

Early-Life *Pseudomonas aeruginosa* Infection in Cystic Fibrosis and Lung Disease Progression

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Abstract

Lung disease in cystic fibrosis (CF) starts early, with studies identifying abnormalities on chest computed tomography (CT) scan even in infancy. In this retrospective study, abnormal chest CT was the main outcome; body mass index (BMI) z score and forced expiratory volume percent predicted (FEV₁%) predicted at age 6 to 7 years were secondary outcomes. *Pseudomonas aeruginosa* infection prior to 12 months of age was the main explanatory variable. There was no association between early *P aeruginosa* infection and abnormal CT after adjustment for CFTR (cystic fibrosis transmembrane conductance regulator) functional mutation class, gender, and other pathogens (odds ratio = 0.30; 95% confidence interval = 0.07-1.35; $P = .11$). No significant associations were demonstrated for BMI z score and FEV₁% predicted. Children with class I-III CFTR mutations had increased risk of abnormal CT findings (odds ratio = 11.67; 95% confidence interval = 1.11-115.06; $P = .035$) and lower FEV₁% predicted ($P = .04$). In the current era, early-life *P aeruginosa* infection in CF might not influence the severity of lung disease in school age as much as previously. Larger studies are needed to confirm this finding.

Keywords

cystic fibrosis, lung function, chest CT scan, BMI, *Pseudomonas aeruginosa*, infection

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Background

An increasing body of evidence indicates that cystic fibrosis (CF) lung disease starts very early in life with studies identifying abnormalities on chest computed tomography (CT) scan even in infancy.^{1,2} Patients develop initially transient *Pseudomonas aeruginosa* infections that can be eradicated, but later in life *P aeruginosa* usually persists and chronic infection develops.³ Chronic infection is associated with worse lung function, nutritional status, and abnormal radiographic scores.⁴⁻⁶

These adverse outcomes were reported prior to the era of aggressive eradication treatment of *P aeruginosa* infections.^{5,7} Cohort studies that included patients after the introduction of eradication strategies, such as the study by Amin et al and the EPIC study, demonstrated that *P aeruginosa* infection was not associated with greater decline in lung function and it did not affect annual change of weight and height. However, in these

reports the mean age of initial *P aeruginosa* acquisition ranged between 6.5 and 7.1 years.^{8,9}

Thus, the aim of the present cohort study was to investigate whether infection with *P aeruginosa* during the first year of life was associated with worse findings

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on chest CT, and lower lung function and body mass index (BMI) at the age of 6 to 7 years. The effect of other pathogens, such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Aspergillus* species, which play a role in disease progression, was also taken into consideration.¹⁰

Materials and Methods

Data Collection

The study was conducted at the Aghia Sophia Children's Hospital Cystic Fibrosis Center and was approved by the hospital's institutional review board. Data of children with CF who (a) were 6 to 10 years old at the time of the study, (b) were diagnosed with CF in the first year of life, and (c) had a routine chest CT scan at the age of 6 to 7 years were analyzed. Patients who were diagnosed after the first year of life were excluded.

Data were collected by review of clinic charts. Parameters that were recorded included cystic fibrosis transmembrane conductance regulator (CFTR) genotype, respiratory culture results and antibiotic courses during the first 6 years of life, and chest CT findings at age 6 to 7 along with the closest BMI and forced expiratory volume percent predicted (FEV₁% predicted) measurements. All CT scans were interpreted by a pediatric radiologist, according to standard hospital protocol, and findings consistent with bronchiectasis, bronchial wall thickening, and infiltrates/atelectasis were noted.

CFTR Mutations, Respiratory Cultures, Growth Parameters, and Spirometry

Categorization of CFTR mutations was based on CFTR mutation class, as follows: "minimal CFTR function" when both mutations belonged to classes I to III and "residual CFTR function" when at least one mutation belonged to classes IV to VI.¹¹⁻¹³ Respiratory specimens were obtained at every visit, at least every 3 months, by cough swab or sputum expectoration and were cultured at the clinical microbiology laboratory according to standard operational procedures.^{14,15} All patients with *P aeruginosa* were treated with oral ciprofloxacin, inhaled antipseudomonal antibiotics, and/or intravenous antipseudomonal antibiotics.

Standing height was measured by a stadiometer and body weight by a calibrated scale. BMI was calculated and converted to *z* scores using the World Health Organization AnthroPlus online calculator. Spirometry was completed according to the American Thoracic Society and European Respiratory Society guidelines. Calculation of FEV₁% predicted values was carried out

using the prediction equations by Wang et al for male children aged 6 to 17 years and female children aged 6 to 15 years.¹⁶ For male patients aged ≥ 18 years and female subjects ≥ 16 years the reference values published by Hankinson et al were applied.¹⁷

Primary Outcome Measures and Data Analysis

Presence of abnormal chest CT findings at age 6 to 7 years was the primary outcome measure and BMI and FEV₁% predicted at the same age were secondary outcomes. The time of *P aeruginosa* acquisition (at least one positive culture in the first year of life vs at the age of 2-6 years). Confounding factors that were considered in the statistical analysis were gender, CFTR mutation class, and acquisition (at least one positive culture) of other pathogens, that is, *S aureus*, *H influenzae*, *Stenotrophomonas maltophilia*, and *Achromobacter xyloxidans*.

The associations between the explanatory variable and the outcome measures were explored using logistic regression analysis (chest CT findings) or linear regression (BMI *z* score and FEV₁% predicted). Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) or standardized coefficients. Statistical analysis was completed using SPSS 20 (SPSS Inc, Chicago, IL).

Results

Patients' Characteristics

A total of 45 children with CF were between 6 and 10 years old when the study was conducted, were diagnosed before 1 year of age, and had a routine chest CT scan at the age of 6 to 7 years. Of those children, 65.6% were female, 84.4% carried mutations with minimal function, and 86.66% were pancreatic insufficient. Most patients were diagnosed based on clinical symptoms as newborn screening is not universally performed yet in Greece. Of the 45 children, 12 (26.7%) presented with meconium ileus, 10 (22.2%) with dehydration, 12 (26.7%) with gastrointestinal symptoms or failure to thrive, 4 (8.9%) with respiratory symptoms, while newborn screening led to the diagnosis in 4 (8.9%).

All 45 children had at least one culture positive for *P aeruginosa* during the first 6 years of life. Mean (\pm) BMI *z* score was 0.47 (± 1.25) and mean FEV₁% predicted was 98.1% (50.7% to 130.7%). Mean age for the first *P aeruginosa* acquisition was 19.4 months (3-84). Twenty-five of 45 (55.5%) patients had their first positive culture for *P aeruginosa* during the first year of life.

Table 1. Association Between Early-Life *Pseudomonas aeruginosa* Infection and Abnormal Chest CT Findings at Age 6 to 7 Years (Primary Outcome Measure; Abnormal Chest CT) in Children With Cystic Fibrosis.

	OR	95% CI	P
Gender	1.02	0.26-4.02	.98
CFTR functional class I to III	11.67	1.12-115.06	.04
Other infection at age less than 1 year	1.00	0.17-5.95	.99
<i>Pseudomonas aeruginosa</i> infection at age less than 1 year	0.30	0.07-1.35	.12

Abbreviations: CT, computed tomography; OR, odds ratio; CI, confidence interval; CFTR, cystic fibrosis transmembrane conductance regulator.

Table 2. Associations Between Early-Life *Pseudomonas aeruginosa* Infection and FEV₁% Predicted or BMI z Score).

	Regression Model 1, FEV ₁ % Predicted	P	Regression Model 2, BMI z Score	P
Gender	-0.074	.621	-0.13	.933
CFTR functional class "minimal"	0.315	.040	0.211	.183
Other infection at age less than 1 year	-0.114	.479	-1.037	.306
<i>Pseudomonas aeruginosa</i> infection at age less than 1 year	0.222	.172	-0.150	.882

Abbreviations: FEV₁%, forced expiratory volume percent predicted; BMI, body mass index.

Moreover, 31 (68.9%) subjects had at least one positive culture during the first year of life for any of the following microbes: *S aureus*, *H influenzae*, *S maltophilia*, and *A xyloxidans*.

Associations Between *Pseudomonas aeruginosa* Infection in the First Year of Life and Outcome Measures

The association between *P aeruginosa* acquisition in infancy and chest CT findings was not significant (OR = 0.30; 95% CI = 0.07-1.35; $P = .12$; Table 1). No significant relationships was demonstrated between age at first *P aeruginosa* infection and BMI z score or FEV₁% predicted ($P = .882$ and $P = .172$, respectively; Table 2). CFTR mutation with minimal function was related to increased risk of abnormal chest CT findings and was negatively associated with FEV₁% predicted ($P = .035$ and $P = .04$, respectively; Table 2).

Discussion

In the present study, CFTR mutation with minimal function but not *P aeruginosa* infection during the first year of life was significantly associated with abnormal findings on CT scan at age 6 to 7 years. This finding is in line with the conclusion of the Early *Pseudomonas* Infection Control (EPIC) observational study, which states that in the current era of early treatment of respiratory infection,

genetic determinants might be more important in CF lung disease progression than *P aeruginosa* acquisition.

In the observational arm of the EPIC study, children with CF less than 12 years of age with baseline respiratory cultures negative for *P aeruginosa* were enrolled and were monitored for a mean of 4.6 years. The mean age of subsequent *P aeruginosa* acquisition was 6.5 years and no significant difference was identified in the annual change of FEV₁% predicted or annual change in weight and height between children who acquired *P aeruginosa* and those who remained negative.⁸

Additionally, in a single-center (Toronto), retrospective cohort study of CF patients who were monitored from 1990 to 2007, it was shown that *P aeruginosa* infection was not associated with decreased lung function. The mean age of *P aeruginosa* new infection was 7.1 years and all patients were treated.⁹ Thus, both the EPIC and the Toronto studies involved older patients when compared with those included in the present cohort.

In another large study (AREST CF), isolation of pro-inflammatory pathogens, namely, *P aeruginosa*, *S aureus*, *H influenzae*, *S pneumoniae*, and *Aspergillus* species from bronchoalveolar lavage fluid during the first 2 years of life was not associated with subsequently reduced lung function after adjustment for other risk factors.¹⁰ Nevertheless, there was a relationship of infection due to pro-inflammatory pathogens and neutrophilic inflammation with chest CT findings in infancy.^{2,18}

The patient sample of the current cohort was representative of our center's patient population. Diagnosis was based on clinical manifestations, and patients who were diagnosed after the age of 1 year were not included in the present analysis. We speculate that the absence of an association between early *P aeruginosa* and abnormal chest CT findings in later life can be attributed to the aggressive treatment interventions for eradication. The potential effect of other pathogens on outcomes was explored but it was not significant.

Oropharyngeal swabs were used to obtain the majority of respiratory samples because most patients were too young to expectorate sputum. Even though this is the standard of care, controversy exists as to whether oropharyngeal cultures are representative of the lower respiratory tract flora.¹⁹⁻²¹ Bronchoscopy with bronchoalveolar lavage were not performed for identifying markers of inflammation, which may have an impact on the selected outcomes.

Conclusion

In conclusion, in the current era of aggressive eradication treatments, genetic determinants might be more important than age of first infection for predicting the severity of lung disease, although larger studies are needed to answer this question.

Author Contributions

AP: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

MPT: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AM: Contributed to design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SED: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

IL: Contributed to conception; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AK: Contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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