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Risk Factors for Onset of Persistent Respiratory Symptoms in Children with Cystic Fibrosis

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Abstract

Objectives—To characterize the onset of persistent signs and symptoms of cystic fibrosis (CF) lung disease and identify characteristics that predict onset.

Study design—Patients in the Epidemiologic Study of CF who were <4 years of age at enrollment and had 2 years of follow-up were included. We defined persistence as a sign or symptom that was present during two consecutive encounters separated by 60–365 days, and persistent clubbing as 50% of encounters with clubbing within 365 days. Predictors were assessed in a Cox proportional hazards model for age at first occurrence of each symptom.

Results—Each sign or symptom met the criterion of persistence in a substantial proportion of patients during a follow-up period of 7 ± 3 years (mean $\pm$ standard deviation; range 2–12). Risk

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factors that predicted earlier onset of signs and symptoms included pancreatic enzyme use, *Pseudomonas aeruginosa* infection, and prior diagnosis of asthma. Other risk factors had variable effects on signs and symptoms.

Conclusions—Signs and symptoms of lung disease begin early in CF. Risk factors previously reported for lower forced expiratory volume in 1 second are also associated with earlier onset of persistent signs and symptoms of CF lung disease, but their impact varies.

Keywords

symptom onset; cough; child health index; *Pseudomonas aeruginosa*

INTRODUCTION

Cystic fibrosis (CF) lung disease is variable in both onset and rate of progression. There is clear and growing evidence that lung disease is present in the first few years of life in children with CF, as demonstrated by abnormalities in infant pulmonary function tests¹ and by air trapping and bronchiectasis on computed tomographic imaging of the chest.² Bronchiectasis is seen in older children with CF who have normal forced expiratory volume in 1 second (FEV₁).³ In spite of advances in our understanding of early CF lung disease, there is limited information about the onset of common clinical signs and symptoms. Understanding the typical age of onset of signs and symptoms, as well as risk factors predicting onset of signs and symptoms, has implications for primary care and specialty clinicians, families, and researchers.

We performed an analysis of the Epidemiologic Study of Cystic Fibrosis (ESCF) to assess the average age of onset of key signs and symptoms of CF lung disease and to describe risk factors for early onset of these signs and symptoms. We previously showed that a substantial proportion of young children with CF have signs and symptoms of lung disease, including cough, sputum production, clubbing, crackles, and wheezing.⁴ We hypothesized that specific risk factors for these signs and symptoms could be identified prior to onset. Because our interest was in persistent signs and symptoms, we did not consider transient episodes to represent the onset, and instead focused on “persistent” signs and symptoms.

METHODS

ESCF was a prospective, multicenter, encounter-based, longitudinal observational study designed to characterize the natural history of CF in a large population of patients in the US and Canada from 1994 through 2005.⁵ Data collected on each patient included demographics, growth and nutritional status, pulmonary signs and symptoms, therapies, microbiology, and pulmonary function. The study was approved by the Copernicus Group institutional review board (tracking number OVA1-03-008) or by local institutional review boards, and participants or their guardians provided informed consent.

We included in this analysis patients who were <4 years of age at enrollment in ESCF and had 2 years of follow-up data with at least one encounter in each of the first 2 years. The date of onset of persistent signs or symptoms was defined as the date of the first encounter

that was then followed by confirming encounters that indicated persistence of these signs or symptoms during the study period. Because cough, sputum, crackles, and wheezing can be signs of acute illness that may resolve over a period of weeks, we defined persistence as at least one confirming encounter within 60–365 days of the first encounter at which that sign or symptom was recorded. In the case of cough and sputum, where frequency was reported as none, occasional or daily, we required that the symptom be “daily” to be considered present at that encounter. Clubbing is usually a permanent change that is nevertheless subject to a clinician’s observation; in ESCF, there was no specific site investigator training for assessment of clubbing. For this reason, we defined persistent clubbing as the presence of clubbing at 50% of encounters within 365 days of the first encounter with documented clubbing.

Risk factors that might predict the onset of signs or symptoms were chosen a priori and were assessed in a multivariable model for each sign or symptom. In addition to demographic and clinical variables, we included two variables associated with the patient’s site of care. To examine whether the onset of persistent signs or symptoms was related to pulmonary function outcomes at the site of care, sites were ranked by mean FEV₁ quartile for patients age 6–12 years for the years 2001–2003 to assess the predictive value of site quartile. The top quartile (25% of sites with the best FEV₁ in this age group) was used as the reference quartile. As a measure of other geographic and social factors associated with the site, we included the Child Health Index (CHI), a state-based ranking system derived from a composite score of physical health (including percentage of low-birth-weight infants, infant mortality rate, child death rate, teen death rate, and teen birth rates). The index ranges from negative through positive numbers; a higher number is associated with better overall child health.⁶ In addition, year of birth was included in the model because we have previously reported that the prevalence of signs and symptoms is decreasing in the CF population.⁷ Age at diagnosis and genotype were not included in the model because of substantial missing data.

Potential risk factors were assessed by means of Cox proportional hazards regressions for age at onset in a separate model for each of the five signs and symptoms. Time-varying covariates included binary indicators of whether a specific condition had ever been present (eg, asthma, liver disease, or pancreatic enzyme use as an indication of pancreatic insufficiency) and whether the patient ever had a positive respiratory tract culture for specific organisms. Respiratory cultures could be sputum or throat, but these sources were not reliably captured in ESCF. Conditions that were not marked as present were assumed to be absent. The collection of diagnostic information was changed to obtain more detail in 2003–2005. For patients not enrolled (or re-enrolled) in 2003–2005, only the less detailed information was available.

Because we assumed that the encounter or culture dates underlying the time-varying covariates occurred some point after the actual onset of the observed condition or microorganism, we chose to date the onset as 30 days prior to first observation in ESCF. This avoids the technical difficulty of estimating a very high hazard ratio because the outcome appears to occur immediately after appearance of a risk factor. The Cox models used backward stepwise selection, keeping predictors with a coefficient *P* value < 0.01.

Figures were generated to show the hypothetical effect of risk factors on age of onset of persistent signs or symptoms. For time-varying covariates, these show the effect as though a patient always or never had the condition. To avoid distortion from the fact that patients cultured very soon after birth were generally sick (eg, hospitalized because of meconium ileus), the small number of patients with positive cultures for *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* obtained within 30 days of birth were omitted.

All statistical analyses were performed using SAS Version 9.1 or later (SAS Institute, Inc., Cary, NC). No adjustment was made for multiple comparisons. Instead, a conservative *P* value of 0.01 was used. It is reasonable to consider each outcome separately in this context.

RESULTS

A total of 6784 eligible patients were included. Demographic data and age at enrollment are shown in Table 1; of note, the average age of enrollment was just under 1.5 years. The duration of follow-up was 7.15 ± 3.02 years (mean $\pm$ standard deviation; range 2–11.96 years). The mean number of visits during this period was 33.5 (median, 30), or 4.8 visits per year. The cumulative proportion of patients with persistent symptoms is shown in Figure 1. The most common persistent symptom was cough; this occurred in 82% of patients and had a median age of onset of 2.3 years.

Results of the Cox proportional hazards models are shown in Table 2. For each outcome, the factors included in the model are each adjusted for the effect of the other variables in the model. This means that coefficients should be interpreted carefully, especially for related variables such as “diagnosis by liver problems” and “liver disease before symptom onset” or “diagnosis by intestinal obstruction/meconium ileus” and “diagnosis by GI problems.” The influence of several risk factors on the estimated cumulative proportion of patients experiencing a persistent symptom is shown in Figure 2.

A number of statistically significant risk factors predicted earlier age at onset of signs or symptoms. Insurance by Medicaid, presence of *P. aeruginosa* on respiratory tract cultures, and diagnosis of asthma were risk factors for early persistence of all signs and symptoms studied. Site FEV₁ quartile below the reference (best) quartile was, in general, a risk factor for early onset of symptoms, but there was no distinct pattern of effect. For example, attending a site in the lowest quartile was a risk factor for onset of sputum and crackles, whereas attending a site in the quartile just above the lowest was a risk factor for cough, sputum, and crackles. Residence in a state with higher CHI, indicating better health status in children, was protective against onset of cough but did not affect other signs or symptoms.

Presence of *P. aeruginosa* in respiratory tract cultures increased the risk for early onset of cough, sputum, clubbing, crackles, and wheezing. *S. aureus* showed a similar increased risk for all of these except for wheezing. The presence of *P. aeruginosa* and *S. aureus* concurrently on a single respiratory tract culture increased the risk of all symptoms. Other risk factors were significant only for a single sign or symptom, such as the association between liver disease at diagnosis and the onset of clubbing.

Diagnosis by newborn screening was protective against the early onset of wheezing; however, it should be noted that only a small percentage of the cohort (18.4%) was diagnosed by newborn screening. The detection of *S. aureus* and *P. aeruginosa* on different respiratory tract cultures decreased the risk for early onset of sputum, clubbing, and crackles. Later year of birth was also protective.

DISCUSSION

These data demonstrate that there is a significant symptom burden early in life from CF lung disease. A substantial proportion of young children with CF develop cough, sputum production, clubbing, crackles, and/or wheezing by the age of 5 years. A number of demographic and clinical variables predict the earlier onset of one or more signs and symptoms. Some of these risk factors are well known to be associated with earlier morbidity and or mortality in CF.⁷⁻¹⁰ Other risk factors were significant only for a single sign or symptom, such as the association between liver disease at diagnosis and the onset of clubbing, and may be due to chance.

The most common persistent sign or symptom was cough, which had earlier onset than persistent sputum production, crackles, or clubbing. These results are consistent with previous studies that have identified cough as an early feature of CF lung disease.^{4,11,12} Farrell et al described onset of frequent cough in half of infants by 10.5 months of age in a prospectively evaluated cohort of infants with CF diagnosed by newborn screening.¹¹ Furthermore, cough was associated with worse chest radiograph scores in this cohort. In a prior analysis of ESCF, we found that 72% of 3-year-olds had occasional or daily cough, and that the presence of cough at age 3 predicted decreased pulmonary function at age 6.⁴ These findings emphasize that it is important for clinicians to query families closely about this symptom. Persistent wheezing was also an early finding in a substantial proportion of children. The clinical impact of early onset of wheezing in CF is unclear.

The demographic variables associated with earlier onset of symptoms have been previously shown to impact morbidity and mortality. Some risk factors for onset of signs and symptoms cannot be modified by care site practices, but have implications for monitoring and care of at-risk patients. Female sex has been associated with earlier mortality in children with CF,^{8,13} a finding that has persisted over time,¹⁴ though a recent study from a single CF program did not show this “gender gap”.¹⁵ Medicaid insurance is a proxy for low socioeconomic status that has been associated with worse nutritional status, worse lung function, more hospitalizations, and increased mortality¹⁰; measuring low socioeconomic status with median income by zip code also shows an increase in mortality.¹³ Hispanic ethnicity is a risk factor for morbidity and mortality even after adjustment for socioeconomic status.^{13,16} The exact mechanisms of how biological, social, economic, and health care system factors contribute to these disparities are not well elucidated, but could provide targets for intervention.

While we predicted that the CHI, which reflects overall child health in a state, might independently predict onset of signs and symptoms, it was limited in its predictive value. Components of the CHI include percent of low-birth-weight infants, infant mortality rate,

child and teen death rates, and teen birth rate, which may not reflect environmental or health care system factors that impact early symptom development in young children with CF.

Site quartile FEV₁ ranking had some value in predicting age at onset of symptoms. In comparison with sites in the highest quartile for FEV₁, sites in lower quartiles had a higher rate of cough, sputum production, and crackles. The finding of more frequent onset of signs and symptoms at sites with lower FEV₁ in 6- to 12-year-olds may indicate differences in care practices in infants and young children who later have worse pulmonary function; while practice patterns were not studied in this analysis, we previously showed that infants at ESCF sites that later had better pulmonary function outcomes had more frequent respiratory tract cultures and were more frequently treated with intravenous antibiotics.¹⁷

Diagnostic presentation had a limited impact on the onset of signs and symptoms in this cohort. Since the cohort was ascertained prior to the advent of widespread newborn screening for CF, the sample size is inadequate to truly assess the impact of newborn screening on sign and symptom development. Patients diagnosed by newborn screening had a reduced risk of wheezing but not a reduction in other signs and symptoms. The study of Farrell et al¹¹ showed early onset of symptoms even in a screened cohort, but, it is still possible that widespread newborn screening will lead to a reduction of respiratory signs and symptoms. For example, management of *P. aeruginosa* infection has changed dramatically over time, with the advent of chronic suppressive inhaled antibiotic therapy and, more recently, widespread adoption of eradication therapy after first or recurrent infection.

The finding that pancreatic insufficiency was a predictor for 4 out of the 5 signs and symptoms was not surprising, since it is well known that pancreatic-sufficient patients have a milder disease course. The diagnosis of asthma prior to persistent wheezing is more difficult to explain. If clinicians did not indicate the diagnosis of asthma until after the onset of persistent wheezing, asthma would not be a predictor in the proportional hazards models (it would not be recorded until on or after the onset of wheezing). We hypothesize that, in cases where asthma precedes persistent wheezing, clinicians made a diagnosis of asthma in connection with one or more episodes of wheezing that did not occur during two consecutive encounters. We previously found that wheezing in 6- to 17-year-olds with CF was associated with a slower rate of FEV₁ decline and speculated that this may represent a tendency of clinicians to provide additional therapies to patients who are wheezing.⁹

Among potentially modifiable risk factors, respiratory tract cultures detecting *P. aeruginosa* and *S. aureus* increased the risk of all signs and symptoms. For patients who had positive cultures for both organisms, differences in persistent signs and symptoms occurred depending on whether patients had concurrently positive cultures, which conferred risk for crackles and sputum but protected against persistent cough, or sequentially positive cultures, which was protective. A biological reason for these unexpected findings is unlikely. It is possible that intermittent positive cultures represented oropharyngeal carriage of organisms; ESCF could not reliably differentiate throat swab from sputum specimens, and many young children with CF are unable to produce expectorated sputum samples.¹⁸ We speculate that antibiotic treatment may have played a role in the apparent protective role of concurrently positive cultures for *S. aureus* and *P. aeruginosa*. Furthermore, increased culture frequency

may have led to more organism detection, and treatment, in children with sequential positive cultures. *Haemophilus influenza*, a risk factor for pulmonary function decline in adolescents with CF,¹⁹ was a risk factor only for clubbing and did not impact other signs and symptoms. Overall, the relationship between respiratory tract pathogens and outcomes appears complicated and undoubtedly is confounded by treatment, which was not assessed in this study.

This study has several limitations. While the definition of onset of “persistent” signs or symptoms required a confirmatory visit, at least 60 days after the finding was noted, to avoid the effects of multiple visits in a short time for an acute illness, we recognize that meeting this definition of persistent signs or symptoms does not imply chronicity or permanence. ESCF was an encounter-based study and therefore data are less robust than, for example, a daily symptom diary. In order to meet inclusion for persistent cough, “daily” cough had to be reported; however, since ESCF was designed to collect data concurrent with clinical care, there is likely variability in the reporting of these signs and symptoms. Furthermore, there are differences in the number of patient visits, respiratory tract cultures, and collection of other data at both the site and patient level. This is a limitation of any encounter-based observational study, but such studies are the only practical way to obtain very large patient numbers and reflect clinical reality. This study did not evaluate therapies as predictors, even though some therapies may delay the onset of persistent signs and symptoms.

In summary, this analysis has examined the age of onset of persistent signs and symptoms of lung disease in a large observational study of young children with CF in North America. There is growing recognition of significant structural and functional abnormalities in the lungs of infants and young children with CF; however, they are not necessarily predictive of the onset of signs and symptoms. We have identified a number of demographic and clinical variables that predict the onset of signs and symptoms. Clinicians can use these variables to identify young children who are at risk of onset of persistent symptoms and could therefore benefit from earlier intervention using currently available therapies. Furthermore, signs and symptoms are common enough in early life that they could be considered as outcome measures in clinical trials of CF therapies for infants and young children.

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ABBREVIATIONS

ABPA	allergic bronchopulmonary aspergillosis
CF	cystic fibrosis
CHI	Child Health Index
CI	confidence interval

ESCF	Epidemiologic Study of CF
FEV₁	forced expiratory volume in 1 second
GI	gastrointestinal
HI	<i>Haemophilus influenzae</i>
HR	hazard ratio
PA	<i>Pseudomonas aeruginosa</i>
SA	<i>Staphylococcus aureus</i>

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Fig. 1. Cumulative percentage of patients reaching onset of persistent symptoms, by age 0 to 15, for cough, crackles, sputum, wheezing, and clubbing.

Fig. 2.

Hypothetical cumulative percentage of patients reaching onset of persistent symptoms according to risk factors, by age 0 to 15. Panel A: Daily cough by risk factors PA (*Pseudomonas aeruginosa*), asthma, Medicaid status, pancreatic enzymes. Panel B: Daily sputum by risk factors PA, asthma, Medicaid status, Site Quartile 1 (sites with best FEV1). Panel C: Wheezing by risk factors PA, asthma, Medicaid status, pancreatic enzymes. Panel D: Clubbing by risk factors PA, asthma, pancreatic enzymes, liver disease.

Table 1

Demographic Characteristics

Patient characteristic	
Age at enrollment, years	1.4 ± 1.2
Female, n (%)	3360 (49.5)
Pancreatic enzyme use, n (%)	6621 (97.6)
Race/ethnicity, n (%)	
Non-Hispanic white	5818 (85.8)
Hispanic white	594 (8.8)
Hispanic non-white	7 (0.1)
Non-Hispanic non-white	10 (0.2)
Other	355 (5.2)

Table 2A
Results of Multivariable Modeling of Risk Factors for Early Onset of Signs and Symptoms: Demographic Characteristics^a

	Cough		Sputum		Clubbing		Crackles		Wheezing	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Female			1.23 (1.14, 1.33)				1.21 (1.11, 1.33)			
Year of birth			0.96 (0.95, 0.98)				0.95 (0.93, 0.97)		0.95 (0.92, 0.97)	
Hispanic			1.48 (1.31, 1.67)		1.21 (1.05, 1.39)		1.52 (1.32, 1.74)		1.31 (1.10, 1.56)	
Medicaid		1.20 (1.13, 1.28)	1.35 (1.25, 1.46)				1.38 (1.26, 1.51)		1.34 (1.20, 1.51)	
Child Health Index		0.94 (0.91, 0.97)								
Center Quartile 1			1.37 (1.23, 1.54)				1.40 (1.25, 1.57)			
Center Quartile 2		1.10 (1.03, 1.18)	1.42 (1.28, 1.57)				1.18 (1.06, 1.31)			
Center Quartile 3			1.18 (1.06, 1.30)							
Center Quartile Unknown (center had few child patients 2001–2003)							1.36 (1.09, 1.70)			

^a Statistically significant predictors included in any of the five models had $P < 0.01$. CI, confidence interval; HR, hazard ratio.

Results of Multivariable Modeling of Risk Factors for Early Onset of Signs and Symptoms: Diagnostic Presentation^a

Table 2B

	Cough		Sputum		Clubbing		Crackles		Wheezing	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Diagnosis by screening									0.75 (0.64, 0.88)	
Diagnosis by liver problems ^b					1.95 (1.24, 3.06)					
Diagnosis by intestinal obstruction/meconium ileus ^b					0.80 (0.69, 0.93)					
Diagnosis by GI problems ^b					0.74 (0.63, 0.86)					
Diagnosis by nutritional insufficiency ^b	1.18 (1.09, 1.29)		1.21 (1.09, 1.34)							
Diagnosis by respiratory problems ^b					1.12 (1.03, 1.22)		1.24 (1.11, 1.39)			
Diagnosis by symptoms ^c							1.40 (1.20, 1.65)			

^aStatistically significant predictors included in any of the five models had $P < 0.01$.

^bPatients enrolled or re-enrolled during 2003–2005 had information on all diagnostic categories presented.

^cPatients enrolled during 1994–2002 but not re-enrolled during 2003–2005 had limited information, only diagnostic categories. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio.

Table 2C
Results of Multivariable Modeling of Risk Factors for Early Onset of Signs and Symptoms: Clinical Characteristics^a

	Cough		Sputum		Clubbing		Crackles		Wheezing	
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Pancreatic enzyme usage before symptom onset	1.75 (1.47, 2.10)				2.20 (1.56, 3.10)		1.64 (1.13, 2.37)		2.20 (1.44, 3.37)	
Asthma before symptom onset	1.60 (1.48, 1.73)		1.45 (1.34, 1.58)		1.16 (1.06, 1.27)		1.51 (1.38, 1.66)		2.95 (2.61, 3.33)	
Liver disease before symptom onset					1.28 (1.12, 1.46)		1.23 (1.08, 1.41)			
ABPA before symptom onset							1.68 (1.25, 2.24)		1.91 (1.26, 2.89)	
HI before symptom onset					1.15 (1.06, 1.26)					
SA before symptom onset	1.23 (1.15, 1.32)		1.36 (1.20, 1.54)		1.35 (1.20, 1.53)		1.37 (1.18, 1.59)			
PA before symptom onset	1.53 (1.41, 1.65)		2.06 (1.80, 2.35)		1.38 (1.20, 1.58)		2.01 (1.72, 2.36)		1.37 (1.21, 1.55)	
SA + PA concurrently before symptom onset	0.86 (0.77, 0.96)		1.21 (1.07, 1.37)				1.39 (1.20, 1.61)			
SA and PA (not necessarily concurrent) before symptom onset			0.74 (0.61, 0.89)		0.80 (0.67, 0.94)		0.74 (0.59, 0.92)			

^a Statistically significant predictors included in any of the five models had $P < 0.01$.

ABPA, allergic bronchopulmonary aspergillosis; CI, confidence interval; HI, *Haemophilus influenzae*; HR, hazard ratio; PA, *Pseudomonas aeruginosa*; SA, *Staphylococcus aureus*.