Demographic transition of the Swedish cystic fibrosis community—results of modern care

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Abstract Assessing the results of modern cystic fibrosis (CF)-care and estimating the future population and its demography is important to evaluate the treatment regimens and to calculate the future needs of health-care resources. This paper updates previous incidence calculations. It assesses the results of modern CF-care in terms of survival and changing demography in Sweden. The incidence of CF in Sweden was calculated as 1/5600 live-births. Of the CF-population alive in 1999 45% were ≥18 years old. The mean annual mortality rate since 1991 was 0.9% (±0.4) and the median age at death 26 years (range 0–72). Of those born ≥1991, 95% were estimated to survive their 25th birthday. The incidence of CF in Sweden is low. Modern CF-care in Sweden shows good results. The CF-population is growing rapidly and the adult part of the population will soon be larger than the paediatric. Continuously adapted resources are required to assure the future treatment quality, especially for the growing adult CF-population.

INTRODUCTION

The importance of centralised and preventive, aggressive treatment in cystic fibrosis (CF)-care is emphasised in discussions (1–7). The different parts of the multifaceted CF-treatment are continuously developing, resulting in improved clinical status and survival (1–11). However, the results of the care differ a lot from one country to another (10) and sometimes from centre to centre (6).

Assessing the results of modern CF-care and estimating the future population and its demography is important to evaluate the treatment strategies and to calculate the future needs of health-care resources (7,12).

This paper includes all known dead and alive Swedish CF-patients until 1999. The updated incidence of CF in Sweden is discussed as well as the median age at death and the mean annual mortality rate for different periods since 30 years have been recorded. Survival is predicted and the size as well as the demography of the future CF-population in Sweden are estimated.

METHODS

Patients

The population studied includes all known dead and alive CF-patients in Sweden until 1999. The CF-diagnosis was based on clinical symptoms consistent with the U.S. Consensus document 1998 (13). All four CF-centres within the country as well as the departments of paediatrics, respiratory medicine and infectious diseases at all local hospitals were contacted both by letter and telephone. They were asked to report presently and previously known CF-patients. The Swedish Cystic Fibrosis Association was initiated in 1969 and has saved all its lists of members. Information from these lists of present and past members was used. Copies of all death certificates where cystic fibrosis or its synonyms were registered both in words and codes were collected from the National Bureau of Statistics from 1971 when the disease started to be registered.

Data/material

All individuals were reported by date of birth, sex and initials in order to eliminate duplications. In doubtful situations, the different units were contacted and suspected duplications were sorted out. Information about the date of diagnosis, date of death, heart/lung, lung or liver transplantation and patients on waiting lists for transplantation were collected. The few death certificates where either diagnosis or code did not fit were
checked and judged whether to be regarded as CF-patients or not by doctors responsible for the CF-care at the regional CF-centre. A coded questionnaire was distributed to all individuals alive, except those who had had the diagnosis within the last year.

Data analysis

Calculations of incidence were limited to the 1980–89 period since several CF-patients born after 1989 may not as of yet have had a CF-diagnosis. A number of youngsters and adults with CF born during that period but expected not yet to have a CF-diagnosis were added. That number was based on findings in the study. Statistical methods used were cumulated 1-year survival, logistic regression and Cox regression. Mortality rate was calculated as the number of deaths per 100 individuals alive at the end of each year. The cumulative 1-year survival was based on those individuals who had lived to a certain age and who had been diagnosed then or earlier. The 1-year survival was then calculated as the proportion of how many survived the following year. The cumulative survival was calculated as the product of the survival rates during consecutive years. In the calculations, patients were divided into cohorts based on year of birth. The estimated number of patients extrapolated to 2011 was based on linear trends between 1980 and 1997 and divided into children and adults. Predicted survival to 2016 was extrapolated from an estimated constant mortality rate for all ages after the first year of living.

RESULTS

Patients

All CF-centres and all hospital departments asked to provide information replied. The questionnaire distributed to the patients was answered by 74%. The total number of known CF-patients in Sweden in 1999 was 628. Of these, 475 individuals were alive at the time of study, 0–63 years old (51% male). Since 1971, 153 individuals with CF have died, 0–72 years old (45% male). Twenty-nine patients had transplantation; 24 lung, 4 heart/lung and 1 liver. Median age at the time for lung or heart/lung transplantation was 28 years (range 11–46). Three individuals were on the waiting list for lung transplantation. Among all the CF-adults, 22% (31 females and 17 males) had children, of whom 5 had adopted their child(ren). Of the adults who had finished school/education, 75% were working part- or full-time.

Of all the 475 CF-patients alive, 97% were in contact with a CF-centre of whom 54% were seen solely at a CF-centre and 43% had their care shared between their home hospital and a CF-centre. The remaining 3% were seen at their home hospital only.

Age at diagnosis

Median age when symptoms appeared was 1 month although symptoms appeared as late as at 58 years of age. Median age at diagnosis was 9 months (0–64 years). Of all the CF-patients alive, 59% had their diagnosis by the age of 1 year, 25% between 1 and 5 years and 6% >18 years old. Of those alive and >35 years old, 12% had their diagnosis by the age of 1 year and 50% <18 years old.

Incidence

So far, 162 individuals of all live-born from 1980 through 1989 have been diagnosed with CF. This gives a mean annual crude incidence of 1/6500 (range 1/4500–1/10 500). In accordance with study findings, the crude incidence was compensated by adding 6% expected to have their diagnosis when older than 18 years and 4% to have their diagnosis when 11–18 years old. The mean incidence of CF in Sweden was thereby calculated to be approximately 1/5600 or 1.8/10 000 live-births. Mean carrier number in Sweden would then be 1/37.

Survival and estimated population

The median age of CF-patients alive was 16 years (Fig. 1) and the mean age was 18 (±12) years. The oldest patient was 63 years old. At the time of the study, 45% were ≥18 years old and 10% were >35 years old (Fig. 1). The mean annual mortality rate since 1991 was 0.9% (±0.4), corresponding results specified for different periods are presented in Fig. 2. This figure also shows the corresponding median age at death, which since 1991 was 26 years (range 0–72). The predicted survival for the different groups until year 2016 are shown in Fig. 3; 95% of the patients born in 1991 or later are predicted to become ≥25 years old. Provided the number of live-births remains the same, the CF-population will have increased with 36% by the year 2011.

DISCUSSION

The ΔF508 is generally associated with a more aggressive disease. The frequency of ΔF508 mutations among CF-alleles within the Swedish CF-population alive is 68.3%, 47% of the patients are homozygous for ΔF508 (I4). Two other mutations are fairly common, 394delTT 8.5% and 3659delC 7.9% (I4). The ΔF508 frequency in our population is comparable to that in other European populations studied where the ΔF508 frequency is reported to be 54–88% (I5).

Another factor associated with severe clinical disease is pancreas dysfunction. Of the Swedish CF-population, 87% within the paediatric and 90% within the adult part received pancreatic enzyme substitution (national
This is comparable to most CF-populations (15, 16). However, a compilation of data enrolled in the European Epidemiologic Registry of Cystic Fibrosis (ERCF) in 1996 including 6858 CF-patients from eight countries, showed 93–97% within different sub-groups <13 years old and 78–94% within different sub-groups >18 years old to be treated with pancreatic enzymes (17). Data from the same registry in 1997 including 11,749 CF-patients from nine countries showed 97% of the <18 years old and 95% of the >18 years old to be treated with pancreatic enzymes (18). To what extent these data are representative remains to be seen, since the number of patients included in the ERCF at the time for the second compilation was estimated to be about half of the whole CF-population in the nine countries (18). In our population, the paediatric group received pancreatic enzyme substitution to a less degree than the adult group, which is surprising. One factor might be the early diagnosing that could result in relatively many of those not needing substitution being included in the paediatric group. This in combination with the fact that some adults who never received substitution as children but who have had gastrointestinal problems as adults have had less symptoms once starting on substitution. Added to this is the fact that differences in diagnostic criteria when it comes to need for pancreatic enzyme substitution can vary and make comparisons difficult (18).

Chronic colonisation of *Pseudomonas aeruginosa* (PA) is generally associated with a more aggressive lung disease. Of our CF-population 48% was chronically colonised with PA: 36% of the paediatric and 62% of the adult population (national CF-registry, unpublished results). This is comparable to the 45% of a Danish CF-population (19). A study including 63% of the North American

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**Fig. 1.** Age distribution of the Swedish CF-population of 1999.

**Fig. 2.** Mean annual mortality rate/period ± SE and median age at death/period in the Swedish CF-population.

**Fig. 3.** Current and estimated survival rates of four different cohorts of Swedish CF-patients.
CF-population reported 61% chronically colonised with PA (16). Of the adults taken care of first by a paediatric and then an adult CF-centre in the U.K. 90% were reported chronically colonised with PA (4).

The incidence calculations were based on the number of diagnosed patients born during 1980–89. This 10-year period was chosen since the disease was commonly known within health care by then and most individuals with CF born during these years ought to have been identified by now. Our calculated incidence for CF in Sweden, of approximately 1/5600, is lower than what has been calculated for the U.S.A. (9) and less or in the lower span of what is calculated for the Western Europe as a whole (2,3,5,8). It is also less than what was calculated for Sweden in 1982 (20) but more than in 1962 (21). One can only speculate in the results of the two Swedish studies carried out with a 20-year interval. One probable reason is under-diagnosing in the 1962 data. All data are not presented in the study published in 1982, which makes the discrepancy from the current results difficult to comment.

Of the whole Swedish CF-population, 6% were diagnosed after age 18 years. Most patients with late diagnosis had a milder disease, but this was not always the case. There were patients who were diagnosed as respiratory insufficient adults. Continuous information and reminders about CF within adult health care of different disciplines remains important.

The proportion adults (≥18 years old) within the Swedish CF-population has increased to 45% (Fig. 1), compared to 32% in 1986 (22). Data from the European CF-registry 1997 including 12 447 individuals with CF from Austria, Belgium, Denmark, France, Germany, Ireland, Netherlands, Sweden and United Kingdom showed 29% of the population to be ≥18 years old (II). Among the CF-patients included in the Cystic Fibrosis Foundation (U.S.A.) Registry 2000, about 1/3 were adults (23).

Data from 114 accredited CF-centres in the U.S.A. in 1990 showed a mortality rate of 2.3% (9) and the mortality rate for the U.K. CF-population was 2.1% during 1995 (3). Frederiksen et al. have reported the best results so far when they showed an annual mortality rate of 0–1.2% during 1989–93 among Danish CF-patients treated at the Copenhagen CF-centre (75% of the whole Danish CF-population) (2). The mean annual mortality rate (since 1991, 0.9%) found in this study which compiles all Swedish CF-patients can very well be compared to the Danish results (Fig. 2). Another parameter of interest when assessing treatment effects for a whole population is median age at death (10). The median age at death in our population since 1991 was 26 years (Fig. 2), which is relatively high in comparison to other reports (2,3,8–11).

The fact that fewer CF-patients die early in life make long-time survival predictions more and more difficult to carry out (3). We decided to make a short prediction which showed 95% of the cohort born ≥1991 predicted to survive their 25th birthday (Fig. 3). The survival probability in Denmark for a child born with CF during 1989–93 and treated at a CF-centre was estimated to be 80% reaching its 45th birthday (2). For patients included in the Cystic Fibrosis Foundation (U.S.A.) Registry 2000, the median survival was predicted to the early 30s (23). Canadian data from 1998 showed predicted survival till adulthood of 80% (24). The largest difference and improvement in our study is seen during the first year of life (Fig. 3), as has been shown by others as well (7). This difference is probably due to the modern CF-care dealing with meconium ileus and malnutrition in a more effective way. The survival rate after the first year of life, or during the last ten years, might be more informative when it comes to evaluating standards for CF-treatment. Differences comparable might then be focusing on the modern CF-care dealing with nutritional factors, pulmonary hyper secretion, infections and physical exercise.

It has been shown that management of CF by specialist teams in centres produce better clinical outcome parameters (1,4). The proportion patients in contact with a CF-centre is big in our population (97%). A large part of the population, 43%, also have a regular contact with their home hospital, shared care. Shared care is said to be appreciated by both the patients living far from a CF-centre and the home hospital staff.

Considering the high median age at death, the major increase of the CF-population will be in the adult group (≥18 years), which in a couple of years is predicted to be larger than the paediatric group. The CF-adults will probably be suffering from ordinary health-care problems with growing age at least to the same extent as people without CF (3). It still remains to be seen as to what CF itself and the treatment does to the body in the long run (25). It is of great importance that resources are kept up with the growing adult population, otherwise the improving survival rate cannot be expected to continue (4,7,12).

CONCLUSION

The incidence of CF in Sweden is relatively low. Internationally compared, the annual mortality rate has been low since 1991 and the median age at death high. For patients born ≥1991 predicted survival at age 25 years is 95%. We credit the improving survival to the centralised, modern, active CF-care in Sweden. The improving survival is leading us to a rapidly growing CF-population with a proportion ≥18 years old that soon outnumber the paediatric patients. This demographic transition will increase the demands on the adult CF-health care.

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