher (SDS = 0.81). BMI was significantly lower than in the reference population (SDS = -0.72). Thirty-nine per cent of the subjects were underweight, and 3% were overweight. Shoulder width was lower than in the reference population (SDS = -0.59). The ratio of chest depth to chest width was also lower (SDS = -0.55). Hip width was slightly lower (SDS = -0.15). On the other hand, chest depth was higher (SDS = 1.07).

For the parameters examined, phenotypic variability greater in the subjects than in the reference population, as evidenced by the large differences between the minimum and maximum values. There were no significant differences between boys and girls (data not shown).

For all of the subjects, the type of CFTR gene mutation was determined by molecular studies. The subjects fell into three groups. (1) Forty-eight per cent of the subjects had the $\Delta 508/\Delta 508$ genotype, which is associated with severe morbidity. (2) Thirty-nine per cent had a $\Delta 508/Mt$ genotype, where Mt represents a mutation other than $\Delta 508$, such as R334W or R117H. Patients with this genotype generally exhibit a milder form of the disease. (3) Thirteen per cent had an Mt/Mt genotype, for example, $3849 + 10kbC \rightarrow T/3849 + 10kbC \rightarrow T$ or $3849 + 10kbC \rightarrow T/3659delC$.

Table I. Anthropometric parameter in 62 Polish children with cystic fibrosis, expressed in terms of standard deviations away from the means of reference values for the population of Poland.

Parameter	Mean \pm SD	Minimum	Maximum	<i>p</i> (Student's <i>t</i> -test)
Body height	-0.92 \pm 1.35	-4.28	1.64	<0.001
Body weight	-0.96 \pm 1.12	-3.22	1.08	<0.001
Body mass index	-0.72 \pm 0.96	-2.92	1.79	<0.001
Leg length	-1.98 \pm 1.71	-5.12	2.87	<0.001
Ratio of leg length to body height	-1.97 \pm 1.79	-5.15	2.27	<0.001
Trunk length	0.81 \pm 1.38	-4.12	3.88	<0.001
Ratio of trunk length to body height	2.03 \pm 1.56	-1.79	5.33	<0.001
Sagittal chest depth	1.07 \pm 1.05	-1.03	4.56	<0.001
Transverse chest width	-0.55 \pm 1.37	-4.82	2.70	<0.01
Chest index	1.70 \pm 1.43	-1.24	6.00	<0.001
Shoulder width	-0.59 \pm 1.57	-4.79	2.70	<0.01
Hip width	-0.15 \pm 1.54	-3.72	4.18	>0.05
Ratio of hip width to shoulder width	0.28 \pm 1.30	-4.44	2.73	<0.05

Eighty-six per cent of the subjects exhibited exocrine pancreatic insufficiency. This group included 100% of the subjects with the $\Delta 508/\Delta 508$ genotype, 76% of the subjects with a $\Delta 508/Mt$ genotype, and 75% of the subjects with an Mt/Mt genotype.

In the subjects in this study, the mean age at which cystic fibrosis was diagnosed in the studied subjects was 3 years, with a minimum of 1 month and a maximum of 18 years. Seventy-five per cent of the subjects were diagnosed before they were 3 years old. Thirty-one per cent of the subjects received antibiotic treatment because of respiratory tract infection caused by *Pseudomonas aeruginosa*.

Mutation type had a significant effect on height, weight and transverse chest width (Table II). Growth and weight were most reduced in subjects with an Mt/Mt genotype, and least reduced in subjects with a $\Delta 508/Mt$ genotype (Table II, Figures 1 and 2). Regardless of mutation type, there was a positive correlation between height and the age at the time of diagnosis. Growth was reduced the most in subjects diagnosed before they were 3 years old (Table II, Figure 3).

Twenty-seven per cent of the girls had undergone menarche. The mean age of menarche was 14.6 ± 1.5 years. The effect of mutation type on age at onset of menarche was not determined because of inadequate sample size.

Discussion

In the subjects in this study, height and weight were significantly lower than in their healthy peers. In other studies on children and adolescents with cystic fibrosis in Poland, there were even greater differences in height and weight between the subjects and their healthy peers (Nowakowska et al. 1995; Walkowiak 1998; Szczepanik et al. 2000). Serious developmental deficiencies have also been reported in adult patients suffering from cystic fibrosis (Kosińska et al. 2005).

Growth retardation in patients with cystic fibrosis has been treated by administering a high-calorie diet together with regular pancreatic enzyme supplementations. Recently, early

Table II. Results of two-way analysis of variance of standardized anthropogenic parameters grouped according to age at time of diagnosis and type of CFTR mutation.

Standardized anthropometric parameters	Age at time of diagnosis			Type of CFTR mutation			Interaction of age at time of diagnosis and type of mutation		
	<i>S</i>	<i>F</i>	<i>p</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>MS</i>	<i>F</i>	<i>p</i>
Body height	5.74	3.88	0.03	6.97	4.12	0.01	2.11	1.43	0.24
Body weight	1.05	0.88	0.42	3.94	3.33	0.04	1.00	0.87	0.51
Body mass index	0.34	0.41	0.66	2.03	2.14	0.13	0.46	0.48	0.74
Leg length	3.50	1.34	0.26	7.39	2.84	0.07	1.29	0.50	0.74
Ratio of leg length to body height	0.20	0.07	0.93	7.71	2.74	0.07	2.24	0.78	0.53
Trunk length	3.80	2.07	0.14	2.05	1.10	0.34	3.45	1.88	0.13
Ratio of trunk length to body height	1.36	0.63	0.54	6.42	2.96	0.06	4.31	1.99	0.11
Sagittal chest depth	0.12	0.11	0.90	2.23	2.00	0.14	0.93	0.81	0.52
Transverse chest width	1.86	1.10	0.34	8.46	5.00	0.01	0.91	0.54	0.41
Chest index	1.33	0.66	0.52	2.84	1.41	0.25	2.00	0.99	0.42
Shoulder width	1.48	0.63	0.54	3.99	1.70	0.19	0.97	0.42	0.80
Hip width	5.81	2.75	0.07	3.84	1.82	0.17	1.96	0.88	0.48
Ratio of hip width to shoulder width	3.18	1.93	0.15	0.20	0.12	0.89	3.65	2.30	0.07

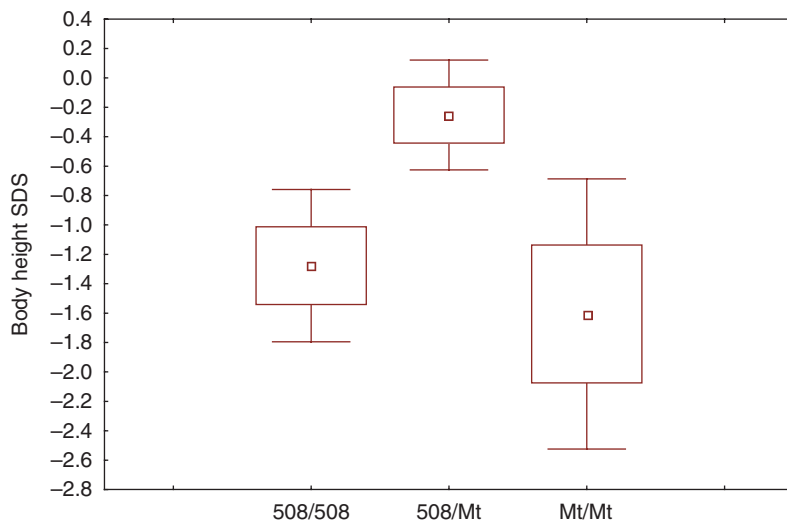


Figure 1. Standardized body height for different types of CFTR gene mutation (means, standard deviations and 95% confidence intervals).

detection followed by the administration of growth hormone have been introduced (Bell and Shepherd 2002; Sinaasappel et al. 2002). Growth hormone therapy increases height, weight and lean tissue mass, but has not yet been confirmed to improve respiratory function (Bucvalas and Chernaussek 2001; Colombo and Battezzati 2004). None of the subjects in the present study received growth hormone therapy; according to Polish regulations, growth hormone therapy is not indicated for cystic fibrosis (Malecka-Tendera 2004).

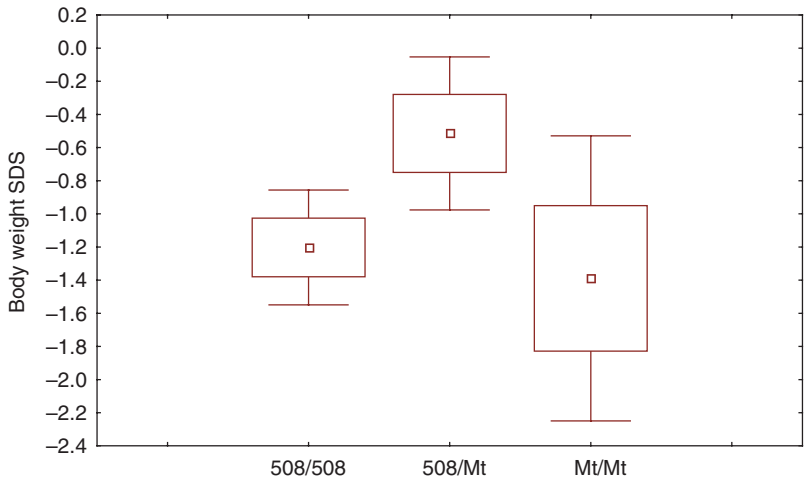


Figure 2. Standardized body weight for different types of CFTR gene mutation (means, standard deviations and 95% confidence intervals).

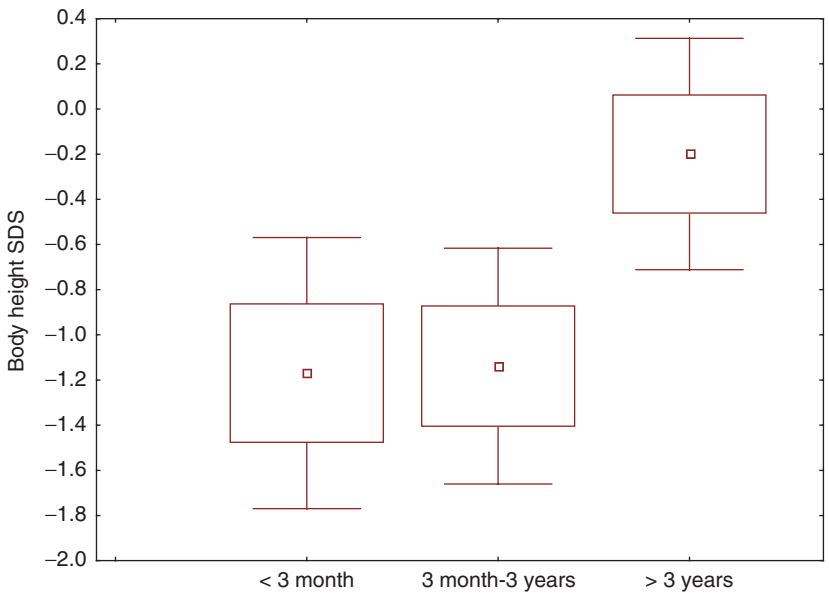


Figure 3. Standardized body height versus age at which cystic fibrosis was diagnosed (means, standard deviations and 95% confidence intervals).

The children in this study had infantile body proportions. Their legs were short and their trunks were long in comparison to their height. The ratio of hip width to shoulder width and the ratio of chest depth to chest width were higher than in their healthy peers. The results of this study cannot be compared with those of previous studies because similar testing has not yet been carried out on children with cystic fibrosis. Infantile trunk and leg proportions have also been found in abused children and in children who have undergone premature puberty (Martinez et al. 1984; Wales et al. 1992).

During the adolescent growth spurt, the legs grow rapidly. In children with cystic fibrosis, the adolescent growth spurt takes place 0.8 years later than in healthy children, and the annual increase in height is more than 1 cm less than in healthy children (Byard 1994). In a longitudinal study on children with cystic fibrosis, the adolescent growth spurt was also delayed and less intense (Haeusler et al. 1994).

Concentrations of insulin-like growth factor I and thyroid hormones are lower in patients with cystic fibrosis (Penesar 1999; Bucuvalas and Chernausek 2001). These hormones play an important role in increasing height.

In the subjects in this study, chest depth was relatively high compared to chest width. This had also been observed in previous studies on children with cystic fibrosis, in which abnormalities in chest structure persisted in spite of treatment (Kurniewicz-Witczakowa et al. 1976; Kosińska et al. 2005).

In this study, the type of mutation was found to be correlated with the age at which cystic fibrosis was diagnosed and with the degree of growth retardation. In a study on the relationship between genotype and phenotype in patients with cystic fibrosis, symptoms appeared earlier, the course of the disease was more severe, respiratory parameters were more impaired, and mortality was higher in patients with the $\Delta 508/\Delta 508$ mutation than in patients with a $\Delta 508/Mt$ mutation (Kerem et al. 1990; Johannes et al. 1991; McKone et al. 2003).

In this study, growth was reduced most in the subjects with the $\Delta 508/\Delta 508$ and Mt/Mt genotypes. Subjects diagnosed after they were 3 years old were closer to normal height than those diagnosed earlier. This is probably due to differences in the type of mutation. Those mutations which impair growth the most are detected earlier.

In the subjects in this study, the onset of menarche occurred on average between 1 and 2 years later than in the general population of Poland (Charzewski et al. 1998; Łaska-Mierzejewska and Olszewska 2003). In an earlier study on 59 girls with cystic fibrosis in Poland, the onset of menarche was found to occur more than 2 years later than normal, and the acquisition of secondary and tertiary sex characteristics was also delayed (Grabowska and Łuczak 1996). In a study on girls with cystic fibrosis in Sweden, menarche was also delayed, although the magnitude of the delay depended on the test used (Johannesson et al. 1998). In one study, girls with cystic fibrosis rarely had their first period before they were 14 years old (Mahaney and McCox 1986).

Malnutrition is the main cause of delayed menarche in girls with cystic fibrosis. However, menarche is also delayed in girls with cystic fibrosis who are well nourished. In one study, the onset of menarche occurred more than 2 years later in girls with cystic fibrosis than in their healthy peers in spite of the fact that the nutritional status of the subjects and the reference population was approximately the same (Johannesson et al. 1997).

A mutation in the CFTR gene may reduce the secretion of gonadotrophin-releasing hormone (GnRH) by the hypothalamus, thereby delaying puberty regardless of the nutritional status of the patient (Johannesson et al. 1998; Galli-Tsinopoulou et al. 2006).

The age at onset of menarche depends on the type of mutation, and is delayed most in patients with the $\Delta 508/\Delta 508$ genotype (Johannesson et al. 1998). In this study, the sample of menstruating girls was too small to identify any unequivocal correlations between the type of mutation and the delay in puberty.

The children in this study were treated in accordance with the guidelines published by the Polish Working Group for Cystic Fibrosis (Bożkova et al. 2002). According to these guidelines, the quality of life and the longevity of patients with cystic fibrosis are to be improved by centralizing medical care including individually tailored high-calorie diets, pancreatic enzyme supplements, effective antibiotic therapy, and physiotherapy.

Twenty-eight per cent of the subjects came to medical centers for follow-up examinations and medical consultation once a month. The rest came less frequently, with 58% coming once every 3 years. It is extremely difficult to determine whether the children and their parents closely followed medical instructions. Socio-economic factors may have had a great effect on the course of the disease.

In the subjects in this study, growth and maturation were slower than in their healthy peers. Most of the subjects suffered from exocrine pancreatic insufficiency. Almost 40% were severely malnourished in spite of individualized dietary adjustments and pancreatic enzyme supplementation.

In spite of continuous improvements in dietary practice and pharmacological therapy, children with cystic fibrosis are still shorter and lighter than healthy children. Further study is needed to determine how growth and maturation in children with cystic fibrosis is affected by clinical practice and socio-economic factors.

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