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Nocardia Colonization: A Risk Factor for Lung Deterioration in Cystic Fibrosis Patients?

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Background: Cystic fibrosis (CF) patients are predisposed to infection and colonization with different microbes. Some cause deterioration of lung functions, while others are colonizers without clear pathogenic effects. Our aim was to understand the effects of Nocardia species in sputum cultures on the course of lung disease in CF patients.

Material/Methods: A retrospective study analyzing the impact of positive Nocardia spp. in sputum of 19 CF patients over a period of 10 years, comparing them with similar status patients without Nocardia growth. Pulmonary function tests (PFTs) are used as indicators of lung disease severity and decline rate in functions per year is calculated.

Results: No significant difference in PFTs of CF patients with positive Nocardia in sputum was found in different subgroups according to number of episodes of growth, background variables, or treatment plans. The yearly decline in PFTs was similar to that recognized in CF patients. The control group patients showed similar background data. However, a small difference was found in the rate of decline of their PFTs, which implies a possibly slower rate of progression of lung disease.

Conclusions: The prognosis of lung disease in CF patients colonized with Nocardia does not seem to differ based on the persistence of growth on cultures, different treatment plans or risk factors. Apparently, Nocardia does not cause a deterioration of lung functions with time. However, it may show a trend to faster decline in PFTs compared to similar status CF patients without isolation of this microorganism in their sputum.

MeSH Keywords: Cystic Fibrosis • Lung Diseases • Nocardia • Respiratory Function Tests

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Background

Nocardia species are aerobic Gram-positive filamentous bacteria of the Actinomycetes order, which are natural inhabitants of soil and water throughout the world. Pulmonary nocardiosis, the most common clinical presentation of infection, is usually acquired by direct inhalation of contaminated soil. Symptoms may include cough, shortness of breath, chest pain, hemoptysis, fever, night sweats, weight loss, and fatigue. The chest radiograph may be variable with nodular and/or consolidation infiltrate as well as cavitary lesions and pleural effusions. Risk factors for acquisition of infection include depressed cell immunity, but up to one-third of patients are immunocompetent [1–3]. Furthermore, Nocardia may be identified in the respiratory tract without apparent infection. This colonization is encountered in patients with underlying structural lung disease, such as bronchiectasis and CF [4].

Published data on Nocardia in cystic fibrosis is sparse and includes mostly case reports [5–9]. Their conclusion was that isolation of Nocardia spp. from sputum usually represents colonization rather than infection. One larger retrospective study of 17 CF patients with a sputum culture positive for Nocardia spp. [10] showed that treatment of Nocardia-positive sputum in CF has no value in improving pulmonary function.

No data has been published comparing the natural course of cystic fibrosis patients with positive Nocardia sputum cultures to matched CF patients without Nocardia. In our study we describe our patients with Nocardia spp. in sputum over a period of 10 years, comparing the severity of lung disease and the rate of pulmonary function deterioration during the study period between those patients with a single episode of growth to patients with recurrent isolations. We also compare these colonized patients to CF control patients of similar status but without Nocardia growth. Therefore, the aim of the study was to determine if colonization by the bacteria affects the natural history of CF disease.

Material and Methods

Study design

Our study was a longitudinal, paired, case-control study of cystic fibrosis patients with and without isolation of Nocardia spp. in sputum from 2003 until December 2013. We collected all positive sputum cultures for Nocardia spp. in CF patients from our clinic – the Israeli National Center for Cystic Fibrosis, Safra Children's Hospital, Sheba Medical Center Israel – found during the study period, using a laboratory microbiology database. All medical records were reviewed and the following data were collected for analysis: age, sex, CFTR mutations, and co-morbidities such as pancreatic sufficiency, CF-related diabetes, liver disease, allergic bronchopulmonary aspergillosis (ABPA), recurrent distal intestinal obstruction syndrome (DIOS), and hemoptysis. Other sputum cultures were recorded for the colonization of microbes such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus fumigatus,* and *Mycobacterium abscessus*. Pulmonary function test (PFT) recordings using percent-predicted values adjusted for age, sex, and height were obtained at different timepoints. FEV1, FEF25–75, and FVC were primarily obtained during 2003 or the first PFTs found in the patients' files (3 of the 19 patients had first PFTs in the years 2006 to 2009 due to young age or late diagnosis). Next, PFTs were obtained 6 months preceding the first episode of positive Nocardia culture, during the episode and 6 months following it. Additionally, updated PFTs were obtained from 2013 (aside from 1 patient whose last record of PFTs was in 2009 due to lung transplantation). The number of episodes of Nocardia growth was recorded. Each episode was defined as positive sputum cultures for Nocardia separated by 2 months' time, with or without a specific treatment trial. Symptoms of pulmonary exacerbation during the episode were recorded, and the need for hospitalization and antibiotic treatment, either intravenous or orally. Concurrent treatments such as Azithromycin, steroids, and chronic use of inhaled antibiotics were recorded. The use of specific anti-Nocardia antibiotics was reported, as was the duration of treatment. Lastly, number of patients undergoing computerized tomography was observed, as well as pathological findings.

Each patient was then matched with a control cystic fibrosis patient of the same mutation class, age, and sex, but without Nocardia isolation in sputum. Medical records of the control group were reviewed for the same study period as the other member of their matched pair, and similar data were collected for comparison. PFTs were compared as well as the trend of decline during the study period years for of each matched pair.

The study was approved by the Institutional Review Board.

Statistical analyses

Categorical variables were reported using frequency and percentage. Continuous variables were described using mean (SD), median (IQR), and range (min-max). Continuous variables were tested for normal distribution using Kolmogorov-Smirnov, Q-Q plots, and histogram. The comparison between pulmonary function tests 6 months before the first episode, during the episode, and 6 months after the episode was conducted using the Friedman test. The Mann-Whitney test was used to compare between pulmonary function tests of symptomatic patients compared to the others and those treated for Nocardia compared to those not. One-sample Wilcoxon signed rank test was used to evaluate whether the decline of

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FEV1 per year during the study period differed from 1.5–2% (the average mean rate of decline per year for cystic fibrosis patients). Categorical variables were compared using the chi-square test or Fischer's exact test. Paired categorical variables were compared using the McNemar Test, and paired continuous variables were compared using the Wilcoxon signed rank test.

Results

Demographics

Of the 160 CF patients treated at our clinic, 19 (12%) were found to have Nocardia spp. isolated from their sputum at some point during their clinical follow-up during the years 2003–2013. The sex distribution was 13 (68.4%) male patients and 6 (31.6%) females. The mean age at first episode was 20.5 years (SD 10.2), ranging from 8.6 years to 51 years of age. Eleven patients (58%) had only 1 episode of being Nocardia-positive. Six patients had recurrent growth of 3–4 episodes (32%) and 2 patients (10%) were found to have chronic positive sputum for Nocardia until the end of the study period (10–11 episodes). There was no evidence of extra-pulmonary disease or dissemination in any of the patients. There were 53% of patients symptomatic during episodes of Nocardia isolation. The symptoms reported included dyspnea, cough, fever, chest pain, and hemoptysis. Parameters evaluated such as related diseases, chronic antibiotic or steroid treatment, and frequency of additional microbes isolated from sputum of the patients are summarized in Table 1. Sixteen patients (84%) underwent computerized tomography imaging during the study period. All had manifestations of cystic fibrosis, such as bronchiectasis and lymphadenopathy. None had specific lesions attributed to Nocardia.

Medication and antibiotic treatment

Sixty-three percent of the patients were not hospitalized during the episodes of positive Nocardia cultures. Of the patients treated with IV Ceftazidime (37%), Piperacillin-Tazobactam or Meropenem combined with Amikacin, 3 were treated IV for less than 2 weeks and continued treatment orally and 4 received treatment for the duration of 3–4 weeks. Most patients (63%) received antibiotic treatment with Ciprofloxacin during the episodes, for a duration of less than 2 weeks (10%), 3–4 weeks (32%), 1–2 months (16%) or continuously (5%). Other antibiotic treatments such as Fucidic acid, Clarithromycin, Sporanox, or Voriconazole for other indications were given in 37% of the patients. After the isolation, specific anti-Nocardial treatments, such as Cotrimoxazole or Minocycline, were used in only 3 patients (16%), for a duration of over 3 months in 2 of them and 3–4 weeks in 1.

Control group data

A group of control patients paired with the 19 patients with positive Nocardia cultures was formed; they were matched by mutation class, age, and sex (Table 1). The McNemar test was used o check the pairing of background details and confounders between cases and controls.

The sex distribution of the control group was 12 (63.2%) male patients and 7 (36.8%) females. The mean age at the end of the study was 25 years for both groups. Related diseases, chronic antibiotic or steroid treatment, and frequency of additional microbes isolated from sputum of the control group patients are summarized in Table 1. Eleven patients (58%) underwent CT imaging during the study period. All had manifestations of cystic fibrosis, such as bronchiectasis and lymphadenopathy.

No statistical differences were found between the background variables, demographic data, chronic treatments and medications, related diseases, prevalence of other microorganisms in sputum, or findings on CT between the study group and the control group.

Pulmonary function tests

Pulmonary function tests were obtained 6 months previous to the first episode of positive Nocardia culture, during the episode, and 6 months afterwards. No statistically significant difference was found during this year in FEV1 (p=0.5), FVC (p=0.15) or FEF 25–75% (p=0.84).

Moreover, no differences were found in mean changes in PFTs during this year between different groups of patients divided into those who were hospitalized, those receiving steroids, those treated with intravenous or oral antibiotics including azithromycin or ciprofloxacin or anti-Nocardial treatment, those on continuous antibiotic inhalations, and those who were symptomatic compared to patients who were not. In addition, no statistical difference in the change in pulmonary functions between the time of isolation and 6 months afterwards was found when comparing the patients who received intravenous or oral anti-Nocardial treatment to those who did not (FEV1 (p=0.6) FVC (p=0.9) FEF25–75% (p=0.72)).

Comparing PFTs during the episode of symptomatic versus asymptomatic patients, no difference was found in mean FEV1 or FVC. However, a significantly lower mean FEF25–75% was found among the symptomatic patients (35.7% *vs.* 73.3%, p=0.01).

Pulmonary function tests of study group and control patients were obtained at the beginning and at the end of the study period on similar dates for each pair (Figure 1). No statistically significant difference was found between the groups for all

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Table 1. Comparison of background parameters between CF patients with positive Nocardia in sputum (n=19) and CF control patients (n=19).

		Study patients	Control patients
Age (2013)	Mean	25.4 yrs	25.5 yrs
	SD	9.8 yrs	9.4 yrs
Gender	Male	13/19 (68.4%)	12/19 (63.2%)
	Female	6/19 (31.6%)	7/19 (36.8%)
Mutations	ΔF508	11/38 (29%)	15/38 (40%)
	W1282X	8/38 (21%)	10/38 (26%)
	G542X	4/38 (11%)	3/38 (8%)
	Y1092X	1/38 (3%)	0
	W1089X	1/38 (3%)	0
Related diseases	CFRD	6/19 (31.6%)	5/19 (26.3%)
	PS	4/19 (21.1%)	2/19 (10.5%)
	Liver disease	5/19 (26.3%)	2/19 (10.5%)
	Gastrostomy	3/19 (15.8%)	0
	Hemoptysis	2/19 (10.5%)	3/19 (15.8%)
	ABPA	4/19 (21.1%)	3/19 (15.8%)
	Nasal polyps	2/19 (10.5%)	2/19 (10.5%)
	Liver tpt.	1/19 (5.3%)	1/19 (5.3%)
	DIOS	2/19 (10.5%)	2/19 (10.5%)
	Lung tpt.	2/19 (10.5%)	0
Microbes in Sputum	*S. aureus*	7/19 (36.8%)	9/19 (47.4%)
	P. aeruginosa	15/19 (78.9%)	13/19 (68.4%)
	Aspergillus sp.	12/19 (63.2%)	4/19 (21.1%)
	M. abscessus	5/19 (26.3%)	4/19 (21.1%)
Steroid tx.	Inhaled	2/19 (10.5%)	6/19 (31.6%)
	Systemic	6/19 (31.6%)	4/19 (21.1%)
Chronic tx.	Azithromycin tx.	11/19 (57.9%)	14/19 (73.7%)
	Inhaled ABX.	17/19 (89.5%)	14/19 (73.7%)

mean PFTs (FEV1, FVC, FEF 25–75%) at the beginning of the study (79.6% *vs.* 75.4% p=0.39, 87% *vs.* 86% p=1.0, 71.8% *vs.* 57.3% p= 0.07, respectively). The mean decline of PFTs per year during the study period was calculated for both groups of patients, and comparing them showed a trend to significance in FEV1 (–1.87% *vs.* –0.5% p=0.08) and FVC (–1.2% *vs.* +0.2% p=0.09), favoring the patients without isolation of Nocardia. No difference between the groups was found in the decline of FEF 25–75% (–3% *vs.* –1.6% p=0.2).

In the evaluation of PFTs from the beginning and until the end of the study period, no difference was found in the yearly decline rates of PFTs (FEV1, FVC or FEF 25–75%) between patients with a single episode of isolation of Nocardia in culture and those with recurrent episodes (p=0.55, 0.97, and 0.24, respectively). Furthermore, no significant difference was found in the mean rate of decline per year of FEV1 (p=0.72), FVC (p=0.21) or FEF 25–75% (p=0.36) in the years prior to the first positive

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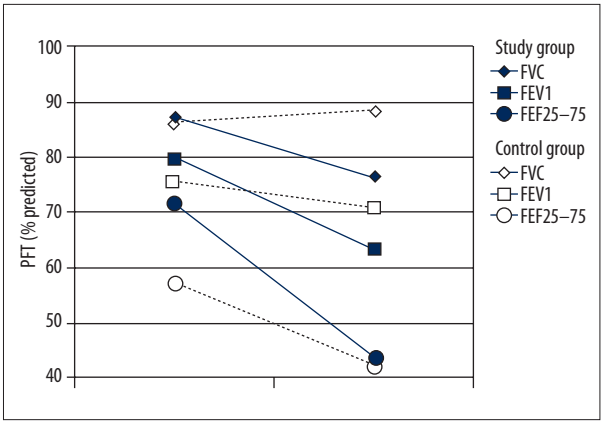

Figure 1. Comparison of mean pulmonary fucntion tests between patients and controls throughout the study period and rate of yearly decline.

Nocardia culture compared to the years following the isolation until the end of the study period.

Discussion

Patients with cystic fibrosis have a predisposition to become colonized and infected by a large array of microbes. Some bacteria, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and *Stenotrophomonas maltophilia,* accelerate the deterioration of pulmonary disease, while others have little or no data to define their role as a pathogen or colonizer in the cystic fibrosis patient, and the benefits of treatment after their isolation is unknown [11,12].

The literature describing Nocardia in CF are mostly case reports, including 1 report describing 3 patients in Australia [5] and a report of 9 patients in Spain [6], which concluded that isolation represents colonization rather than infection. Three more case reports of children with CF and Nocardia isolation were published and found other risk factors for infection, such as corticosteroid treatment for ABPA [7–9]. Most patients described were treated with cotrimoxazole, but the outcomes for the treated versus the untreated patients were similar or unknown [5–9].

To the best of our knowledge, the present study is the first to evaluate such a large cohort of patients, 25% of them carriers of a unique mutation prevalent in Israel (W1282X), for such a long period of time (10 years). We found no statistically significant difference in PFTs before or after the Nocardia isolation. No difference in PFTs were found between patients with a single episode versus those with recurrent Nocardia growth, nor in those treated with antibiotics, some for prolonged periods of time, versus those who were not treated. There was no difference in mean FEV1 or FVC between symptomatic versus asymptomatic patients during the episode, but a significantly lower mean FEF 25–75% was found among the symptomatic patients (35.7 *vs.* 73.3, p=0.01). Regarding this finding, we hypothesized that a graver disease of the smaller airways and perhaps a more parenchymal involvement could result in subjective pulmonary symptomatology.

In this study we expanded the follow-up period and evaluated the changes in pulmonary functions throughout the entire period of 10 years and not only during the year of the episode of Nocardia isolation, realizing that in some cases a bacteria could colonize the lungs without growing in our sputum cultures. Furthermore, we compared our study group patients to paired CF patients with similar status as their peers by mutation class, age, and sex, but no Nocardia isolation, a comparison not carried out until this time. In these patients we found a mean decline of FEV1 per year of –1.87%, similar to the average rate of decline known for CF patients. No difference in the rate of decline was found comparing the period prior to the positive Nocardia culture to the years following the isolation until the end of the study period.

Surprisingly, the mean decline of FEV1 per year for our control group CF patients was -0.5%. Comparing the rates for both groups showed a trend to significance in FEV1 (p=0.08) and FVC (p=0.09), with no difference in FEF25–75% (p=0.2), meaning that the cystic fibrosis patients who had positive sputum cultures with Nocardia declined faster than matched controls without isolation of this microbe. It is possible that this difference was not statistically significant because of the small study group. Since it does not seem that Nocardia causes a deterioration of lung functions, we hypothesized that this microbe might grow more often in patients with more significant lung disease and worse prognosis. Perhaps other genetic or environmental factors affect the lungs of this group of patients or protect the lungs of the "healthier" patients and differentiate them from each other. These factors will need to be studied in larger groups of patients.

In a previous retrospective study from Arizona [10], 17 patients with CF had a sputum culture positive for Nocardia spp. during the years 1997–2007 (of 123 CF patients – 14%), a similar percentage as in our clinic. Several patients had persistent positive Nocardia sputum cultures despite repeated antibiotic courses and did not appear to have different outcomes from the ones with a single isolated culture. As opposed to our center, in Arizona 78% of episodes were treated with antibiotics. Despite this, mean FEV1 and FVC values showed no significant linear trend before, during, and after an episode of positive Nocardia isolation in sputum, which led to the conclusion that treatment likely has no value in improving pulmonary function. Our study strengthens these conclusions of our colleagues.

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Optimal treatment recommendations for pulmonary Nocardiosis have not been firmly established due to variable *in vitro* antimicrobial susceptibility patterns. Sulfonamides have been the antimicrobials of choice since they were introduced 50 years ago [13], but resistance has been described lately in up to 15% of the isolates [14]. Alternative antibiotics used orally are minocycline or doxycycline, while some strains of Nocardia are moderately sensitive to amoxicillin-clavulanate or to fluoroquinolones. Several intravenous antibiotics are also effective against Nocardia such as carbapenems, ceftriaxone, cefotaxime, amikacin, and linezolid. When treating pulmonary Nocardiosis, combination therapy should be considered and a duration of 6–12 months of therapy is recommended. However, as shown in the literature and highlighted in our study, in CF patients the need to treat as well as the duration of treatment is less well defined.

Despite all this, it is believed that Nocardia eradication or a very long period of treatment might be needed in some patients with CF, especially if they are to undergo lung transplantation or are in need of prolonged and high doses of corticosteroids, such as for treatment of ABPA. The reason for this is that the corticosteroids as well as the immunosuppressive regimen during the post-operative period are well-established risk factors for invasive Nocardiosis and disseminated disease that lead to high rate of mortality [15,16].

Indeed, mediastinal mass and pericardial effusion with cardiac tamponade was diagnosed as an invasive Nocardial infection in a renal transplant immunosuppressed patient [17].

There are some limitations to our study. The major limitation is the small study sample, making firm conclusions difficult. However, it is the largest study group assessed so far, to the best of our knowledge. It seems that a multi-center study with more cases could provide more information and better statistics. The retrospective method of our study is another limitation. Accordingly, we significantly expanded the period of follow-up of the patients to the entire study period, enabling us to estimate yearly changes in pulmonary functions. Another limit of our study was the lack of differentiation of Nocardia into different species and establishment of drug sensitivity in our microbiologic laboratory, which could possibly separate the patients into different sub-groups according to the virulence and resistance of the specific microbe.

Conclusions

As shown in the literature, our study supports the fact that Nocardia isolation in sputum of CF patients is usually due to colonization without true infection, and its presence does not significantly affect the natural history or pulmonary deterioration of their lung disease. Furthermore, no difference was found between patients with different risk factors for infection, those who were symptomatic during the episodes of growth and those who were treated accordingly, compared to the others. Therefore, it seems the need for Nocardia treatment should be evaluated on an individual basis and in the context of the clinical picture. Our study found that the rate of decline in lung functions per year in patients of similar status but without isolation of Nocardia showed a slower trend than average for CF patients. It seems possible that these patients have less colonization of different microbes in their sputum, but larger, multi-center studies are needed to confirm this.

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