Respiratory Medicine 131 (2017) 241–246

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Clinical impact of *Pseudomonas aeruginosa* colonization in patients with Primary Ciliary Dyskinesia

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ARTICLE INFO

Article history:
Received 3 May 2017
Received in revised form
1 August 2017
Accepted 24 August 2017
Available online 1 September 2017

Keywords:
Primary ciliary dyskinesia
Pseudomonas colonization
Lung function
Airway infection
Lung deterioration

ABSTRACT

Background: Airway infections in Primary Ciliary Dyskinesia (PCD) are caused by different microorganisms, including *pseudomonas aeruginosa* (PA). The aim of this study was to investigate the association of PA colonization and the progression of lung disease in PCD.
Methods: Data from 11PCD centers were retrospectively collected from 2008 to 2013. Patients were considered *colonized* if PA grew on at least two separate sputum cultures; otherwise, they were classified as *non-colonized*. These two groups were compared on the lung function computed tomography (CT) Brody score and other clinical parameters.
Results: Data were available from 217 patients; 60 (27.6%) of whom were assigned to the *colonized* group. Patients *colonized* with PA were older and were diagnosed at a later age. Baseline forced expiratory volume at 1 s (FEV_1) was lower in the *colonized* group (72.4 ± 22.0 vs. 80.1 ± 18.9, % predicted, $p = 0.015$), but FEV_1 declined throughout the study period was similar in both groups. The *colonized* group had significantly worse CT-Brody scores (36.07 ± 24.38 vs. 25.56 ± 24.2, $p = 0.034$). A subgroup analysis with more stringent definitions of colonization revealed similar results.
Conclusions: Lung PA colonization in PCD is associated with more severe disease as shown by the FEV_1 and CT score. However, the magnitude of decline in pulmonary function was similar in *colonized* and *non-colonized* PCD patients.

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http://dx.doi.org/10.1016/j.rmed.2017.08.028
0954-6111/

List of abbreviations

PCD	Primary ciliary dyskinesia
PA	*Pseudomonas aeruginosa*
FEV_1	forced expiratory volume in 1 s
CT	computed tomography
MCC	mucociliary clearance
nNO	nasal nitric oxide
EM	electron microscopy
BMI	body mass index
FI	first isolation
SD	standard deviation
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MRSA	Methicillin-resistant *Staphylococcus aureus*

1. Background

Primary ciliary dyskinesia (PCD) is an autosomal recessive disease caused by specific primary structural and/or functional abnormalities of the motile cilia, leading to impaired mucociliary clearance (MCC) in the respiratory system [1], with varying degrees of different clinical manifestations [2,3]. Recurrent and chronic infections and persistent inflammation of the respiratory system result in progressive lung damage [1,4]. In a previous cross sectional study, we found that among the Hadassah Medical Center PCD patient population, 41% of the patients had PA growth in their sputum cultures at least once [5]. There was no correlation between PA infection and FEV_1% predicted values or chest CT scan scores in patients with PCD, in contrast to patients with cystic fibrosis (CF) at the time of the study [5]. Both PCD and CF are characterized by impaired MCC [6]. In CF, PA infection is a significant risk factor for severity of lung disease and prognosis [7–11]. It is therefore important to investigate the impact of PA respiratory infection in patients with PCD. Since the number of patients with PCD in our previous study was too small to draw conclusions, we performed a larger scale collaborative study to investigate the putative associations between PA infection and lung disease in patients with PCD.

2. Methods

This retrospective study was conducted on patients with a confirmed diagnosis of PCD treated at 6 centers in Israel (Hadassah Medical Center, Schneider Medical Center, Rambam Medical Center, Soroka Medical Center, Shaare Zedek Medical Center and Carmel Medical Center), and 5 other centers across Europe: University Hospital Gasthuisberg, Leuven, Belgium, University of Padova, Italy, Ospedale dei Bambini, G. Di Cristina, ARNAS Civico, Palermo, Italy, Azienda Ospedaliera di Verona, Italy and Children's University Hospital, Hannover, Germany. Data covering 6 years (January 2008 to December 2013) were extracted from the clinical records at the 11 centers and were transferred to a central database that was centrally reviewed. Included were patients who had been followed-up for at least 3 years, and for whom data from two or more sputum cultures were recorded. PCD was diagnosed according to European guidelines [12–17]. Since the frequency of clinic visits of patients with PCD is in general much lower than for patients with CF, we used several definitions of *colonized* and *non-colonized* with PA. The most rigorous definition, which is used for CF patients, is the Leeds criteria [18]. However, only a few patients in our study could meet the Leeds criteria Therefore, we classified patients as *non-colonized* if they had never been cultured with PA or cultured only once, whereas *colonized* patients were defined as having had least two positive sputum cultures for PA during the study period. Subsequently, we re-analyzed the data by stratifying the colonized patients according to several more rigorous criteria. *Colonized* groups were defined as having) at least four positive cultures during the study period (n = 41), at least six positive cultures during the study period (n = 28) or c) two or more consecutive positive cultures or two consecutive years with at least one positive PA culture each year(n = 54). Comparisons were made between the *colonized* and *non-colonized* patients in each group.

The following clinical data were retrieved from the patients' records: date of birth, sex, current age, weight, height, body mass index (BMI), current forced expiratory volume in 1 s (FEV_1), % predicted, age at PCD diagnosis, current PA status (sputum samples obtained by induced sputum, physiotherapy induced sampling and or bronchoalveolar lavage), age at first isolation (FI) of PA, other pathogens at FI, FEV_1 at FI of PA, all pathogens isolated from sputum cultures during each study year, best annual FEV_1% predicted. All chest CT scans evaluated by Brody score analysis during the study period were examined by an experienced radiologist who was blind to the patients' records or by a specifically trained pediatric pulmonologist. Decline of FEV_1% predicted throughout the study period was calculated numerically by subtracting the first best FEV_1 from the last one in the study, divided by the number of years each participant took part in the study. Brody scores were calculated with a slight modification; namely hyperaeration of the lungs was assessed instead of air trapping, because expiratory images could not be obtained from all patients [19].

The study was approved by the hospitals' IRB and informed consent was obtained from the patients or parents.

3. Statistical analysis

Two-sample t-tests and the non-parametric Mann-Whitney tests were used to compare quantitative variables between the study groups. The association between two categorical variables was assessed by the Chi-square test. The significance of the change between two time points for quantitative variables was tested using paired t-tests. All tests were two-tailed, and a p-value of 5% or less was considered statistically significant. Data when normally distributed are presented as means (±SD).

4. Results

Records of 266 patients followed at 11PCD centers were reviewed; 49 were excluded due to a lack of at least 2 sputum cultures during the study period. Thus, the final study cohort was made of 217 patients from 11 CF-PCD centers; 102 of the patients were ≥18 years old at the time of the study.

As shown in Table 1, patients *colonized* with PA were older at the end of the study period than the *non-colonized* group, and were diagnosed at a later age than the *non-colonized* patients. Tables S1–S3 show that analysis according to the more rigorous classification of colonization led to similar results.

Fig. 1 shows the results of sputum cultures for the 217 patients. The most common bacterium grown was *Haemophilus influenza* found in 38–53% of the patients, followed by PA grown from 30 to 35% of the patients. The prevalence of methicillin-sensitive *Staphylococcus aureus* (MSSA) rose during the study period from 13% to 27%; however, there was no significant change in the prevalence of the other bacteria during the same period. Overall, PA was isolated from at least 60/217 (27.6%) patients, of whom 22 patients were <18 years old, and 38 patients were ≥18 years old. At the time of the first PA isolation, 24 out of 60 patients with PA (40%) were also colonized with other pathogens.