1-9-2007

Diagnosis of cystic fibrosis in the Republic of Ireland: epidemiology and costs.

Philip Farrell
University of Wisconsin Madison

Steven Joffe
University of Pennsylvania

Linda Foley
University College Dublin

Gerrard J. Canny
Our Lady's Hospital for Sick Children, Dublin

Philip Mayne
Royal College of Surgeons in Ireland, philipmayne@rcsi.ie

See next page for additional authors

Authors
Philip Farrell, Steven Joffe, Linda Foley, Gerrard J. Canny, Philip Mayne, and Marjorie Rosenberg

Diagnosis of Cystic Fibrosis in the Republic of Ireland: Epidemiology and Costs

P Farrell,S Joffe,L Foley,GJ Canny,P Mayne,M Rosenberg

Ir Med J. 2007 Sep;100(8):557-60

P Farrell[1], S Joffe1, L Foley[2], GJ Canny[3], P Mayne[4], M Rosenberg[1]

[1]Department of Paediatrics, University of Wisconsin, Madison, WI

[2]The Cystic Fibrosis Registry of Ireland, Dublin

[3]Paediatrics and Paediatric Respirology, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12

[4]Children's University Hospital, Temple Street, Dublin 1 and Associate Professor of Biochemistry and Paediatrics, Royal College of Surgeons in Ireland

Abstract

There were four objectives in this study: (1) determine the incidence of cystic fibrosis (CF) in Ireland; (2) estimate the cost of diagnosing CF; (3) clarify the characteristics and outcomes of the nationwide diagnostic efforts and (4) identify disparities. Surveys were conducted to determine the number, methods, costs and outcomes for sweat tests in Ireland from 2001 through 2003. The results allowed us to determine that Ireland's CF incidence is the world's highest at 1:1353. The average cost for diagnosis was €2663 per patient. Analyses of data in The Cystic Fibrosis Registry of Ireland revealed longer delays when diagnosis followed respiratory symptoms, rather than gastrointestinal signs, and also in girls compared to boys, particularly those presenting with respiratory symptoms. Although expenditures for diagnosing of CF in Ireland are relatively modest, the high incidence and age of diagnosis, as well as gender-related disparities, are sufficient to warrant investment in national newborn screening.

Introduction

Cystic fibrosis (CF), the most common life-shortening autosomal recessive disease, is diagnosed either through newborn screening (NBS) or the traditional method of performing a sweat test after signs/symptoms appear. Although the original estimates suggest that CF affects about one in every 2000 live births (1:2000) in Western European regions[1], recent data indicate great regional variation[2,3] with a range from 1:1500 to 1:10,000.

The Republic of Ireland seems to have a relatively high incidence with an estimate of approximately 1:1500 in one study[4]. Previous research has examined clinical aspects in the Irish population[5], but no study has characterized the epidemiology of CF in Ireland based on data at the time of diagnosis.

Although a working group convened by the Chief Medical Officer of the Department of Health and Children in 1999 recommended establishing a NBS programme for CF, primary sweat testing after appearance of signs/symptoms of the disease or a positive family history remains the established method of diagnosing CF in the Republic of Ireland. Since sites doing sweat tests are well known, we organized this study to quantify costs and new CF patients during 2001-2003. In addition, we determined the age of diagnosis using The Cystic Fibrosis Registry of Ireland.

Methods

To quantify the number of sweat tests being performed in Ireland, we surveyed all clinical centres that were performing sweat tests. Each centre received a questionnaire that requested information on the total number of sweat tests performed during 2001, 2002, and 2003, and all responded fully. These sites were also asked to report the sweat test method used and the outcomes. The questionnaire summaries were used to compute the national number of sweat tests performed and how many of these were positive (thus diagnosing CF). Finally, the above data allowed us to compute the incidence of CF in Ireland for 2001-2003 using the mid-2002 population data collected from the Irish Central Statistics Office[6]. In collaboration with the University of Wisconsin, diagnostic data from the Cystic Fibrosis Registry of Ireland were analyzed in a similar fashion to previously published U.S. Registry studies[7].

The data from the collected questionnaires also supplied some of the necessary information to estimate the cost of performing sweat tests for CF diagnoses nationally. All of the costs were computed in Euro during 2003 using expenses for both labour (per hour) and materials obtained, from three of the major sweat testing centres in Dublin: Our Lady's Children's Hospital (Crumlin), The National Children's Hospital (Tallaght), and The Children's University Hospital (Temple Street). We only considered direct costs in this estimation and calculated method-specific costs because we learned that three different procedures are being used for sweat testing in Ireland (Table 1). Both the Wescor electrolyte (chloride and/or sodium) method and the Wescor conductivity method required approximately one hour to complete, while the filter paper chloride method involved approximately one hour and 45 minutes to complete. In order to calculate

the annual total cost for diagnosing CF, we computed the cost per test at each site based on the method multiplied by the total number of tests.
The final objective of this study was to determine the gender- specific average age of diagnosis of CF patients in Ireland. Initially, we reviewed the hospital charts of the Crumlin CF Centre at Our Lady's Children's Hospital which receives CF patient referrals from the entire country; the charts were then abstracted for 36 patients diagnosed in 2001, 2002, and 2003 of whom 12 had meconium ileus (MI) or intestinal obstruction of the newborn. Subsequently, we analyzed observations on de-identified data according to gender, age, and the presenting symptoms at diagnosis for Irish patients registered during 2004-2006.

Results

There were a total of 17 hospitals performing sweat tests. The number of annual tests per centre ranged from 3 to 368. Four centres responsible for 48% of the Irish sweat tests used filter paper/electrolyte analysis, five (30%) used the Wescor collection system with electrolyte analysis, and the remaining eight did Wescor/conductivity testing (22% of annual sweat tests). As shown in Table 1, the 3-year annual average of the number of annual sweat tests was 2025, and the 3-year annual average number of positive sweat tests was 44. Thus, there was an average of 45 negative sweat tests for each CF patient diagnosed (range, 40 to 56). Based on these data, the incidence of CF in Ireland was 1:1353 during 2001-2003 (95% CI=1:1045-1916).

Table 1 Annual Sweat Test Statistics

Year	Total	Positive results	% Positive results	Births	Incidence
2001	1823	44	2.44	57854	1:1315
2002	2046	50	2.15	60503	1:1210
2003	2206	39	1.77	61529	1:1578
Average	2025	44	2.20	59962	1:1353

The 95% confidence interval is 1:1045-1:1916

The costs computed for sweat tests by three methods are shown in Table 2. The direct costs data indicate that the national expense for performing 1,823 sweat tests in 2001 was €106,229. The cost per sweat test was €58.27 and the direct cost per patient diagnosed was €2,414. Using the 3-year average data, we calculated €117,160 total, €57.86 per sweat test and €2663 per patient diagnosed from 2001-2003.
Based on the sample of 36 patients referred in 2001-2003 to Our Lady's Children's Hospital in Crumlin, which is 27% of the total identified nationally, the mean age of diagnosing of CF was 20.7 months, including

infants with meconium ileus (MI); however, without MI patients, the mean age was 31.0 months. The patient sample included 19 females and 17 males. The mean age of diagnosis of the male patients was 18.6 months including the patients with MI and 24.3 months excluding the MI population, while the corresponding ages for females were 22.6 and 35.7 months, respectively.

Table 2 Costs and Types of Collection/Analysis Systems used for Sweat Testing in Ireland

Collection/ Analysis System	Filter paper collection system/analysis by chloride and/or sodium (cost in Euro)	Wescor method collection system/ analysis by conductivity (cost in Euro)	Wescor method collection system/ analysis by chloride and/or sodium (cost in Euro)
Macroduct materials	0	46.50	46.50
Filter paper materials	2.00	0	0
Reagents	2.00	0	2.00
Analysis labor cost	40.25	23.00	23.00
Cost per test	44.25	69.50	71.50

Table 3 presents a summary of observations at diagnosis on patients enrolled through 2006 in the Cystic Fibrosis Registry of Ireland. MI was present in 18%, which is similar to U.S. data[7]. The average age of diagnosis was delayed to 24.6 months, but some differences were identified when presenting signs/symptoms and gender-specific comparisons were performed according to clinical factors leading to a sweat test. Specifically, the mean age of 133 patients presenting principally with respiratory symptoms at diagnosis (56.0 months; ±7.79) was older ($p<.0001$) than the 231 presenting with later gastrointestinal symptoms (20.8 months ±2.77). In addition, as shown in Table 3, females experienced a longer delay overall, particularly when they presented with respiratory symptoms, i.e., girls were 78.9 months old and boys 33.5 on the average. This difference was confirmed in a statistical comparison of median ages of diagnosis after respiratory signs/symptoms (66 girls=24.7 months compared to 67 boys=9.99 months; $p=.0202$ by the Kruskal-Wallis test). However, both females ($p=.0003$) and males ($p=.0267$) showed a much older age at diagnosis when they presented principally with respiratory signs/symptoms compared to gastrointestinal manifestations; the differences in the mean values were 55.6 and 22.1 months, respectively.

Table 3 Age at Diagnosis in Months for Patients in the CF Registry of Ireland through 2006				
	Age at Diagnosis (in months)			
	N	Mean	Std Error	p –value
All (excluding missing) *	649	24.6	2.32	
Meconium Ileus (MI) Status				
No MI	531	29.7	2.79	
With MI (18 %)	118	1.27	0.23	
Gender				
Female	311	30.5	4.03	
Male	338	19.1	2.45	
Gender and MI Status				
Female and MI	63	1.18	0.29	
Male and MI	55	1.38	0.38	
Female and No MI	248	37.9	4.95	
				0.0077
Male and No MI	283	22.6	2.88	
Patients principally diagnosed with later gastrointestinal signs/symptoms (36%)				
Female and No MI	105	23.30	5.38	
				0.4391
Male and No MI	126	18.73	2.40	
Patients principally diagnosed after respiratory symptoms (20%)				
Female and No MI	66	78.9	13.9	
				0.0036
Male and No MI	67	33.5	6.08	
Patients diagnosed because of a positive family history of CF (11%)				
Female	35	13.4	7.38	
				0.3986
Male	35	6.24	4.12	

*Review of the 2006 Registry revealed that 26 (10 female and 16 male) of 675 registered patients (3.9%) had missing or uncertain data and were therefore excluded from these analyses.

Discussion

During the current decade, many countries have transformed from the traditional method of CF diagnosis to NBS[8]. Early diagnosis of CF through NBS has been underway in Northern Ireland for nearly 25 years. There are a number of reasons why screening programs have been implemented such as:

1. concerns about difficulties and delays in diagnosis[9];
2. the morbidity[8] or mortality[10] associated with delays;
3. disparities related to geographical or demographic factors such as gender[7]; and
4. anticipated financial savings in costs for diagnosis[11] and/or treatment[12].

The incidence of CF which we determined in the Irish population of 1:1353 confirms the previous estimate of 1:1461 by Devaney et. al.[4] but was calculated with more reliable methodology over 3 years. Ireland's incidence is the highest among Western European nations[3] and is much higher than North American countries[2]. This is probably attributable to a high CFTR mutation prevalence and consanguinity. To our knowledge, no European nation has evaluated the direct costs of diagnosing CF by the traditional method, taking into account all sweat tests performed. In fact, only one study elsewhere by Lee, et. al.[11] examined the costs of diagnosing CF in Wisconsin with traditional methods compared to newborn screening. Irish records, however, unlike those available in the USA, made it possible to study retrospectively the population of CF patients diagnosed nationally by sweat test analysis. It is interesting to compare regions with regard to CF diagnostic expenditures. In Wisconsin[11] the estimated cost per newly diagnosed patient with CF was calculated at U.S. $9,952 during 2000 using the traditional method of diagnosis and $9,025 with NBS. Ranieri et al[13] in South Australia estimated the cost of diagnosis for CF with a neonatal screening program as $4,590. In a study conducted by Scotet et al[9] in 1998, the estimated cost of the CF newborn screening program in Brittany, France, was $6,825 per child diagnosed with CF. In The Republic of Ireland, the average direct cost per CF diagnosis with the traditional method is lower at €2,663 or $3,435, using a conversion factor of 1.29.

There are some limitations in this assessment of diagnostic costs. First, our estimates are limited to direct costs of a sweat test, and we found a lack of standardization as a number of sites were not diagnosing CF based on the recommendations of the UK National External Quality Assurance Schemes (NEQAS) as suggested to be the standard in Ireland[14]. There were many sites that were using conductivity[15] as an alternative method for diagnosis instead of a quantitative pilocarpine test with electrolyte analyses. Although conductivity may correlate well with sweat chloride concentrations, it has not been approved for diagnosis of CF by any organization. In addition, there may be missed cases of CF; however, previous research2 in the USA

has shown that these small numbers have very little effect on estimating incidence or for cost calculations.

It was possible to discover the gender difference among Irish CF patients because of the development of The Cystic Fibrosis Registry of Ireland. Data accrued and analyzed annually have continued to reveal this male/female disparity. These results confirm for the first time the disparity reported by Lai et al[7] in age of diagnosis between male and female CF patients in the United States. Moreover, we have been able to extend those findings by demonstrating that it is specifically CF females presenting with respiratory symptoms who show the greatest delays. It is somewhat alarming these girls are on the average 78.9 months old at diagnosis, 45 months older then boys, particularly when one considers the worse prognosis of females after adolescence[16]. Because the survival of most CF patients ultimately depends on the severity of lung disease, it is also disconcerting that those with respiratory manifestations are diagnosed at a much older age than patients with gastrointestinal signs, especially when the onset of such symptoms seems to occur at a similar age[7]. This greater delay might be attributable to the non-specificity of the respiratory symptoms and/or medical practice habits.

The question arises as to why there would be such a strikingly inordinate delay in diagnosis in girls with CF. Lai et al[7] after presenting unequivocal evidence of similarly evolving respiratory signs/symptoms, discussed physicians' practice patterns and a potential "unconscious bias" related to cultural attitudes and "child-rearing practices." Whatever the cause, there is no doubt that diagnosis through NBS eliminates the gender-related disparity[7,9]. This diagnostic method also resolves the disparity related to the gastrointestinal versus respiratory symptoms onset because the lungs of CF patients are normal at birth. Therefore, although the costs of CF diagnoses by traditional methods are relatively modest in Ireland, the high incidence of CF, long diagnostic delays in general and especially for girls, the likelihood of preventable deaths[10] and excessive therapeutic costs[12], make it important to implement a national NBS programme without delay. The nutritional benefits of early diagnosis through NBS are well established, as are the unique opportunities for enhanced pulmonary care, while the only risks of harm are manageable and preventable[8].

References

1. Boat TF, Welsh MJ and Beaudet AL. Cystic fibrosis In the metabolic basis of inherited disease, McGraw-Hill, New York, 1989, 2649- 2680.
2. Kosorok MR, Wei W, Farrell PM. The incidence of cystic fibrosis. Stat Med 1996;15:449-62.
3. Southern KW, Munck A, Pollitt R, on behalf o the ECFS CF Neonatal Screening Working Group. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros 2007;6:57-65.
4. Devaney J, Glennon M, Farrell G, et al. Cystic fibrosis mutation frequencies in an Irish population. Clin Genet 2003: 63: 121-125.
5. Cashman SM, Patino A, Delgado MG, Byrne L, Denham B, DeArce M. The Irish cystic fibrosis database. J Med Genet, 1995;32:92-975.
6. Central Statistics Office, Ireland. www.indexmundi.com/Ireland/.
7. Lai HC, Kosorok MR, Laxova A, Makholm LM, Farrell PM. Delayed diagnosis of US females with cystic fibrosis. Am J Epidemiol 2002;156:165-73.
8. Farrell PM. Improving the health of patients with cystic fibrosis through newborn screening. Advances in Pediatrics 2000;47:79- 115.
9. Scotet V, Braekeleer M, Roussey M, et al. Neonatal screening for cystic fibrosis in Brittany, France: assessment of 10 years' experience and impact on prenatal diagnosis. Lancet 2000;356:789-94.
10. Grosse SD, Rosenfeld M, Devin OJ, Lai HJ, Farrell PM. Potential impact of newborn screening for cystic fibrosis on child survival: A systematic review and analysis. J Pediatr 2006;362-366.
11. Lee DS, Rosenberg MA, Peterson A, et al. Analysis of the costs of diagnosing cystic fibrosis with a newborn screening program. J Pediatr. 2003;142:617-623.
12. Sims EJ, Mugford M, Clark A, et al., on behalf of the UK Cystic Fibrosis Database Steering Committee. Economic implications of newborn screening for cystic fibrosis: a cost of illness retrospective cohort study. Lancet 2007;369:1187-95.
13. Ranieri E, Lewis BD, Gerace RL, et al. Neonatal screening for cystic fibrosis using immunoreactive trypsinogen and direct gene analysis: four years' experience. Br Med J 1994; 308:1469-72.
14. Baumer JH. Evidence based guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. Arch Dis Child; Dec 2003; 88, 12; 1126-1127.
15. Lezana JL. Vargas MH. Karam-Bechara J. Aldana RS. Furuya ME. Sweat conductivity and chloride titration for cystic fibrosis diagnosis in 3834 subjects. J Cystic Fibrosis. 2003;2:1-7.
16. Rosenfeld M, Davis R, FitzSimmons S, et al. Gender gap in cystic fibrosis mortality. Am J Epidemiol 1997;145:794-803.

Author's Correspondence
P Farrell Professor of Paediatrics
University of Wisconsin School of Medicine and Public Health
610 Walnut Street, WARF 785, Madison, WI 53726
Email: pmfarrell@facstaff.wisc.edu

Acknowledgement
Grant Sponsors: US National Institutes of Health Grant DK 34108 and the S hapiro Foundation, Madison, WI, USA
We thank the physicians caring for patients with CF at the 17 centres partici pating in this survey and in the creation
of The Cystic Fibrosis Registry of Ireland. We are grateful to Dr. HuiChuan L ai and Kathy Holland, both at the University of Wisconsin-
Madison, for their help with organizing the Registry and preparing this manu script, respectively.

Other References
No References