ABSTRACT. Objective. Pancreatitis is an infrequent complication among patients with cystic fibrosis (CF). It has mainly been reported for patients with pancreatic sufficiency (PS). Previous studies involved only a small number of patients because they contained data from single centers. The aim of this study was to evaluate the incidence of pancreatitis in a large heterogeneous CF population, to determine the relationship with pancreatic function, and to assess whether pancreatitis is associated with specific CFTR mutations.

Methods. Physicians caring for patients with CF were approached through the CF Thematic Network or through the European Cystic Fibrosis Foundation newsletter. They were asked to provide data on their current patient cohort through a standardized questionnaire and to report how many patients they had ever diagnosed as having pancreatitis. A detailed questionnaire was then sent, to be filled out for all of their patients for whom pancreatitis had ever occurred. We defined pancreatitis as an episode of acute abdominal pain associated with serum amylase levels elevated above the ranges established by each participating center’s laboratory. General clinical data included age, genotype, age at diagnosis of CF, sweat chloride concentrations, pancreatic status, biometric findings, and respiratory status. CFTR mutations were also reported according to the functional classification of classes I to V. Patients were categorized as having PS, pancreatic insufficiency (PI), or PI after an initial period of PS. PI was defined as a 72-hour stool fat loss of >7 g/day, fat absorption of <93%, or fecal elastase levels of <200 μg/g feces. Clinical data on pancreatitis included age at the first episode, amylase and lipase levels, possible triggers, and occurrence of relapses or complications.

Results. A total of 10,071 patients with CF, from 29 different countries, who were undergoing follow-up monitoring in 2002 were surveyed. Among this group, pancreatitis had ever been diagnosed for 125 patients (1.24%; 95% confidence interval [CI]: 1.02–1.46%). There was variability in the reported rates of pancreatitis for different countries. Twenty-six centers in 15 different countries sent detailed clinical data on their patients with pancreatitis and on their whole CF clinic. This involved 3,306 patients with CF and 61 cases of pancreatitis, leading to a prevalence of 1.84% (95% CI: 1.39–2.30%). The mean age of the patients with pancreatitis ever was 24.4 years (SD: 10.8 years). The first episode of pancreatitis occurred at a mean age of 19.9 years (SD: 9.6 years). The median serum amylase level at the time of pancreatitis was 746 IU/L (interquartile range: 319–1630 IU/L), and the median lipase level was 577 IU/L (interquartile range: 229–1650 IU/L). The majority of patients had PS (34 of 61 patients, 56%; 95% CI: 43–68%). Pancreatitis occurred for 15 patients with PI (25%; 95% CI: 14–33%). Eight patients developed PI after initial PS. The occurrence of pancreatitis among patients with PS was 34 cases per 331 patients, ie, 10.27% (95% CI: 7.00–13.53%); the occurrence of pancreatitis among patients with PI was 15 cases per 2,971 patients, ie, 0.5% (95% CI: 0.25–0.76%). The mean age (in 2002) of the CF cohort with pancreatitis did not differ between the PS and PI subgroups. The forced expiratory volume in 1 second was significantly lower among the patients with PI than among the patients with PS, ie, 65% (SEM: 7%) vs 79% (SEM: 4%). The mean age at the occurrence of pancreatitis and the amylase and lipase levels during pancreatitis were not different for patients with pancreatitis and PI versus PS. In the group with PS, 31 of 34 patients carried at least 1 class IV or V CFTR mutation. In the groups with PI and PI after PS, 5 of 15 patients and 3 of 8 patients, respectively, carried 2 class I, II, or III CFTR mutations. Relapses and/or evolution to chronic pancreatitis occurred for 42 patients. Pancreatitis preceded the diagnosis of CF in 18 of 61 cases. These patients were significantly older than the rest of the cohort, ie, age of 28.4 years (SEM: 3.4 years) vs 22.7 years (SEM: 1.3 years). Their median age at the diagnosis of CF was also significantly greater, ie, 21.5 years (interquartile range: 11.9–31 years) vs 7.6 years (interquartile range: 0.4–17.0 years). However, the ages at the occurrence of pancreatitis were similar, ie, 21.0 years (SEM: 3.0 years) vs 19.5 years (SEM: 1.2 years).

Conclusions. This study of 10,071 patients with CF from 29 different countries revealed an estimated overall occurrence of pancreatitis among patients with CF of 1.24% (95% CI: 1.02–1.46%). The incidence of pancreatitis was much higher among patients with PS. However, pancreatitis was also reported for 15 patients with PI from 11 centers in 9 different countries. A correct diagnosis of pancreatitis for the reported patients with PI was supported by amylase and lipase levels increased above 500 IU/L, similar to those for patients with PS and pancreatitis. A correct diagnosis of PI for these patients with pancreatitis was supported by the adequacy of the methods used. We chose the cutoff values used to distinguish between patients with PI and control subjects without gastrointestinal disease. For one half of the patients, the diagnosis of PI was established on the basis of low levels of stool elastase (mean: 97 μg/g stool). With a cutoff value of 200 μg/g stool, this noninvasive test has high sensitivity (>95%) and high specificity (>90%) to differentiate patients with PI from control subjects with normal pan-
Cystic fibrosis (CF) is the most common inherited disease among whites. It is caused by defects in the CF transmembrane conductance regulator (CFTR) gene, which encodes a protein that functions as a cAMP-regulated chloride channel. Defects in the CFTR protein cause abnormal chloride transport across the apical membranes of epithelial cells in the airways, pancreas, intestine, and vas deferens, leading to progressive lung disease, pancreatic and intestinal insufficiency, and ductal insufficiency. 

Pancreatitis is a rare complication among patients with CF. It occurred for 1.24% (95% CI: 1.02–1.46%) of a large CF cohort. Pancreatitis occurs mainly during adolescence and young adulthood. It is much more common among patients with CF and PS (10.3%), but it can occur among patients with PI (0.5%). Pancreatitis can be the first manifestation of CF. Pancreatitis was reported for patients carrying a wide range of mutations. 

**METHODS**

Physicians caring for patients with CF were approached through the CF Thematic Network or through the European CF Foundation newsletter (www.ecsfoc.org). They were asked to provide data on their current patient cohort through a standardized questionnaire and to report how many patients they had ever diagnosed as having pancreatitis. A detailed questionnaire was then sent, to be filled out for all of their patients for whom pancreatitis had ever occurred. We defined pancreatitis as an episode of acute abdominal pain associated with serum amylase and lipase levels elevated above the ranges established by each of the participating center’s laboratories.

General clinical data included date of birth, genotype, age at diagnosis of CF, sweat chloride concentrations, pancreatic status, body mass index, and respiratory status. CFTR mutations were also reported as functional class I to V. Patients were categorized as having PS, PI, or PI after an initial period of PS. PI was defined as 72-hour stool fat loss of >7 g/day, fat absorption of <95%, or fecal elastase levels of <200 μg/g feces. Patients taking oral pancreatic enzyme supplementation to maintain weight growth but without proof of PI or with discordant results were not classified. SD scores for height and weight were calculated with the standards reported by Hernandez et al. Clinical data on pancreatitis included age at first episode, amylase and lipase levels, possible triggers, and occurrence of relapses or complications.

If normally distributed, results of continuous data were expressed as means (with SDs and/or SEMs) and analyzed with Student’s t test. Variables that did not show normal distribution were expressed as medians (with interquartile ranges) and compared with the Mann-Whitney U test. Categorical data were analyzed with Fisher’s exact test. P values of <.05 were considered statistically significant.

**RESULTS**

**Overall Prevalence of Pancreatitis Among 10,071 Patients With CF**

A total of 10,071 patients with CF, from 29 different countries, who were undergoing follow-up monitoring in 2002 were surveyed. Among this group, pancreatitis had ever been diagnosed for 125 patients (1.24%; 95% CI: 1.02–1.46%). There was variability in the reported rates of pancreatitis in different countries. The prevalence of pancreatitis was apparently higher in Slovakia (14.04%) and Israel (4.53%) and lower in Australia (0.40%) and the United Kingdom (0.06%) (Fig 1).
and 29 female patients with pancreatitis are summarized in Table 1. The mean age of the cohort was 24.4 years (SD: 10.8 years). The first episode of pancreatitis occurred at the mean age of 19.9 years (SD: 9.6 years). The median serum amylase level at the time of pancreatitis was 746 IU/L (interquartile range: 319–1630 IU/L), and the median lipase level was 577 IU/L (interquartile range: 229–1650 IU/L).

Pancreatic Status

The occurrence of pancreatitis among patients with PS was 34 cases per 331 patients, ie, 10.27% (95% CI: 7.00–13.55%); the occurrence of pancreatitis among patients with PI was 15 cases per 2971 patients, ie, 0.5% (95% CI: 0.25–0.76%). For one half of the patients, the pancreatic status was determined through fecal fat analysis; for the other one half, fecal elastase levels were used. The mean stool elastase level in the PI subgroup was 97 μg/g stool (SEM: 28 μg/g stool) (n = 8), and that in the PS subgroup was 362 μg/g stool (SEM: 42 μg/g stool) (n = 16) (P = .0006, unpaired t test).

Pancreatitis Among Patients With PS Versus PI

The mean age (in 2002) of the CF cohort with pancreatitis did not differ between the PS and PI subgroups (Table 1). The forced expiratory volume in 1 second (FEV1) was significantly lower among the patients with PI than among the patients with PS, ie, 75 (3) vs 24.1 (2.0) vs 23.2 (3.0) vs 25.6 (3.5) vs 36.2 (2.8). The majority of patients with pancreatitis demonstrated PS, ie, 34 of 61 patients (56%). PI from diagnosis was reported for 15 of 61 patients (25%). PI after an initial period of PS was reported for 8 of 61 patients (13%). Three of those 8 patients had PS at the time of the pancreatitis, and 2 patients already had PI before the occurrence of pancreatitis, with fecal fat loss of 17 g/day and 8.4 g/day. For 3 patients, it was unclear whether PI preceded pancreatitis. For 4 patients (6%), pancreatic status was not classified; 3 of those patients were taking pancreatic enzymes without objective proof of PI (based on fecal fat content or fecal elastase levels), and fecal elastase levels showed discordant results for 1 patient (70, 113, 458, and 71 μg/g feces).
65% of normal values (SEM: 7%) vs 79% (SEM: 4%) (P < .05, unpaired t test). The median age at the diagnosis of CF was lower in the PI group, but the difference was not statistically significant. The mean age at the occurrence of pancreatitis did not differ between the PS and PI groups. Patients with PS and patients with PI did not have significantly different amylase or lipase levels.

Pancreatitis and Diagnosis of CF

For 18 patients, the diagnosis of pancreatitis preceded the diagnosis of CF; 12 of those 18 patients had PS, 4 had PI, and 2 had PI after PS. For 13 of those 18 patients, the diagnosis of CF was made within 12 months after the occurrence of pancreatitis. The diagnosis of pancreatitis preceded the diagnosis of CF for 8 of 13 Israeli patients, which was significantly more frequent than for the rest of the cohort (P = .004, Fisher’s exact test). Patients for whom the diagnosis of pancreatitis preceded the diagnosis of CF were significantly older than the rest of the cohort, ie, age of 28.4 years (SEM: 3.4 years) vs 22.7 years (SEM: 1.3 years) (P < .05, unpaired t test). Their median age at the diagnosis of CF was also significantly greater, ie, 21.5 years (interquartile range: 11.9–31 years) vs 7.6 years (interquartile range: 0.4–17.0 years) (P < .001, Mann-Whitney U test). However, their ages at the occurrence of pancreatitis were similar, ie, 21.0 years (SEM: 3.0 years) vs 19.5 years (SEM: 1.2 years). There were no differences in serum amylase or lipase levels when pancreatitis occurred. Their sweat chloride levels were somewhat lower, ie, 83 mEq/L (SEM: 6 mEq/L) vs 91 mEq/L (SEM: 4 mEq/L), their FEV, values predicted somewhat better, ie, 79% (SEM: 8%) vs 74% (SEM: 4%). Neither of these differences was statistically significant.

Triggers of Pancreatitis

There was no difference in the frequency of triggers mentioned between patients with PS and patients with PI. For 6 of 34 patients with pancreatitis and PS, 1 or several triggers were mentioned, including fatty food (4 patients), alcohol (1 patient), lithiasis (1 patient), stress (1 patient), and medication (1 patient). For 4 of 15 patients with pancreatitis and PI, the triggers mentioned included fatty food (3 patients), small amounts of alcohol (1 patient), coffee (1 patient), and discontinuation of pancreatic enzyme therapy (1 patient).

Complications of Pancreatitis

Complications of pancreatitis were reported for 5 patients, including transient elevation of serum glucose levels (1 patient with PS), onset of insulin-dependent diabetes mellitus (1 patient with PI), pancreatic stones (1 patient with PI and 1 patient with PI after PS), and onset of PI immediately after the episode of pancreatitis (1 patient; fecal elastase levels decreased from 305 μg/g stool before to 102 μg/g stool after the episode of pancreatitis).

Outcomes

For 42 of 61 patients, relapses and/or evolution to chronic pancreatitis occurred. Thirty five of 61 patients had relapses after the first episode of pancreatitis; 10 patients had 1 relapse and the others had up to 8 episodes. Ten patients experienced evolution to chronic pancreatitis; for 7 of these patients, the first episode never cleared but immediately led to chronic pancreatitis. Relapses of pancreatitis occurred more frequently among patients with PS (21 of 34 patients with PS, compared with 5 of 15 patients with PI; P = .04, Fisher’s exact test). Evolution to chronic pancreatitis was more frequent among patients with PI (3 of 34 patients with PS, compared with 6 of 15 patients with PI; P = .01, Fisher’s exact test).

Genotype and Pancreatic Status

Pancreatitis was reported for patients carrying a wide range of mutations. In Table 2, patients are categorized according to pancreatic phenotype. For 24 of 34 patients with PS, both mutations were known; 21 of 24 carried at least 1 class IV or V mutation and 3 patients carried 2 class I to III mutations. The remaining 10 patients carried 1 class I to III mutation and the other mutation was unknown. Among the 15 patients with PI, 1 refused genotype testing, 5 carried 2 class I to III mutations, and 7 carried 1 class IV or V mutation. One patient demonstrated F508del/I1005R. The I1005R mutation is reported with severe pulmonary disease but mild pancreatic disease. The reported patient had PI, however, because stool elastase levels were 0 μg/g. Class IV and V mutations reported among the patients with PI included D1152H (n = 2), A455E (n = 2), R1066H (n = 1), S13F (n = 1), and 1898+3A>G (n = 1). Of the patients with PI after PS, 3 of 8 carried 2 class I to III mutations.

DISCUSSION

This study of 10 071 patients with CF from 29 different countries revealed an estimated overall occurrence of pancreatitis among patients with CF of 1.24% (95% CI: 1.02–1.46%). The current survey supports the fact that pancreatitis does occur among patients with PI. In addition, in this large cohort, the correlation between genotype and pancreatic status does not seem as rigid as in some earlier reports.

The occurrence of pancreatitis in Canada13 (1.7%) was similar to that reported in the present study. Lower rates were reported by Shwachman et al8 for the United States (0.5%). The reasons for geographic variability and the lower occurrence rate in the United States could be multiple. The exact numbers in the cohort reported by Shwachman et al8 are not known (10 patients with pancreatitis in a population of >2000 patients). In 1975, survival rates were worse and patients might have died too young for pancreatitis to occur. Underdiagnosis of a thus far unknown complication was likely, and lack of genetic testing and nasal potential difference measurements might have led to missed diagnoses of atypical CF.

In the present survey, the incidence of pancreatitis was significantly higher in Israel and Slovakia (Fig 1). Full clinical data were available for the 13 Israeli patients and confirmed an accurate diagnosis of pancreatitis for all of them, including 2 patients with PI with elastase levels of 110 and 48 μg/g stool. The
higher incidence of pancreatitis in Israel could be attributable to a larger proportion of patients with PS, a larger proportion of specific mutations\textsuperscript{17} possibly more frequently associated with pancreatitis, or increased awareness of a possible diagnosis of CF for patients with pancreatitis. The latter is likely, because the diagnosis of pancreatitis preceded the diagnosis of CF for 8 of 13 patients. This was significantly more often than for the rest of the cohort. Physicians from Slovakia reported 32 patients with pancreatitis (14.04%). Unfortunately, we did not receive full clinical data for those patients. The lower incidence in Britain and Australia could be attributable to underdiagnosis or a different genetic background for CFTR mutations, as well as possible modifier genes.

The incidence of pancreatitis is much higher among patients with PS. However, pancreatitis was also reported for 15 patients with PI from 11 centers in 9 different countries. More than 85% to 95% of the exocrine pancreatic function is destroyed before a clinical phenotype of PI with fecal fat loss occurs.\textsuperscript{18} Waters et al\textsuperscript{19} documented that 37% of infants with CF had substantial preservation of pancreatic function, with only 21% of them developing PI before 4 years of age. In addition, most patients with PS do not have fully normal pancreatic function, and some patients with PI do have some residual pancreatic function.\textsuperscript{18,20,21} A correct diagnosis of pancreatitis for the reported patients with PI is supported by amylase and lipase levels increased above 500 IU/L, similar to values for patients with PS and pancreatitis (Table 1). A correct diagnosis of PI for these patients with pancreatitis is supported by the adequacy of the methods used. We chose the cutoff values used to distinguish between patients with PI and control subjects without gastrointestinal disease. For one half of the patients, the diagnosis of PI was established with low levels of stool elastase (mean: 97 μg/g stool). With a cutoff value of 200 μg/g stool, this noninvasive test has high sensitivity (>95%) and high specificity (>90%) to differentiate patients with PI from control subjects with normal pancreatic function.\textsuperscript{22,23} It is not clear what the best cutoff value would be to distinguish patients with CF and PI from patients with CF and PS. Beharry et al\textsuperscript{23} used a cutoff value of 100 μg/g feces; the mean stool elastase level for 18 patients with CF and PS was 589 μg/g stool, with only 2 patients having values of <200 μg/g feces, and all patients with CF and PI had values of ≥100 μg/g stool. The mean elastase level for patients with PI who were homozygous for F508del was reported as 16 μg/g feces, but the value increased when CF cohorts with PI included genotypes other than F508del.\textsuperscript{24} The latter authors suggested using a cutoff value between 160 and 200 μg/g feces. Elastase levels between 100 and 200 μg/g are rare and may be more difficult to interpret. In addition, variability is obvious with repeat measurements for some patients.\textsuperscript{25} In the current PI cohort, 5 of 8 patients had elastase levels below the more stringent cutoff value of 100 μg/g stool. For the other one half of the patients with PI in the cohort, the pancreatic status was determined on the basis of the 3-day fecal fat balance. A cutoff value of 7 g of fat loss per day was chosen. Walkowiak et al\textsuperscript{22} reported that approximately three fourths of patients with CF and PI had steatorrhea of >15 g/day; for the others, steatorrhea was milder. Although it is less likely, we cannot exclude the possibility that steatorrhea could result from nonpancreatic causes for some patients in the reported PI cohort.

Pancreatitis among patients with PI has been described before. De Braekeleer et al\textsuperscript{26} reported that 4
patients with PI experienced several episodes of pancreatitis. For all 4, the diagnosis of CF was made and the PI was well documented several years before the first episode of pancreatitis. Two patients carried A455E/F508 and 2 carried A455E/621+1G>T. Munck reported acute pancreatitis as a presenting symptom during heat stroke for 3 patients with CF; 1 patient had PS and a fecal elastase level of 500 μg/g feces, and the others had moderate PI and stool elastase levels of 102 and 162 μg/g.

The most likely reason for pancreatitis occurring among patients with PI is that some residual pancreatic tissue is present among these patients. It is unlikely that, during an attack of acute abdominal pain, lipases and amylases would be derived from lingual or salivary sources. In this study, pancreatitis among patients with CF and PI was rare (−0.5%), especially compared with the 10.3% occurrence among patients with CF and PS. In the smaller cohort reported by Durno et al., not 1 patient with pancreatitis had PI but the incidence of 13.7% among patients with PS was quite similar.

At first glance, the rather poor correlation between genotype and pancreatic status in the current survey is unexpected. Only one third of patients with PI had 2 class I to III mutations; the others carried a mutation of class IV or V, usually associated with PS. Of the 34 patients with PS and pancreatitis, 3 carried 2 class I to III mutations. For several mutations, variable pancreatic status has been described. S1251N is normally associated with PI but was included in the report by Durno et al. as being associated with PS. A455E, the Dutch mutation, is considered a class IV mutation but 50% to 75% of patients were reported to have PI. G85E, the Mediterranean mutation, was reported by Durno et al. with PS, but it is actually a class II mutation with some variability in pancreatic function. In the present study, well-accepted methods of stool analysis (fat loss of >7 g/day or elastase levels of <200 μg/g stool) were chosen to determine pancreatic status as PS or PI. To classify their patients as having PI or PS, Durno et al. stated that “at diagnosis the pancreatic status is assessed by a combination of tests,” but they did not specify what cutoff values were used. In their cohort, all patients with PI had 2 class I to III mutations but 2 of 72 patients with PS carried 2 class I to III mutations, including 1 patient homozygous for F508del. In the European database, 90% of patients carrying 2 class I to III mutations were reported as taking pancreatic enzymes and thus having PI, and 50% of patients carrying 1 class IV or V mutation were reported as not taking pancreatic enzymes and having PS. For a French cohort of 224 patients, definitions of PS and PI were not given but the authors stated that 14% of patients with PI carried 1 class I to III mutation and 6% of patients with PS carried 2 class I to III mutations. In other large surveys, genotype and pancreatic status did not exhibit perfect correlations; 2 class I to III mutations were described with PS, and PI was reported for patients with 1 class IV or V mutation. It is not known whether the polythymidine haplotypes or other modifier genes have effects on the expression of pancreatic dysfunction. Among patients with CF, pancreatic disease covers a very wide spectrum, from (almost) normal to total loss of function. According to the definition used to determine the pancreatic status, the closeness of a correlation between genotype and pancreatic status may differ. This survey clearly shows that pancreatitis can occur among patients with CF and PI defined according to generally accepted criteria. There seems to be a skew toward patients with PI and retention of some functional pancreatic tissue, however, and the later age at diagnosis, 7 of 15 patients with PI having 1 class IV or V mutation, and the mean elastase level being higher than that reported for a cohort homozygous for F508del support this fact.

CFTR mutations play an important role in pancreatitis among patients without classical CF. Studies by Sharer et al. and Cohn et al. demonstrated a significant increase in CFTR gene mutations among patients with so-called idiopathic pancreatitis. The finding of many patients with CF in the present survey experiencing relapses or evolution to chronic pancreatitis is in agreement with the recent report by Frulloni et al. They reported that relapses and evolution to chronic pancreatitis were more common among patients with pancreatitis and CFTR mutations.

Pancreatitis tends to be a complication for adolescent and adult patients with CF, and the reasons are unclear. Fatty meals are the trigger most often mentioned. Are the increased nutritional demands during puberty the trigger that stresses an already compromised pancreatic gland? This is not likely a major factor, because pancreatitis occurs well past puberty for most patients. Few investigators mentioned alcohol as a possible precipitating factor, consumption of which may start during adolescence. One investigator specifically mentioned that minor amounts of alcohol produced an attack. In the present survey, some cases were reported at 3 to 8 years of age; in the Canadian cohort, several patients were only 10 to 12 years of age. It is possible that the diagnosis is missed more often among younger patients, because abdominal pain is a common complaint and bouts of pancreatitis may remain undiagnosed.

This study is the first large-scale study that can answer general questions regarding the occurrence and outcomes of pancreatitis in different geographic populations and among patients with different genotypes. There are inherent weaknesses associated with multicenter surveys, however. The study was retrospective in nature and, although strict definitions were used, the assays were performed in a variety of laboratories, with possible differences in the quality of data analysis and reporting.

Many results of this survey were in accordance with data reported by Durno et al., such as the frequency of the occurrence of pancreatitis, the mean age at the diagnosis of pancreatitis, and the diagnosis of pancreatitis preceding the diagnosis of CF for approximately one third of patients. The latter finding emphasizes the point that the diagnosis of CF must be pursued with refined diagnostic techniques for all patients with idiopathic pancreatitis.
with CF. It occurred for 1.24% (95% CI: 1.02–1.46%) of a large CF cohort. Pancreatitis mainly occurs during adolescence and young adulthood. It is much more common among patients with CF and PS (10.3%), but it can occur among patients with PI (0.5%). Pancreatitis can be the first manifestation of CF.

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