Delayed Cystic Fibrosis Presentation in Children in the Absence of Newborn Screening

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1*In memoriam of Mrs Linda Foley

Abstract

Newborn cystic fibrosis (CF) screening facilitates early diagnosis and nutritional intervention, which prevents malnourishment and improves growth in childhood. To provide baseline information on the natural history of CF in the Republic of Ireland, where newborn screening has not yet been introduced and CF incidence is high (1:1353 live births), we examined the effect of presentation mode, symptom type and gender on age at diagnosis. Median age at diagnosis was calculated by gender and for presentation mode/symptom type for 601 CF registry children diagnosed 1986-2007. Modes of presentation were each significantly associated with delayed presentation. An adjusted odds ratio of 4.5 (95% CI: 1.8, 11.1) was determined for presentation with family history, 4.3 for gastrointestinal symptoms (95% CI: 1.8, 10.4), 9.9 for both respiratory and gastrointestinal symptoms (95% CI: 3.8, 24.2), and 11.4 for respiratory symptoms (95% CI: 4.5, 29.7). Children with respiratory symptoms had the greatest likelihood of delayed diagnosis (median age: 37 months), whereas gastrointestinal symptoms following meconium ileus, other symptoms, or investigation due to family history/testing of newborn siblings of known CF patients. Gender was not significantly associated with a delayed presentation when presentation mode was taken into account.

Introduction

At 1:1353 live births, 1 the Republic of Ireland (RoI) has one of the highest reported incidences of cystic fibrosis (CF) in the world. Pregnancy termination is illegal and historically, family sizes have been large. In some European countries, a decline in CF birth incidence has been partially attributed to the effect of prenatal diagnosis introduced by pregnancy termination. Randomised investigations of newborn CF screening have demonstrated the value of early diagnosis with nutritional intervention in preventing malnourishment and improving growth in childhood. In Northern Ireland, universal screening has occurred since 1983, but has not yet been introduced in the Republic. Instead, diagnosis follows presentation with meconium ileus, other symptoms, or investigation due to family history/testing of newborn siblings of known CF patients.

Non-specificity of clinical signs and symptoms can result in delayed presentation for all patients. Time from birth to CF presentation is often disproportionately longer in females than in males; median age at diagnosis was 18 months later in females than in males presenting with respiratory symptoms in the US, and 9 months later in females in the UK. Although differences in clinical outcomes were not observed, the RoI's affect of gender and mode of presentation on time to diagnosis has not been fully assessed, although cursory analysis of registry data in 2006 showed that mean age at diagnosis following respiratory symptom presentation was greater in females than in males. The absence of newborn screening combined with the high rate of CF renders the RoI a unique pre-screening environment, in which to study the natural history of the condition and examine the effect of patients' mode of presentation, symptom type and gender on age at diagnosis. Using 2009 registry data covering >90% of the CF population, we analyse clinical presentation data, focussing specifically on children (as there is evidence of skewness in the distribution of age at diagnosis) and apply suitable non-parametric methods.

Methods

Required demographic and diagnostic data were provided by the Cystic Fibrosis Registry of Ireland (CFRI). Using a comparable observation period to that selected in UK and US studies, we used data of diagnosis to define the study period as 1986-2007. As in those studies, we excluded CFRI registered patients diagnosed prior to 1986 to minimise bias in age at diagnosis caused by patients diagnosed prior to the introduction of CF screening and surviving beyond 1986. Also, enteric-coated enzyme substitution therapies were introduced in the Republic of Ireland in 1986, denoting a new generation of patients with an increased likelihood of improved nutrition. Unlike the selected populations in UK and US studies, we sought to focus on a population of children, requiring an increased number of patients in this study period to have been diagnosed before their sixteenth birthday. Patients were first categorised into three groups reflecting events preceding a patient's CF diagnosis (mode of presentation); meconium ileus, other symptoms and family history without symptoms.

Following the method used in other studies, 8 patients whose mode of presentation included 2 of these categories were excluded, as precedence of one category over another could not be established. Patients classified in the symptomatic mode of presentation category were further divided into three categories: respiratory (lower respiratory infection/symptoms, sinus disease, nasal polyps, finger clubbing), gastrointestinal (steatorrhoea, malnutrition, failure to thrive, electrolyte imbalance, pancreatitis, hepatitis-biliary disease, prolonged jaundice, faecal prolapse), and a combination of respiratory and gastrointestinal. Differences in age at diagnosis according to mode of presentation and symptom type were investigated. To explore gender differences, proportions of males and females in each diagnostic and symptomatic category were compared. Factors (gender, mode of presentation/symptomatic category) independently associated with having a delayed presentation (diagnosed from 3 months to <16 years of age) were identified.

Statistical analysis was performed using SPSS (version 14, SPSS Inc, Chicago, Illinois). Chi-squared tests were used to compare frequency distributions between the sexes. As data were fairly skewed, the Kruskall Wallis procedure was used to compare median age at diagnosis. A two-sided p-value of less than 0.05 was considered statistically significant. A binary logistic regression model was developed to identify independent factors associated with a delayed presentation. Significant categorical variables and mode of presentation/symptom category were entered into the model. Crude and adjusted odds ratios were based on the logistic regression model.

Results

Seven hundred and one CFRI-registered patients were diagnosed 1986-2007. Data were excluded for 100 patients because diagnosis occurred on or after 16 years of age (n=29, age range 16-48 years), mode of presentation was unknown (n=6), CF was diagnosed via newborn screening outside of Ireland (n=1), or following methods used in comparable studies, when multiple modes of presentation were recorded (11 presented with meconium ileus (MI) and family history (FH); 9 with MI and symptomatic (SYM) and 44 with FH and SYM). The study population therefore consisted of 601 children, 54.6% (N=328) were male and 96.5% (N=580) were of Irish ethnicity.

Mode of presentation and symptom categories

Two thirds (66.4%) presented with symptoms (n=399), 18.5% with MI (n=111), and 15.1% with FH (Table 1A). Amongst the 399 symptomatic children, similar proportions of patients presented with gastrointestinal (35.6%), respiratory (30.4%) and respiratory and gastrointestinal symptoms combined (31.8%) prior to diagnosis. Greater proportions of females than males presenting with respiratory and a combination of respiratory and gastrointestinal symptoms, but more males reported gastrointestinal symptoms alone than females (Table 1B).
Relationship between age at diagnosis and mode of presentation

The study population had a median age at diagnosis of 4.7 months, a mean of 22 months
(range: 1 day-15 years), and 20th and 75th percentiles were 1.3 and 24.4 months respectively.
Females had an earlier median age at diagnosis than males (4.4 versus 6.8 months), a difference that was not statistically significant (Table 2A). Children presenting with symptoms had a median age at diagnosis of 11 months, which was significantly later than children with other modes of presentation (p=0.001) (Table 2B).

Relationship between age at diagnosis and presenting symptom

Median age at diagnosis differed significantly by symptom type (p=0.001). When symptom types were analysed separately, similar median ages at diagnosis were observed for males and females with respiratory symptoms alone and with both respiratory and gastrointestinal symptoms (Table 2B). Males presenting with gastrointestinal symptoms alone were diagnosed 8.6 months later than females (not statistically significant).

Gastrointestinal symptoms

To explore this pattern of gastrointestinal symptoms in greater detail, further analysis was undertaken. Nearly one third (25.4%) of children with gastrointestinal symptoms were categorised as malnourished, 31.6% had steatorrhoea, 25.4% had malnourishment and steatorrhoea, and 11.3% had other symptoms (Table 1C). On comparing males and females at age diagnosis within each gastrointestinal symptom category (Table 2C), males with malnourishment were diagnosed significantly later (5.7 months) than females (p=0.01).

Factors associated with delayed presentation

A binary logistic regression model was developed to examine factors associated with delayed presentation. Interaction terms between gender and mode of presentation were not statistically associated with delayed presentation and were therefore omitted from the final model. When gender and diagnostic method/symptom categories were entered into the model (Table 3), the different modes of presentation were each significantly associated with delayed presentation (compared to important bias). The factors associated with delayed presentation included: family history (without symptoms), gender, diagnostic method and symptom category.

Discussion

Baseline data on clinical presentation of CF children diagnosed 1986-2007 in the Republic of Ireland mirrors the pattern of delayed presentation observed in other countries, showing that the greater delay in diagnosis is experienced by patients presenting with symptoms other than meconium ileus. Family history (without symptoms) led to a diagnosis in a greater proportion of patients (15.1%) than observed in the UK (9.5%) and USA (4%). This may reflect the high incidence of disease (1:1353 live births) in a country where newborn CF screening does not occur, pregnancy termination is illegal, and family size is large.2 Unlike other studies, gender was not significantly associated with a delayed presentation when presentation mode was taken into account. Within our study population, males (n=328) had a later median (6.0 versus 4.4 months) age at diagnosis than females (n=273), a difference that did not reach statistical significance. Differences in age at diagnosis were neither detectable between genders for any mode of presentation (MI, FH, SYMP), nor symptom type, and this may reflect power considerations, as there are necessarily small numbers in our population. The longest delay in presentation was experienced by children presenting with respiratory symptoms (median age of 20.4 months). A gender gap in age at diagnosis of symptomatic patients (favouring early diagnosis of males) has been observed in UK and US studies, and was most pronounced in the respiratory symptom category. Our data presents a contrasting picture, in which median age at diagnosis of males and females presenting with respiratory symptoms does not differ (20.3 and 20.3 months respectively).

Our findings are in contrast to an earlier analysis of Republic of Ireland data, which found a gender gap in mean age at diagnosis following respiratory symptom presentation. This analysis benefitted from increased registry coverage of the CF population (80% in the 2007 study). Due to skewness in the distribution of age at diagnosis, we focused on children >16 years and also performed non-parametric statistical techniques. In addition, mode of diagnosis was categorised differently in this analysis. Although not significant, males presenting with gastrointestinal symptoms in this study population were diagnosed nearly 7 months later than females (5.1 and 11.8 months for females and males). In the UK, gastrointestinal symptoms were detected later in females, while US females were diagnosed at 5.5 months and males at 5.6 months, a difference that was not statistically significant. Our analysis of gastrointestinal symptom type also determined that malnourished males (n=34) presented significantly later than females (n=28) had a later median (6.0 versus 4.4 months) age at diagnosis than females (n=273), a difference that did not reach statistical significance. Differences in age at diagnosis were neither detectable between genders for any mode of presentation (MI, FH, SYMP), nor symptom type, and this may reflect power considerations, as there are necessarily small numbers in our population. The longest delay in presentation was experienced by children presenting with respiratory symptoms (median age of 20.4 months). A gender gap in age at diagnosis of symptomatic patients (favouring early diagnosis of males) has been observed in UK and US studies, and was most pronounced in the respiratory symptom category. Our data presents a contrasting picture, in which median age at diagnosis of males and females presenting with respiratory symptoms does not differ (20.3 and 20.3 months respectively).

As the registry was initiated in 2002, retrospective clinical presentation reporting may have incurred recognised difficulties with data accuracy. Our data may be limited by the absence of patients not registered with the CFRI, who declined to participate in the registry. This resulted in an estimated 40% of patients 1986-2007 without registering with the CFRI. Changes in case finding approaches may have occurred over the study period, influencing medical diagnostic practices and patients health seeking behaviours. Our logistic regression analysis found that by adjusting for mode of presentation, gender was not independently associated with delayed presentation when presentation mode was taken into account. Within our study population, males (n=328) had a later median (6.0 versus 4.4 months) age at diagnosis than females (n=273), a difference that did not reach statistical significance. Differences in age at diagnosis were neither detectable between genders for any mode of presentation (MI, FH, SYMP), nor symptom type, and this may reflect power considerations, as there are necessarily small numbers in our population. The longest delay in presentation was experienced by children presenting with respiratory symptoms (median age of 20.4 months). A gender gap in age at diagnosis of symptomatic patients (favouring early diagnosis of males) has been observed in UK and US studies, and was most pronounced in the respiratory symptom category. Our data presents a contrasting picture, in which median age at diagnosis of males and females presenting with respiratory symptoms does not differ (20.3 and 20.3 months respectively).

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