

Predictors of deterioration of lung function in Polish children with cystic fibrosis

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Submitted: 20 May 2014

Accepted: 21 August 2014

Arch Med Sci 2016; 12, 2: 402–407

DOI: 10.5114/aoms.2016.59268

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Abstract

Introduction: Severity of lung disease varies in patients with the same CFTR genotype. It suggests that other factors affect the severity of cystic fibrosis (CF). The aim of the study was to identify risk factors that determine lung function decline in Polish cystic fibrosis children.

Material and methods: The follow-up time was no less than 5 years of respiratory status observation based on the forced expiratory volume in 1 s value (FEV₁). The socio-economic data, perinatal interview, presence of meconium ileus (MI), time of CF diagnosis, initiation of tobramycin inhalation solution (TIS), pancreatic function, sensitization to *Aspergillus fumigatus*, presence of impaired glucose tolerance (IGT) or diabetes mellitus, chronic bacterial colonization and number of exacerbations and hospitalizations were assessed.

Results: The mean age of 61 included children was 13.3 ±7.6 years. Delta F508 homozygosity was detected in 45.9%, 44.3% were delta F508 heterozygous, and 9.8% had other genotypes. FEV₁ decline was observed among 20% of patients; the rest of the patients presented stable values of FEV₁ during at least 5 years of observation. The most significant predictors related to the decline of FEV₁ were presentation of MI ($p = 0.0344$), IGT ($p = 0.0227$), number of exacerbations ($p = 0.0288$), and early *Pseudomonas aeruginosa* (PA) chronic colonization ($p = 0.0165$) followed by late TIS initiation after the first detection of PA ($p=0.0071$). Neither time of diagnosis nor type of CFTR mutation was statistically significant as a predictor of lung deterioration.

Conclusions: The presence of MI, IGT, chronic PA colonization, and number of exacerbations are risk factors for lung function deterioration.

Key words: cystic fibrosis, children, risk factors, deterioration, lung function.

Introduction

Respiratory failure due to endobronchial infection is the most important cause of morbidity and mortality in patients suffered from cystic fibrosis (CF) [1–3]. Bacterial colonization and chronic pulmonary inflammation develop subsequently. It seems that the severity of lung disease could depend on the type of mutation in the cystic fibrosis transmembrane conductance regulator gene (CFTR) [1–4]. However, there is wide

variability in course of the disease, even among patients presenting the same mutation. The genotype-phenotype dependence is still unclear and the course of cystic fibrosis very individual [5, 6]. This fact reflects the influence of multiple factors such as genetic, environmental, immunological, time of diagnosis, bacterial colonization and methods of treatment on the disease. Our research with data showing risk factors for lung function deterioration in Polish population can contribute to direct intervention for the relevant patients.

We hypothesized that there are identifiable risk factors in children associated with accelerated lung function aggravation. The aim of the study was to identify risk factors that determine lung disease deterioration in Polish CF children.

Material and methods

We collected information on all living children born between 1996 and 2009 (before the start of newborn screening in Poland) attending the Cystic Fibrosis Outpatient in Copernicus Hospital in Lodz, Poland. The data were obtained retrospectively after review of patient charts. Each patient was observed from the diagnosis until the age of 18; the average time period was 8 years. The data were analyzed in July 2013. The diagnosis of CF was confirmed by clinical symptoms and elevated sweat chloride concentrations (above 60 mmol/l) measured by the quantitative pilocarpine iontophoresis method. The CFTR mutations were analyzed by established DNA molecular techniques. Four patients had one unknown mutation, and the rest had a fixed mutation in both alleles.

The socio-economic data were analyzed. These included number of siblings and siblings with CF, a place of living (defined as big city above 100 000 inhabitants, small city 10 000–100 000 inhabitants and village below 10 000 inhabitants). The perinatal interview contained data: delivery date and weight, Apgar score and presence of meconium ileus (MI). Time of CF diagnosis and start of CF standard therapy (supplementation with pancreatic enzymes, dornase α inhalation, tobramycin inhalation solution (TIS), chronic oral azithromycin intake) were also analyzed. Patients were classified as pancreatic sufficient (PS) or insufficient (PI) by low fecal elastase concentration ($< 200 \mu\text{g}$ elastase/g). Sensitization to *Aspergillus fumigatus* (allergic bronchopulmonary aspergillosis – ABPA) was defined as a positive level of serum specific IgE and serum specific IgG antibodies to *Aspergillus* and presence of associated clinical findings. The concomitant diseases were assessed: asthma was established by a personal history and a family history of atopy and asthma in first degree relatives and by the presence of bronchi-

al obstruction, bronchial reactivity [7]; impaired glucose tolerance (IGT)/diabetes mellitus (DM) by the oral glucose tolerance test (OGTT) (2-hour OGTT blood plasma glucose between 7.8 mmol/l (140 mg/dl) and 11.1 mmol/l (200 mg/dl) – IGT; above 7.8 mmol/l (140 mg/dl) – DM); nasal polyps by laryngological examination; abdomen abnormalities by ultrasonography, viral hepatitis by presence of the hepatitis B surface antigen (HBsAg) and level of antibodies against hepatitis C virus (anti-HCV). Chronic bacteria colonization (*Pseudomonas aeruginosa* (PA), methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella* sp., *Haemophilus influenza*, *Serratia marcescens*) was defined as three positive consecutive sputum cultures over a period of 6 months. Respiratory status was assessed by the test of forced expiratory volume in 1 s (FEV_1) in spirometry, expressed as percentages of predicted values for height, weight, age, and gender. All analyzed measurements were done in the same month, once a year, only in stable periods (with a Jaeger MasterScreen Body spirometer; E Jaeger GmbH; Wurzburg, Germany). The tests were performed according to American Thoracic Society standards [8]. A substantial decline was defined as a decrease of 20 or more percent in $\text{FEV}_1\%$ predicted value during at least 5 years of observation. The evaluation of number of bronchopulmonary exacerbations and number of hospitalizations (due to pulmonary or abdominal disease, longer than 3 days) each year of observation was performed. Pulmonary exacerbation was defined as excessive sputum expectoration, general malaise, and need for antibiotics.

The study was approved by the Ethical Committee of the Medical University of Lodz, Poland.

Statistical analysis

Here we defined possible risk factors (independent variables) of decline in FEV_1 among CF children during 5 years of observation (dependent variables). Logistic regression was used to assess the relationship between dependent variables and each of the independent variables. All of the statistical analyses were performed using Statistica 8.0. The null hypothesis was rejected if $p < 0.05$.

Results

There were 61 patients registered in the Cystic Fibrosis Outpatient Clinic in Copernicus Hospital in Lodz, Poland. The mean age of the group was 13.3 ± 7.6 years, and 50.8% were male. Patient demographic and clinical characteristics are shown in Table I. Most of our children were delta F508 homozygous (45.9%), 44.3% were delta F508 hetero-

Table I. Baseline characteristics

| Variables | Result |
|-----------------------------------------------------------------|----------------|
| Age, mean \pm SD [years] | 13.3 \pm 7.6 |
| Male gender, <i>n</i> (%) | 31 (50.8) |
| Birth weight, mean \pm SD [g] | 3259 \pm 522 |
| APGAR, median (quartile range) [points] | 9 (8–9) |
| Number of siblings, median (quartile range) | 1 (0–1) |
| Siblings with CF, <i>n</i> (%) | 14 (23.3) |
| Meconium ileus, <i>n</i> (%) | 15 (24.6) |
| Place of living, <i>n</i> (%): | |
| Village | 12 (19.7) |
| Small city | 31 (50.8) |
| Big city | 18 (29.5) |
| Time of diagnosis, median (quartile range) [months] | 24 (3–69) |
| Sweat chloride concentrations [mmol/l], median (quartile range) | 100 (90–113) |
| Mutation (CFTR), <i>n</i> (%): | |
| Delta F508/other | 27 (44.3) |
| Delta F508/Delta F508 | 28 (45.9) |
| Others | 6 (9.8) |
| Impaired glucose tolerance, <i>n</i> (%) | 14 (23.3) |
| Pancreatic insufficiency, <i>n</i> (%) | 53 (98.1) |

zygous, and 9.8% had other genotypes. Mean time of the CF diagnosis was 24 months from birth.

All continuous variables with skewed distribution were log-transformed before analysis. The most significant predictors related to the decline of FEV₁ (Table II) were presentation of MI in newborn and number of exacerbations. Impaired glucose tolerance was a risk factor in CF children older than 10 years of age. Patients with early PA chronic colonization and late TIS introduction (after first detection of PA) showed faster decline of FEV₁. Neither time of diagnosis nor type of CFTR mutation was statistically significant as a predictor of lung deterioration. Other demographic, clinical and health care utilization characteristics described in Table II were not predictors of substantial decline. In the analysis cohort, FEV₁ decline was observed among 20% of patients; the remaining 80% of patients presented quite stable values of FEV₁ during at least 5 years of observation (Figure 1).

Discussion

Although this type of analysis has been published in numerous other settings among CF pop-

ulations in North America and Western Europe, a similar analysis in this population is useful to show differences in health systems and access to therapies. Our research team has collected large amount of data over many years, and the concept of what factors determine lung function decline in some CF children is an important one for clinicians and researchers. We observed wide variability in disease severity even among children with the same CFTR mutation. Pulmonary function is the best predictor of morbidity in patients with cystic fibrosis and is the most widely used clinical end point in therapeutic trials and to describe and compare groups in a regression model [9, 10]. In our study, the analyzed data present two patterns of changes in lung function in time: a continuous decline in values of FEV₁, and a second pattern that showed lung function at quite a stable level over time despite genotype and related medical interventions in accordance with the guidelines. We observed that children with an important decline in FEV₁ started the observation period with an initial lower FEV₁. This is consistent with the previous finding that patients with lower FEV₁ were at further risk of a substantial decline [11]. At high risk of unfavorable presentation of the disease was the group of children with MI in newborn and IGT at the age of 10 years. Earlier acquisition of chronic *Pseudomonas aeruginosa* colonization was associated with faster deterioration of lung function. The administration of inhaled antibiotics, especially inhaled tobramycin, had a beneficial effect on the general condition of CF patients with PA colonization. Moreover, patients who started treatment with TIS earlier had slower decline of FEV₁. Interestingly, the time of diagnosis of CF was not prognostic for the severity of the disease, even if patients presented severe mutation in both alleles of CFTR. This highlights the fact that the CFTR genotype known at the time of CF diagnosis is not representative for estimating phenotype of the disease in the future.

Meconium ileus is a unique manifestation among infants with CF and is the earliest clinical symptom, with the prevalence of 10–21% [12, 13]. Despite the fact that children presenting MI are diagnosed and adequate treatment is initiated soon after birth, many researchers have noted in these patients poor growth, nutritional status and worse lung function [12–15]. Additionally, publications by the Wisconsin CF Neonatal Screening Project showed that MI children with CF present a specific phenotype, predisposing to malnutrition, severe pulmonary deterioration, and reduced survival [15–17]. Likewise, in the present study, a worse course of the disease was observed particularly among children who were treated surgically due to MI, and who experienced more exacerbations and admis-

Table II. Risk factors of decline in FEV₁ in univariate model of logistic regression analysis

| Coefficient | OR ^a | Lower 95% CI | Upper 95% CI | P-value |
|-----------------------------------------------|-----------------|--------------|--------------|---------------|
| Age (continuous variable) | 1.07 | 0.96 | 1.19 | 0.2435 |
| Time of diagnosis [months] | 1.01 | 0.99 | 1.02 | 0.4315 |
| Gender | 0.86 | 0.21 | 3.44 | 0.8280 |
| Weight | 1.00 | 1.00 | 1.00 | 0.1755 |
| Apgar score | 1.50 | 0.64 | 3.56 | 0.3527 |
| Meconium ileus | 5.83 | 1.14 | 29.90 | 0.0344 |
| Place of living | Ref | | | |
| Small city | 1.00 | 0.16 | 6.25 | 1.0000 |
| Big city | 1.09 | 0.15 | 8.12 | 0.9323 |
| Siblings | 1.03 | 0.46 | 2.32 | 0.9392 |
| Siblings with CF | 0.64 | 0.12 | 3.48 | 0.6021 |
| CFTR mutation | 1.75 | 0.43 | 7.19 | 0.4377 |
| Sweat chloride concentration | 1.00 | 0.97 | 1.04 | 0.9280 |
| Impaired glucose tolerance | 5.62 | 1.27 | 24.86 | 0.0227 |
| ABPA | 1.21 | 0.79 | 1.83 | 0.3814 |
| First exacerbation in life | 1.03 | 0.99 | 1.07 | 0.1615 |
| First hospitalization in life | 1.01 | 0.98 | 1.05 | 0.3668 |
| Exacerbations (all) | 1.09 | 1.01 | 1.17 | 0.0288 |
| Hospitalizations (all) | 1.10 | 0.99 | 1.22 | 0.0872 |
| Start of nebulised dornase α | 1.00 | 0.98 | 1.01 | 0.6638 |
| Start of tobramycin inhalation solution | 1.02 | 1.00 | 1.03 | 0.0071 |
| Start of chronic oral azithromycin | 1.00 | 0.99 | 1.02 | 0.3854 |
| First <i>Pseudomonas aeruginosa</i> infection | 1.00 | 0.99 | 1.01 | 0.5039 |
| Chronic <i>Pseudomonas aeruginosa</i> | 1.01 | 1.00 | 1.02 | 0.0165 |
| Chronic MRSA infection | 1.01 | 1.00 | 1.02 | 0.1690 |
| Chronic MSSA infection | 1.00 | 0.99 | 1.01 | 0.9718 |
| First <i>Hemophilus influenzae</i> infection | 0.99 | 0.97 | 1.01 | 0.4507 |
| First <i>Klebsiella</i> sp. infection | 1.01 | 1.00 | 1.02 | 0.1235 |
| First <i>Serratia</i> sp. infection | 1.01 | 0.99 | 1.02 | 0.4257 |

^aDependent variable: decline in FEV₁.

sion to the hospital per year. They presented more impaired growth and severe malnutrition status in comparison to patients without MI. However, there are also suggestions that if the follow-up period was extended to 20 years of age, the influence of MI on the morbidity diminished [18].

Most studies report rapid decline of lung function in diabetic CF patients [19, 20]. Nowadays, the significance of IGT as a risk factor of worse clinical condition, undernutrition and impaired pulmonary function is also increasingly empha-

sized [6, 21–23]. A similar observation was noted in our study. We found that glucose abnormalities are related to the faster decline of FEV₁. These findings open the question whether early treatment of mild alterations of glucose metabolism with short-acting insulin may lead to improvement of clinical status in CF patients. Moran *et al.* [21] reported that insulin therapy in children with IGT improved lung function and restored body mass index (BMI). In the study by Lanng *et al.* [22] weight loss and decrease of lung function were

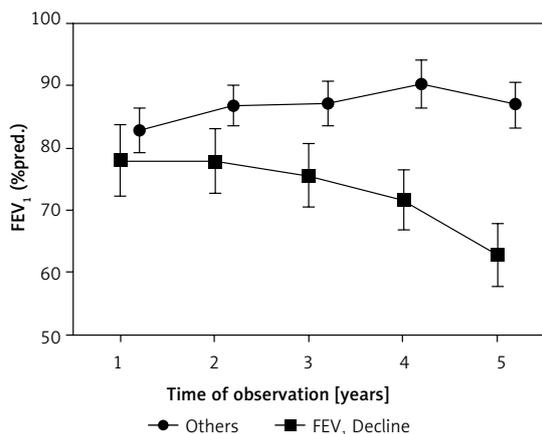


Figure 1. Lung function decline among 20% of CF patients (■) and stable values of FEV₁ among 80% of CF patients (●) during five years of observation

observed in CF patients 1–4 years before DM diagnosis. Early treatment with short-acting insulin in CF patients with IGT without fasting hyperglycemia is still not generally recommended. There is a need for further investigation and changes in the guidelines.

Colonization with *Pseudomonas aeruginosa* remains the major contributor to the shortened survival in CF patients. For over a decade tobramycin inhalation solution (TIS) has been recommended for the treatment of PA infection in CF. Our results showed that early initiation of TIS treatment resulted in improved lung function and reduced the risk of airway exacerbations, which was confirmed in other studies [24–26]. What is very important, Moss *et al.* [26] proved that delay in initiation of TIS therapy is associated with reduced long-term improvement over baseline, suggesting an irreversible component to lung function decline. They also demonstrated that long-term, intermittent TIS therapy may lead to significant improvement of body weight in growing adolescents. They also strongly suggested that in order to be maximally effective, TIS treatment should begin soon after first detection of PA. In accordance with that study, we found a slower decline in FEV₁ among children whose TIS was administered shortly after chronic infection of PA. Unfortunately, in Poland TIS is only available for patients with chronic PA (positive sputum culture over 6 months).

This study has some limitations. Only patients who had at least five visits in the 5 years before the data collection were included in the analysis cohort. This allowed more rigorous assessment, but reduced the available cohort.

In our study, multivariable analysis would be of interest; however, all statistical predictors of FEV₁ decline defined in our study seem to have different pathophysiological meaning, and collinearity is less possible.

In conclusion, our study revealed that presence of meconium ileus, impaired glucose tolerance, chronic *Pseudomonas* colonization, and number of exacerbations are risk factors for lung function deterioration. Patients with these characteristics should receive early and aggressive treatment. Despite genotype and treatment, 80% of our patients had stable lung function in time, which is probably associated with other genetic factors.

Conflict of interest

The authors declare no conflict of interest.

References

- Halicioglu O, Akman SA, Sutcuoglu S, Coker I. Diverse genotypical features and impacts on clinical course and severity of cystic fibrosis: early childhood experience. *Minerva Pediatr* 2011; 63: 169-75.
- Aeffner F, Abdulrahman B, Hickman-Davis JM, et al. Heterozygosity for the f508del mutation in the cystic fibrosis transmembrane conductance regulator anion channel attenuates influenza severity. *J Infect Dis* 2013; 208: 780-9.
- Dębska G, Mazurek H. Factors related to changes in the quality of life among Polish adolescents and adults with cystic fibrosis over a 1-year period. *Patient Prefer Adherence* 2015; 15: 1763-70.
- Ooi CY, Durie PR. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in pancreatitis. *J Cyst Fibros* 2012; 11: 355-62.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-38.
- Flores JS, Rovedder PM, Ziegler B, et al. Clinical outcomes and prognostic factors in a cohort of adults with cystic fibrosis: a 7-year follow-up study. *Respir Care* 2016; 61: 192-9.
- Antunes J, Fernandes A, Borrego LM, Leiria-Pinto P, Cavaco J. Cystic fibrosis, atopy, asthma and ABPA. *Allergol Immunopathol* 2010; 38: 278-84.
- Schaedel C, de Monestrol I, Hjelte L, et al. Predictors of deterioration of lung function in cystic fibrosis. *Pediatr Pulmonol* 2002; 33: 483-91.
- Weiler CA, Drumm ML. Genetic influences on cystic fibrosis lung disease severity. *Front Pharmacol* 2013; 4: 40.
- Knowles MR, Drumm M. The influence of genetics on cystic fibrosis phenotypes. *Cold Spring Harb Perspect Med* 2012; 2: a009548.
- VandenBranden SL, McMuller A, Schechter MS, et al. Lung function decline from adolescence to young adulthood in cystic fibrosis. *Ped Pulm* 2012; 47: 135-43.
- Zybert K, Mierzejewska E, Sands D. Clinical status and somatic development of patients with or without meconium ileus diagnosed through neonatal screening for cystic fibrosis. *Dev Period Med* 2015; 19: 41-9.
- Lavie M, Manovitz T, Vilozni D, et al. Long-term follow-up of distal intestinal obstruction syndrome in cystic fibrosis. *World J Gastroenterol* 2015; 21: 318-25.
- Kelly T, Buxbaum J. Gastrointestinal manifestations of cystic fibrosis. *Dig Dis Sci* 2015; 60: 1903-13.
- Monajemzadeh M, Ashtiani MTH, Sadrian E, et al. Variation in plasma leptin levels in young Iranian children with cystic fibrosis. *Arch Med Sci* 2013; 9: 883-7.

16. Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic fibrosis Neonatal Screening Study Group. *Pediatrics* 2001; 107: 1-13.
17. Lai HC, Kosorok MR, Laxova A, Davis LA, FitzSimmon SC, Farrell PM. Nutritional status of patients with cystic fibrosis with meconium ileus: a comparison with patients without meconium ileus and diagnosed early through neonatal screening. *Pediatrics* 2000; 105: 53-61.
18. Efrati O, Judith N, Fraser D, et. al. Meconium ileus in patients with cystic fibrosis is not a risk factor for clinical deterioration and survival: the Israeli multicenter study. *J Pediatr Gastroenterol Nutr* 2010; 50: 173-8.
19. Bridges N. Diabetes in cystic fibrosis. *Paediatr Respir Rev* 2013; 14: 16-8.
20. Widger J, Ranganathan S, Robinson PJ. Progression of structural lung disease on CT scans in children with cystic fibrosis related diabetes. *J Cyst Fibros* 2013; 12: 216-21.
21. Moran A, Pekow P, Grover P, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the Cystic Fibrosis Related Diabetes. Therapy trial. *Diabetes Care* 2009; 32: 1783-8.
22. Lanng S, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infection. *Acta Paediatr* 1994; 83: 849-53.
23. Hameed S, Jaffé A, Verge CF. Advances in the detection and management of cystic fibrosis related diabetes. *Curr Opin Paediatr* 2015; 27: 525-33.
24. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* 1999; 340: 23-30.
25. Sawicki GS, Signorovitch JE, Zhang J, et al. Reduced mortality in cystic fibrosis patients treated with tobramycin inhalation solution. *Pediatric Pulmonol* 2012; 47: 44-52.
26. Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. *Chest* 2002; 121: 55-63.