Journal of Cystic Fibrosis 15 (2016) 652–659

www.elsevier.com/locate/jcf

Original Article

Reversible airway obstruction in cystic fibrosis: Common, but not associated with characteristics of asthma

Hagit Levine [a,b,1], Malena Cohen-Cymberknoh [c,d,1], Nitai Klein [d], Moshe Hoshen [e], Huda Mussaffi [a,b], Patrick Stafler [a,b], Oded Breuer [c,d], Eitan Kerem [c,d,1], Hannah Blau [a,b,*,1]

[a] *Pulmonary Institute and Graub Cystic Fibrosis Center, Schneider Children's Medical Center, Petah-Tikva, Israel*
[b] *Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Tel Aviv, Israel*
[c] *CF Center, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[d] *Hebrew University Hadassah Medical School, Jerusalem, Israel*
[e] *Clalit research institute, Clalit health services, Tel-Aviv, Israel*

Received 8 September 2015; revised 17 December 2015; accepted 11 January 2016
Available online 28 January 2016

Abstract

Background: As asthma-like symptoms are common in CF, we evaluated reversible airway obstruction and associated characteristics.
Methods: Retrospective analysis of charts including spirometry and bronchodilator response.
Results: Of 190 CF patients (103 at Schneider's, 87 at Hadassah), aged 14.4 (4–76) years, median (range), 39% had reversible obstruction (ΔFEV_1% predicted $\geq$ 12%), associated with younger age ($p = 0.01$) and severe genotype ($p = 0.02$). There was no association with family history of asthma, serum IgE, blood eosinophils, pancreatic status, $FEV_1 < 40\%$ predicted, Aspergillus or pseudomonas infection. Of patients with reversible obstruction, 74% were on bronchodilator and 68% on inhaled corticosteroid therapy but 54% and 57% respectively receiving these therapies did not have reversible obstruction.
Conclusions: Reversible airway obstruction is common in CF, more frequent in younger patients and with severe genotype, with no correlation to markers of atopy or CF clinical severity. Bronchodilator and inhaled corticosteroid therapies are commonly prescribed even without reversible obstruction.

Keywords: Cystic fibrosis; Asthma; Bronchodilator; Reversibility; Airway obstruction; Hyperreactivity

1. Introduction

Cystic fibrosis (CF) is an obstructive airways disease [1]. Nevertheless the association between CF and bronchial asthma is unclear. The term 'CF asthma' refers to asthma-like symptoms and bronchial hyper-responsiveness in CF patients [2]. Both CF and asthma are characterized by airway inflammation and smooth muscle contraction due to inflammatory mediators, although the nature of the inflammation may differ. Severe neutrophilic inflammation is the hallmark of CF lung disease whereas eosinophilic inflammation is more characteristic of asthma [1,3].

Airway obstruction in atopic asthma is characterized by smooth muscle contraction, mucosal edema and increased mucus secretion resulting from a Th2 lymphocytic immune response associated with IgE-mediated inflammation. While reversible bronchospasm is central, structural airway remodeling occurs [3]. In CF lung disease, absent *CFTR* within airway smooth muscle may cause a persistent contracted state. With

* Corresponding author at: Pediatric Pulmonary Institute and Graub CF Center, Schneider Children's Medical Center, Petah Tikva 49202, Israel. Tel.: +972 3 9253654; fax: +972 3 9253308.
E-mail address: hblau@post.tau.ac.il (H. Blau).
[1] Contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.jcf.2016.01.003

time, a dysregulated vicious cycle of inflammation and infection results in development of severe cystic bronchiectasis over time. Chronic *Pseudomonas aeruginosa* infection is associated with a predominant Th2 immune response [4].

There is no consensus on how to define 'CF asthma'. As asthma is a common disease in the general population, with a prevalence of 5–17% worldwide [5], it is difficult to determine which CF patients have asthma as well as CF, and which have asthma-like symptoms due to changes in bronchomotor tone or CF lung inflammation. The diagnosis of asthma in CF patients is mainly clinical, based on suggestive features such as a strong family and personal history of atopy, and a family history of asthma, in addition to CF [2].

Our study aims to describe the prevalence of reversible airway obstruction and bronchodilator use in patients with CF and to assess its possible association with different characteristics of this disease thus leading to a better understanding and rationale for therapy of CF lung disease.

2. Methods

Patients with CF followed at the Graub CF Center, Schneider Children's Medical Center and the CF Center at Hadassah-Hebrew University Medical Center were studied by retrospective chart review between 1991 and 2014. Inclusion criteria were a diagnosis of CF according to accepted criteria [6], the ability to perform spirometry according to ATS/ERS guidelines [7] and at least one recorded response to bronchodilator in the patient's chart.

2.1. Pulmonary function tests

Both CF centers used the Polgar prediction equations for children up to the age of 18 years, and the ECSC/ERS or Knudson prediction equations for patients aged 18 years and above. Laboratory protocol for evaluating the response to bronchodilator required at least 6 h since the last dose of short acting beta agonist (SABA) and at least 12 h since the last dose of long acting beta agonist (LABA) or combined LABA-inhaled corticosteroid (ICS) inhalation. We evaluated spirometry pre- and post-bronchodilator routinely during annual review but also when increased reversibility was suspected at times of increased wheezing or bronchial obstruction. The spirometry result demonstrating maximal improvement in FEV_1 following bronchodilator was recorded from the patients' charts.

2.2. Definitions

We defined reversible airway obstruction according to ATS/ERS guidelines [8] as an improvement in %predicted FEV_1, (ΔFEV_1) of $\geq 12\%$. An improvement in $MEF_{25-75\%}$ ($\Delta MEF_{25-75\%}$) of $\geq 30\%$ following bronchodilators reflected reversibility of small airway obstruction [9]. Allergic bronchopulmonary Aspergillosis (ABPA) was defined according to the CF foundation consensus criteria [10]. A stool elastase of <200 mcg/g was required for the definition of pancreatic insufficiency [11]. We classified patients as having a severe *CFTR* genotype if they had 2 mutations from class I, II or III, known to be associated with minimal *CFTR* function and a mild *CFTR* genotype if they had at least one mutation from class IV or V, known to be associated with residual *CFTR* function [12]. If patients had 1 unknown and 1 severe mutation or 2 unknown mutations we classified them as of unknown genotype severity and did not include them in the analysis of the association of genotype with bronchodilator reversibility. Chronic infection with *P. aeruginosa* was defined as at least 3 positive sputum cultures over a period of at least 6 months [13].

2.3. Patient data

Data collected from each patient included demographics at the time of selected spirometry result: weight, height and BMI; CF disease characteristics including *CFTR* mutations, sweat chloride, fecal elastase, chronic *P. aeruginosa* infection, Aspergillus infection; a diagnosis of ABPA, positive RAST for *Aspergillus fumigatus*; and the following markers of atopy: highest recorded serum IgE and highest recorded total eosinophil count. Information available regarding a family history of asthma in a first degree family member was also documented.

We detailed whether patients were receiving SABA, ICS or combination therapy of LABA with ICS at the time of the selected spirometry test.

2.4. Statistics

Descriptive statistics were used, and data is expressed as mean ± standard deviation or as median and range as appropriate. Among the patients with complete data, we tested differences between subgroups of patients with χ^2 test or Fisher-Exact test (for 2×2 tables) for categorical variables and *t* tests for Normally distributed continuous variables. We used compared means of Normally distributed variables using ANOVA. When distribution of continuous variables (such as age across categories) was not Normal we compared group distribution using the Mann–Whitney test. In measures with levels of missing data we categorized the data and introduced missingness as an independent category to test significance, using χ^2 test. The statistical analysis was performed with SPSS 22.0 for Windows. Statistical significance was defined by a two-sided alpha level of 0.05.

The Rabin Medical Center and Hadassah Medical Center Research Ethics Committees granted approval for this retrospective study (Rabin ERB number: 0427-13-RMC; Hadassah ERB number: 0592-12).

3. Results

Of the 190 CF patients that fulfilled the inclusion criteria, 103 were from the Graub CF Center at Schneider Children's Medical Center and 87 from the CF Center at Hadassah-Hebrew Medical Center. Median age was 14.4 years with a range of 4–76 years, and 110 (58%) were males.