Delayed Diagnosis of US Females with Cystic Fibrosis

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Received for publication August 28, 2001; accepted for publication March 15, 2002.

This study was conducted to examine a patient’s age and condition at the time of diagnosis as one potential factor contributing to the “gender gap” in cystic fibrosis. The study population consisted of 11,275 US patients diagnosed during 1986–1998 and reported to the Cystic Fibrosis Foundation Registry in the same or the following calendar year. Parallel analyses were performed for Wisconsin patients identified prospectively during 1985–1994 to obtain more detailed information on their condition at diagnosis. Analyses of the registry data showed that females identified because of symptoms other than meconium ileus were diagnosed at significantly older ages (median, 12.7 months) than were males (median, 8.7 months) (p < 0.001). The delay in diagnosis for females was most evident among patients presenting with respiratory symptoms only (median, 40.7 vs. 22.3 months; p < 0.001). Analyses of Wisconsin patients demonstrated no significant gender differences in cough and wheezing experiences or in chest radiographic severity scores between males and females during their first 10 years of life, although a disproportionately high number of males were referred for diagnostic sweat testing. A delay in diagnosis of females with cystic fibrosis was discovered, suggesting either differential recognition of respiratory symptoms or a gender bias. Am J Epidemiol 2002;156:165–73.

age of onset; cough; cystic fibrosis; diagnosis; lung diseases; neonatal screening; sex

Abbreviation: CF, cystic fibrosis.

Cystic fibrosis (CF) is a life-threatening, autosomal-recessive disorder with variable manifestations and severity. Most patients have intestinal malabsorption, and virtually all develop lung disease (1). Long-term clinical outcomes vary depending on factors such as age at diagnosis, genotype, extent of gastrointestinal abnormalities, degree of malnutrition, and severity of pulmonary disease (2–9). In addition, a variety of studies have shown that life expectancy is shorter in females compared with males with CF (2–5, 10–13). This “gender gap” has been observed among CF patients in Canada (2, 3), the United States (4, 10, 11), and the United Kingdom (12, 13). The relation between gender and mortality associated with CF has been repeatedly examined in the past, and many potential risk factors have been suggested (2–4, 10, 13–15). The largest known study (10) to date examining the gender issue used data from the 1988–1992 CF Foundation Registry and identified nutritional status, pulmonary function, and Pseudomonas aeruginosa colonization as predictors of mortality; however, these factors were unable to explain the observed gender difference in survival. In another study (14), females were found to be infected with mucoid P. aeruginosa 1.7 years earlier than males, and this observation was hypothesized to partially explain the gender gap in CF.

We have shown, in a randomized clinical trial of newborn screening, that early diagnosis leads to better nutritional status (16–18), and observational studies by others (19, 20) suggest less severe lung disease as well. These findings imply that age at diagnosis may be important in predicting clinical progression and survival of patients with CF, although no convincing data have been reported to demonstrate that delayed diagnosis is an independent risk factor for mortality or lung disease outcome. Surprisingly little has been done to analyze the age and condition of patients at the...
time of diagnosis as one potential factor contributing to the gender gap. In the present study, we examined age and mode of presentation in relation to gender at the time of CF diagnosis for patients diagnosed during 1986–1998 and reported to the CF Foundation Registry in the same or the following calendar year, and we compared the results with observations on patients identified through neonatal screening in Wisconsin.

MATERIALS AND METHODS

Sources of data

The CF Foundation Registry documents the diagnosis and annual follow-up evaluations of CF patients who are seen at accredited centers in the United States, as described in detail elsewhere (4). Although this registry was initiated in the early 1970s, the data have been more reliable since the mid-1980s because of more consistent reporting and quality control mechanisms. For the present study, CF Foundation Registry data for the years 1986–1998 were obtained. Wisconsin patients documented in the registry were excluded because separate analyses were performed, as described below. Among the 26,067 non-Wisconsin patients reported to the 1986–1998 CF Foundation Registry, 13,636 were patients diagnosed prior to 1986 (year-of-diagnosis range, 1944–1985) and receiving ongoing care, and 12,431 were new CF cases diagnosed during 1986–1998. The 13,636 patients diagnosed prior to 1986 were excluded from the present study because of two considerations. First, data on their conditions at the time of CF diagnosis were either missing or may be unreliable, which was particularly evident for patients diagnosed prior to 1980. Second, the 13,636 patients diagnosed prior to 1986 represent those who survived at least to 1986; therefore, data from this population regarding the age and condition of diagnosis are biased because of survival effect.

Of the 12,431 new cases diagnosed during 1986–1998, reporting to the CF Foundation Registry was delayed by more than 2 calendar years (range, 2–12 years) for 1,156 of the cases. These 1,156 cases were also excluded from the present study because data on their conditions at diagnosis may not be recorded reliably in the registry. However, note that the results remained unchanged when these 1,156 cases were included. The remaining 11,275 patients were included in the present study, and data related to their diagnostic conditions were retrieved.

The Wisconsin databases. The Wisconsin CF Neonatal Screening Project, as described elsewhere (16–18, 21, 22), contains data on all CF patients born from April 15, 1985, to June 30, 1994, and diagnosed in the state of Wisconsin. For half of the randomly assigned newborns, early diagnosis of CF was established via neonatal screening, while the diagnosis of CF in newborns randomized to the control arm was established via conventional methods—meconium ileus, family history, and signs or symptoms of CF. Other data used in the present study were extracted from the Madison CF Center Sweat Test Database. For neonatal screening purposes, the state of Wisconsin is divided into two geographic areas with comparable population sizes for sweat testing; one region is assigned to the Milwaukee CF center and the other to the Madison CF center. Therefore, patients referred to the Madison CF center for sweat testing are representative of half of the Wisconsin geographic area. The Madison CF Center Sweat Test Database documents all sweat tests that have been performed at this center since 1980. Beginning in the spring of 1992, data on “the reason for sweat test” were collected. In the present study, data from 1993 to 2000 were analyzed.

Study design

We performed a sequence of analyses to examine whether there are gender differences regarding age and condition when CF is diagnosed. In the first analysis, we segregated patients into four groups representing diagnosis-precipitating factors, namely, meconium ileus, positive neonatal/prenatal screening, positive family history, and symptoms of CF other than meconium ileus. The rationale for this strategy was that patients identified by the presence of meconium ileus or via positive neonatal/prenatal screening results are likely to receive diagnostic sweat tests in early infancy.

Next, the subgroup of patients identified after neonatal recognition was studied further to determine whether age at diagnosis was influenced by the nature of subsequent symptoms. For this analysis, data on “reasons leading to diagnosis” documented in the CF Foundation Registry were reclassified into six mutually exclusive categories: 1) “respiratory”: patients presenting with “acute or persistent respiratory symptoms” but without other symptoms; 2) “gastrointestinal”: patients presenting with “failure to thrive/malnutrition” and/or “steatorrhea/abnormal stools/malabsorption” but without other symptoms; 3) “respiratory + gastrointestinal”: patients presenting with both respiratory and gastrointestinal symptoms; 4) “other + respiratory and/or gastrointestinal”: patients presenting with other symptoms (which included electrolyte imbalance, nasal polyps/sinus disease, rectal prolapse, liver problems, and other unspecified symptoms) in combination with respiratory and/or gastrointestinal symptoms; 5) “other, without respiratory or gastrointestinal”: patients presenting with other symptoms only; and 6) “unknown”: patients presenting with unknown symptoms.

The third analysis was conducted to examine whether males and females differ in the onset or severity of lung disease before CF is recognized, a factor that may influence the timing of diagnosis. To investigate this possibility, we examined prospectively obtained information on signs and symptoms of lung diseases for patients enrolled in the Wisconsin CF Neonatal Screening Project (18, 22). Signs and symptoms of lung diseases include cough and wheezing experiences and quantitative chest radiography; the Shwachman-Kulczycki scoring system (23), the Brasfield scoring system (24), and the Wisconsin scoring system (25) were used. At each follow-up visit, parents/caregivers reported the patient’s cough experiences, and their severity was recorded as 0 = none, 1 = rare/occasional, 2 = mild dry cough, 3 = mild productive cough, or 4 = frequent/severe. Wheezing experiences were recorded as 0 = clear, 1 = mild,
2 = moderate, and 3 = severe. We considered cough to be present if the score was 2 or higher and wheezing to be present if the score was 1 or higher. Chest radiography scores were determined at the time of diagnosis, age 2 years, age 4 years, and every year thereafter. Separate analyses were performed for CF patients identified before 3 months of age via neonatal screening (n = 51) and for patients identified because of symptoms other than meconium ileus (n = 35).

In an additional analysis, we determined whether gender differences existed in the process of identifying males versus females for sweat testing. This analysis used data extracted from the Madison CF Center Sweat Test Database and examined demographic and presenting characteristics at the time of referral for sweat testing.

Statistical analysis

SAS (version 8; SAS Institute, Inc., Cary, North Carolina) and R (Internet address: http://www.r-project.org, (26)) software was used for data processing and analyses. For variables with a single observation per patient, the nonparametric analysis of variance was used to compare medians, and chi-square or Fisher’s exact test was used to compare frequency distributions. For variables with longitudinal, multiple observations per patient, repeated-measures analysis with generalized estimating equations with a working assumption of independence among observations was used (27). The identity link was used for continuous outcomes, and the logit link combined with the binomial variance function was used for dichotomous outcomes. When appropriate, analyses were adjusted for the potential cohort effect by including calendar years of diagnosis as a covariate.

RESULTS

Spectrum of age at diagnosis

Of the 11,275 new cases of CF diagnosed during 1986–1998, the majority of patients (70 percent) were identified because of symptoms other than meconium ileus. The remaining patients were identified because of meconium ileus (22 percent), positive neonatal/prenatal screening (4 percent), or positive family history (4 percent). The relative percentage of patients identified because of these four diagnostic precipitating factors did not differ significantly between males and females (p = 0.99). The distribution of age at diagnosis was profoundly skewed, with a range of 0–70.7 years and a median of 5.8 months. Figure 1 shows the distribution of age at diagnosis categorized by these four precipitating factors leading to diagnosis of CF. Median age at diagnosis was the youngest among patients with meconium ileus and those identified via neonatal/prenatal screening; 60 percent of patients were diagnosed during the neonatal period, that is, the first 28 days of life. Patients identified because of symptoms other than meconium ileus were diagnosed at significantly earlier ages than those presenting with symptoms other than meconium ileus (p < 0.001). Of the patients identified because of symptoms other than meconium ileus (figure 1), females were found to be diagnosed at significantly older ages (median age at diagnosis,
TABLE 1. Age at diagnosis of cystic fibrosis patients identified because of symptoms other than meconium ileus, United States

<table>
<thead>
<tr>
<th>Age at diagnosis (months)</th>
<th>No. of patients</th>
<th>Male-to-female ratio</th>
<th>Median</th>
<th>Range</th>
<th>Age at diagnosis (months)</th>
<th>No. of patients</th>
<th>Male-to-female ratio</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data from the 1986–1998 CF Foundation Registry,† categorized by birth cohort</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1970</td>
<td>176</td>
<td>231</td>
<td>0.76</td>
<td>380.0</td>
<td>390.9</td>
<td>200–807</td>
<td>197–848</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970–1979</td>
<td>209</td>
<td>236</td>
<td>0.89</td>
<td>183.5</td>
<td>192.3</td>
<td>83–338</td>
<td>75–340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980–1985</td>
<td>555</td>
<td>493</td>
<td>1.13</td>
<td>61.8</td>
<td>54.1</td>
<td>1–207</td>
<td>1–202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986–1998</td>
<td>3,146</td>
<td>2,878</td>
<td>1.09</td>
<td>6.0</td>
<td>7.0*</td>
<td>0–151</td>
<td>0–147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data from the Wisconsin CF Neonatal Screening Project (1985–1994)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>20</td>
<td>19</td>
<td>1.05</td>
<td>3.9</td>
<td>5.0</td>
<td>1–65</td>
<td>1–75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screened group</td>
<td>31</td>
<td>20</td>
<td>1.55</td>
<td>1.5</td>
<td>1.6</td>
<td>1–3</td>
<td>1–3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.001 comparing males with females.
† Patients diagnosed during 1986–1998 and reported to the Cystic Fibrosis (CF) Foundation Registry in the same or the following calendar year.
‡ Patients in the control group were referred for sweat testing via the conventional method because of symptoms other than meconium ileus; patients in the screened group were identified via neonatal screening and were diagnosed by 3 months of age.

12.7 months) than males (median age at diagnosis, 8.7 months) (p < 0.001).

Additional analyses on the subgroup of patients identified because of symptoms other than meconium ileus revealed that, of the 4,086 males, 176 (4 percent) were born before 1970, 209 (5 percent) were born between 1970 and 1979, and 555 (14 percent) were born between 1980 and 1985 (table 1), whereas the corresponding percentages for females (n = 3,838) were higher (7 percent, 6 percent, and 17 percent for before 1970, 1970–1979, and 1980–1985, respectively). In addition, the male-to-female ratios of patients born before 1980 (i.e., fewer males, more females) were found to be reversed from those for patients born in later cohorts (i.e., more males, fewer females). These results suggest the possibility that more males were being diagnosed in early childhood, but their female counterparts were being diagnosed in later childhood or adulthood. It is also noteworthy that, in the youngest birth cohort (1986–1998), median age at diagnosis of patients identified because of symptoms other than meconium ileus remained significantly older for females compared with males (table 1). A similar trend was found for Wisconsin patients identified because of symptoms other than meconium ileus but not for those identified via screening (table 1).

Relation between age at diagnosis and presenting symptoms

The most common presenting manifestations at the time of CF diagnosis were combined respiratory and gastrointestinal symptoms, accounting for 36 percent of the patients, followed by the “gastrointestinal” group (22 percent) and the “respiratory” group (22 percent). Fourteen percent of the patients presented with other symptoms (including nasal polyps/sinus disease, rectal prolapse, electrolyte imbalance, liver problems, and other unspecified symptoms) in combination with respiratory and/or gastrointestinal symptoms, and another 4 percent presented with other symptoms only. The distribution of age at diagnosis for each symptom category is shown in figure 2. Of the three most frequent symptom categories, median age at diagnosis was the youngest for patients presenting with gastrointestinal symptoms only, followed by those presenting with combined respiratory and gastrointestinal symptoms, and it was the oldest for patients presenting with respiratory symptoms only (p < 0.001).

Comparison within each symptom category revealed that the delay in diagnosis for females compared with males was the longest for patients presenting with respiratory symptoms only, that is, a median 18-month difference (p < 0.001). Females presenting with the combination of respiratory and gastrointestinal symptoms were also diagnosed at significantly older ages than the corresponding group of males (p = 0.003). The delayed diagnosis for females presenting with “respiratory” or “respiratory + gastrointestinal” symptoms was found to be invariably present throughout calendar years 1986–1998 and remained significant when the analysis was restricted to younger patients born after 1986 (median age at diagnosis, 6.3 months for 1,773 males and 7.9 months for 1,634 females; p < 0.001).

An opposite trend of gender difference was observed in the subgroup of patients presenting with other symptoms only, in which the median age at diagnosis (figure 2) was found to be significantly younger in females (33.1 months) than males (44.1 months) (p = 0.02). Examination of the profile of this symptom category showed that 28 percent of males and 26 percent of females had an electrolyte imbalance; 30 percent of males and 23 percent of females had nasal polyps; 18 percent of males and 34 percent of females had rectal prolapse; 9 percent of males and 4 percent of females had...
liver disease; 15 percent of males and 8 percent of females had other, but unspecified symptoms; and 4 percent of males and 6 percent of females had various combinations of these symptoms. No gender difference was observed regarding median age at diagnosis except for patients who had rectal prolapse; females were diagnosed earlier than males (29.4 vs. 34.8 months, \( p = 0.007 \)).

**Onset and severity of lung disease**

Of the 35 Wisconsin patients identified because of symptoms other than meconium ileus, 41 percent of males and 47 percent of females were reported to experience cough at the time of diagnosis \( (p = 0.73) \), and 35 percent of males and 24 percent of females were reported to experience wheezing \( (p = 0.45) \). A lower occurrence of cough (29 percent in males compared with 25 percent in females, \( p = 0.75 \)) and wheezing (16 percent in males compared with 10 percent in females, \( p = 0.53 \)) was observed in patients \( (n = 51) \) identified before 3 months of age via neonatal screening at the time of diagnosis; however, gender differences remained insignificant \( (p = 0.7) \). Consistently, chest radiography scores obtained at the time of diagnosis, as evaluated by using all three systems \( (23–25) \), revealed no significant gender differences \( (p > 0.8) \). Additional longitudinal analysis of screened patients demonstrated that the percentage of patients experiencing cough increased and chest radiography scores worsened from diagnosis to age 10 years, but gender differences remained insignificant \( (p > 0.54) \) (figure 3). On the other hand, the percentages of patients who experienced wheezing appeared similar throughout the first 10 years of life but tended to be higher among males compared with females, although this trend was not statistically significant \( (p = 0.07) \) (figure 3). The age at first *P. aeruginosa* acquisition also did not differ significantly between males (46.0 (standard deviation, 32.4) months) and females (45.1 (standard deviation, 37.5) months) \( (p = 0.7) \).

**Analyses of patients referred for sweat testing**

Table 2 summarizes the characteristics of patients referred for sweat testing at the Madison CF center during 1993–2000. A total of 1,226 sweat tests were performed, and males outnumbered females by a ratio of 1.13. The disproportionately high number of males referred for sweat testing was apparently attributable to the subgroup of patients referred because of symptoms other than meconium ileus and was invariably found for all symptom categories (table 2). In addition, median age at diagnosis was significantly older for females than for males in the subgroup of patients identified.
because of symptoms other than meconium ileus ($p = 0.03$). This difference was most evident in the subgroup of patients presenting with respiratory symptoms only, in which the median age at sweat test was 17 months later for females than for males ($p = 0.004$).

**DISCUSSION**

A gender difference in survival of patients with CF has been demonstrated by several analyses (2–5, 10–13), although its basis has not been elucidated. Previous studies (5, 10) investigating this gender gap examined factors believed to affect the prognosis of CF patients, but they did not focus on age at diagnosis. Although Rosenfeld et al. (10) explored age and symptoms at the time of diagnosis, their analyses did not allow a comprehensive assessment of this issue. The strategy of combining analysis of the large CF Foundation Registry with the Wisconsin database’s more detailed, prospectively obtained, clinical observations proved particularly helpful, as in the past (28). By performing in-depth, comprehensive analyses that included segregation of patients by diagnostic precipitating factors, we uncovered new insights into the gender gap. Specifically, we discovered for the first time that, over many years, females have been diagnosed with CF at significantly older ages than males (median age at diagnosis, 12.7 vs. 8.7 months). While the implications of this 4-month delay in diagnosis at the population level with regard to disease outcome need further investigation, this time interval is comparable with that observed between screened and nonscreened patients in the Wisconsin (16, 17) and the Australian (19) neonatal screening programs. These screening programs have demonstrated significant, long-lasting nutritional benefits (16, 17, 19) and some pulmonary benefits (19) associated with early diagnosis. Furthermore, the delayed diagnosis of females compared with males occurs during the first year of life, a critical stage of development and perhaps the best opportunity for intervention.
The delayed diagnosis of females with CF was most evident among patients presenting with respiratory symptoms only. The underlying explanation for this gender disparity is not clear. Taking into account the bronchopulmonary and physiologic differences reported (29, 30) when normal boys and girls are compared, it seemed to us that the most obvious explanation is that the onset and severity of respiratory symptoms might be different in females than in males prior to CF diagnosis. Although this issue cannot be examined nationally because data are not collected until patients are identified and reported to the CF Foundation, we were able to test this hypothesis by analyzing the signs and symptoms of CF lung disease in patients enrolled in the Wisconsin trial (18, 22). Our analyses revealed no significant gender differences in cough (the symptom most characteristic of CF), quantitative chest radiography (perhaps the most useful measure of lung disease in young children with CF (25)), and age at first acquisition of *P. aeruginosa* during the first 10 years of life. Although wheezing was found to be somewhat more prevalent in males than in females with CF, a finding consistent with the non-CF population (31), the difference observed was not statistically significant. In addition, genotype differences can apparently be ruled out in the CF Foundation Registry, where the percentage of patients homozygous for the ∆F508 mutation was similar (*p = 0.5*) between males (35.5 percent) and females (33.7 percent) among those presenting with respiratory symptoms only. Taken together, these findings indicate that the relative delay in diagnosis of females with CF identified in our study could not be explained by the presence of a milder form of CF in young females relative to males. 

Studies on cardiovascular diseases (32, 33) have illustrated how physicians’ management and practices can differ between male and female patients with respect to recognizing symptoms and recommending treatment. In children, the prevalence of recurrent wheezing is 1.5 times higher in males than in females (31), and, for boys less than 10 years of age, the risk of developing asthma is almost double that for girls (34, 35). These perceptions may affect physician decisions about whether to refer young children with respiratory symptoms for diagnostic tests. Therefore, another possible explanation for the striking gender difference in age at diagnosis of CF patients presenting with respiratory symptoms is the existence of an unconscious bias that reduces the likelihood of obtaining a sweat test in girls. This possibility is supported by our findings of a disproportionately smaller number of females relative to males in this symptom category who were referred for sweat testing and that females were diagnosed at older ages than males. Although the routine statewide CF neonatal screening program in Wisconsin initiated in July 1994 (36) might have altered decisions regarding sweat test referral, this possibility is not likely to have been a factor before then because primary care physicians were repeatedly urged not to change their practice patterns (37). After 1994, primary care physicians might have gradually relied more on the screening program to identify CF patients; however, we have no reason to suspect that this change would affect males and females unequally. Thus, we conclude that it should not have confounded our analyses of gender comparisons.

One other conceivable explanation might be parental variations in attention paid to signs and symptoms of CF, reflecting trends in American culture that have led to socially constructed gender biases regarding child-rearing practices (38–40). For example, traditional parental practices related to gender typing encourage boys to be more physically active than girls. Therefore, parents may notice, or become

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**TABLE 2. Age at sweat test for patients referred to the Madison Cystic Fibrosis Center for sweat tests during 1993–2000, Wisconsin**

<table>
<thead>
<tr>
<th>No. of patients sweat tested</th>
<th>Male</th>
<th>Female</th>
<th>Male-to-female ratio</th>
<th>Age at sweat test (months)</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>650</td>
<td>576</td>
<td>1.13</td>
<td>13.8</td>
<td>14.2</td>
<td></td>
<td>0–1,089</td>
<td>0–875</td>
</tr>
<tr>
<td>By precipitating factors leading to referral for sweat tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>3</td>
<td>5</td>
<td>0.60</td>
<td>1.5</td>
<td>1.0</td>
<td></td>
<td>0–57</td>
<td>0–65</td>
</tr>
<tr>
<td>Neonatal screening</td>
<td>176</td>
<td>197</td>
<td>0.89</td>
<td>1.1</td>
<td>1.2*</td>
<td></td>
<td>1–516</td>
<td>1–875</td>
</tr>
<tr>
<td>Family history</td>
<td>33</td>
<td>43</td>
<td>0.77</td>
<td>22.1</td>
<td>42.6</td>
<td></td>
<td>1–516</td>
<td>1–875</td>
</tr>
<tr>
<td>Symptoms</td>
<td>432</td>
<td>327</td>
<td>1.32</td>
<td>22.5</td>
<td>30.4*</td>
<td></td>
<td>1–1,089</td>
<td>1–875</td>
</tr>
<tr>
<td>By categories of symptoms in the subgroup of patients presenting with symptoms</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory + gastrointestinal</td>
<td>24</td>
<td>19</td>
<td>1.26</td>
<td>17.8</td>
<td>20.3</td>
<td></td>
<td>3–216</td>
<td>4–110</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>106</td>
<td>74</td>
<td>1.43</td>
<td>15.3</td>
<td>13.2</td>
<td></td>
<td>2–997</td>
<td>2–875</td>
</tr>
<tr>
<td>Respiratory</td>
<td>243</td>
<td>196</td>
<td>1.24</td>
<td>32.5</td>
<td>49.4*</td>
<td></td>
<td>1–1,089</td>
<td>1–875</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>26</td>
<td>1.42</td>
<td>46.2</td>
<td>40.7</td>
<td></td>
<td>1–65</td>
<td>1–143</td>
</tr>
<tr>
<td>Unknown</td>
<td>22</td>
<td>12</td>
<td>1.83</td>
<td>8.7</td>
<td>9.3</td>
<td></td>
<td>1–65</td>
<td>1–143</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01 comparing males with females.
concerned about, a boy sooner than a girl if the child shows limited stamina or develops respiratory symptoms.

Although the very long delays in the diagnosis of CF observed for decades began to decrease in the United States after 1970, age at diagnosis has not improved during the last decade (18). Clearly, delay can lead to more severe malnutrition (16–18, 41), potentially accelerated respiratory problems (19), and possibly greater mortality risk, as pointed out in early studies by Shwachman et al. (8) and by George and Norman (9).

On the basis of findings from the present study, it is tempting to ascribe the higher mortality rate observed for females to their delayed diagnosis, with potential consequences of greater decline in lung disease or mortality. Although it is possible to assess lung disease outcome and survival by analyzing the CF Foundation Registry data, evaluation of the impact of delayed diagnosis may not be accurate because of the presence of confounding factors that affect age at diagnosis but are not available in the CF Foundation Registry database. For example, limited access to medical care and/or disadvantageous socioeconomic status could lead to delayed diagnosis, with resultant progression of disease due to inadequate treatment, which would create a negative association between age at diagnosis and outcome. In contrast, milder cases of CF are often diagnosed later because of late presentation of sufficient signs to warrant a sweat test; this situation would create a positive association between age at diagnosis and outcome.

The definitive answer regarding whether delayed diagnosis increases mortality risk awaits results from clinical trials of neonatal screening such as the Wisconsin CF Neonatal Screening Project (18), which will require many more years to complete with regard to mortality analyses because of a dramatically improved life expectancy. However, recent studies by Merelle et al. from the Netherlands (42), Waters et al. from Australia (19), and Doull et al. from the United Kingdom (43) reported favorable results regarding lung disease profile (19, 42) and survival (42, 43) in CF patients identified through neonatal screening.

In view of the potential risks associated with delay in diagnosis and the long-standing observation of a gender gap, neonatal screening may be the only way to ensure unbiased early diagnosis of CF and a “healthy start” (18). When neonatal screening is not available, it is important for primary care physicians to be aware of potentially delayed diagnosis and the survival disadvantage observed for females with CF when making referrals or treatment decisions for young children who present with respiratory symptoms.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants R01-DK34208, T32-DK07665, K01-DK02891, and M01-RR03186.

The authors thank Dr. Preston W. Campbell of the Cystic Fibrosis Foundation for providing the Registry data. The authors are grateful to all members of the Wisconsin Cystic Fibrosis Neonatal Screening Research Group, especially Madison and Milwaukee Cystic Fibrosis center directors Drs. Michael J. Rock and Mark Spleaegard. The authors also thank Drs. Robert F. Lemanske and Audrey Tluczek for reviewing the manuscript and providing suggestions related to gender bias.

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