COMPLICATIONS ASSOCIATED WITH SYMPTOMATIC DIAGNOSIS IN INFANTS WITH CYSTIC FIBROSIS

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Objective To determine the complication and hospitalization rates in children with cystic fibrosis (CF) by mode of diagnosis.

Study design Newly diagnosed cases of CF were identified from the Cystic Fibrosis Foundation National Patient Registry for 2000 through 2002. Cases were categorized as symptomatic diagnosis (SYMP; n = 1760), prenatal diagnosis (PRE; n = 66), diagnosis by means of newborn screening (NBS; n = 256), or presentation with meconium ileus (MI; n = 484). Complications were defined for the calendar year of diagnosis as stunting (length <3rd percentile), wasting (weight <3rd percentile), positive *Pseudomonas aeruginosa* culture results, and hypoelectrolytemia or edema and hypoproteinemia.

Results For infants (age <12 months), 70% of patients with SYMP had at least 1 complication or hospitalization, compared with 29% for patients with NBS diagnosis ($P < .0001$). Cross-sectional data for 2002 showed that patients with SYMP had significantly more complications compared with patients with NBS diagnosis as old as 20 years. When compared with patients with NBS diagnosis, patients with SYMP had increased mucoid *P aeruginosa* ($P < .05$) and decreased pulmonary function as assessed by means of forced expiratory volume in 1 second ($P < .01$).

Conclusions SYMP of CF is associated with increased complication rates throughout infancy, childhood, and adolescence when compared with NBS diagnosis. *(J Pediatr 2005;147:S37-S41)*

Cystic fibrosis (CF) is a common, inherited condition characterized by elevated sweat electrolyte levels, exocrine pancreatic insufficiency, and *Pseudomonas aeruginosa* lung infection in most patients.[1] Numerous complications can occur in affected individuals. Sweat electrolyte loss can lead to hypoelectrolytemia, often accompanied by seizures.[2] Exocrine pancreatic insufficiency commonly leads to malnutrition accompanied by stunting and wasting and occasionally leads to severe protein-calorie malnutrition characterized by hypoalbuminemia and edema.[1,3] Exocrine pancreatic insufficiency can also lead to severe nutrient deficiency.[4,5,6] *P aeruginosa* lung infection leads to progressive airways damage and respiratory morbidity.[7] All these complications frequently occur in infancy and early childhood in patients in whom CF has not been diagnosed.

Several lines of evidence suggest that early diagnosis accompanied by care at a specialized CF center could prevent or ameliorate these complications. Sweat electrolyte abnormalities and exocrine pancreatic insufficiency occur in most patients by 2 months of age, providing a physiologic basis for early treatment.[8] Nutritional benefits of early diagnosis through newborn screening (NBS) versus symptomatic diagnosis (SYMP) include less stunting and wasting in the early diagnosis group.[9] The importance of growth in infants with CF has been underscored in recent studies linking improved growth to better pulmonary outcome.[10] Also, data are accumulating that treatment of *P aeruginosa* in young infants is feasible.[11] All these points suggest benefit from early diagnosis and treatment. However, in at least 1 study[12] early diagnosis through NBS was associated with

CF	Cystic fibrosis	NBS	Newborn screening
FEV_1	Forced expiratory volume in 1 second	PRE	Prenatal diagnosis
IQR	Interquartile range	SYMP	Symptomatic diagnosis
MI	Meconium ileus		

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Table I. New diagnoses of cystic fibrosis on the basis of the Cystic Fibrosis Foundation Patient Registry for 2000 to 2002

Means of diagnosis	2000	2001	2002	Total
All new diagnoses (<20 years)	825	894	847	2566
SYMP	583	607	570	1760
SYMP 1-20 years	304	342	295	941
SYMP <1 year	279	265	275	819
NBS	62	80	114	256
NBS 1-20 years	4	4	3	11
NBS <1 year	58	76	111	245
MI	161	185	138	484
MI 1-20 years	12	15	13	40
MI <1 year	149	170	125	444
Prenatal	19	22	25	66
Prenatal 1-20 years	0	0	0	0
Prenatal <1 year	19	22	25	66

increased risk of positive *P aeruginosa* culture results and worse chest radiography scores compared with SYMP.

Although most patients with CF are identified after symptoms appear, there is little information about rates of complication in children with SYMP compared with children in whom CF is diagnosed by other means. Accordingly, we examined data from the CF Foundation National Patient Registry to determine complication rates in patients in whom CF was diagnosed symptomatically, through NBS, with prenatal diagnosis (PRE), or presentation with meconium ileus (MI), an intestinal obstruction usually present soon after birth.[1] We examined complications of CF, including stunting, wasting, and respiratory tract culture results positive for *P aeruginosa*, and hospitalizations and days hospitalized by mode of diagnosis. In addition, we examined presentation with electrolyte imbalance or edema and hypoproteinemia, 2 severe complications of CF. We focused particularly on complications in infancy, because disruption of growth in infants has immediate and long-term consequences and because complications are potentially preventable with early diagnosis and treatment of exocrine pancreatic insufficiency and electrolyte imbalance. Finally, to begin to examine long-term effects of mode of diagnosis, we performed a cross-sectional comparison of complications in all patients <20 years old.

METHODS

Patient Population

The source of our patient population was the CF Foundation National Patient Registry for the years 2000, 2001, and 2002. This registry has been used for previous epidemiologic investigations of CF.[10] The number of cases available for analysis is shown in Table I. Twenty-three patients could not be placed into a diagnostic category because of insufficient information and are therefore excluded from the analyses.

Definition of Complications

The registry provides specific information required to classify the diagnosis of patients by SYMP, NBS, PRE, or MI. The registry also includes data on complications of CF. The registry provides the "best" length and weight in the calendar year. We defined stunting as length less than the third percentile for age and wasting as weight less than the third percentile for age. Specific information about symptoms present at first CF work-up or present at diagnosis is also included in the registry. "Electrolyte imbalance" and "edema and/or hypoproteinmia/hypoalbuminemia" are 2 specific complications recorded in the registry at the time of diagnosis. The registry also provides information about *P aeruginosa*- and mucoid *P aeruginosa*-positive culture results, number of hospitalizations, and days hospitalized. We categorized *P aeruginosa*-positive culture results as "any *P aeruginosa* (nonmucoid or mucoid)" and "mucoid *P aeruginosa*." Pulmonary function data for forced vital capacity and forced expiratory volume in 1 second (FEV_1; both absolute values and percent predicted) are available. We also performed a cross-sectional study of complications recorded in all patients younger than 20 years using the 2002 registry report. The 2002 registry report listed 1028 patients in the 0-to-1-year range, 2732 in the 2-to-5-year range, 3895 in the 6-to-10-year range, and 6992 in the 11-to-20-year range, for a total of 14647 patients. The age at death and the proportion of patients within each group who died were compared across diagnostic groups.

Statistical Analysis

The SAS System for Windows (version 8.02, Carey, NC) was used for all statistical analyses. Ninety-five percent confidence intervals were determined through normal approximation to the binomial distribution. Rates of complications were compared between modes of diagnosis by means of chi-square analysis or Fisher exact test when appropriate. Means were compared by using analysis of variance, with linear contrasts to test specific comparisons between groups. Odds ratios (ORs) and adjusted ORs are presented with 95% CIs. Adjusted ORs were calculated by using logistic regression in a step-forward manner. Formal statistical testing is presented for NBS diagnosis versus SYMP. We also performed statistical testing between the SYMP group and a "pre-symptomatic group" consisting of NBS diagnosis and PRE. Comparisons of pulmonary function data were adjusted for height and age. *P* values <.05 were considered to be significant. Data are presented as medians with interquartile (25th-75th) range (IQR) or means plus SE.

RESULTS

Age at Diagnosis

The median age at diagnosis of all new cases was 5.3 months (IQR, 0.7-38.0 months). The median age of diagnosis with SYMP was 14.5 months (IQR, 4.2-65.0 months). The