HHS Public Access

Author manuscript

Pancreas. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Pancreas. 2019 August ; 48(7): 888–893. doi:10.1097/MPA.0000000000001350.

Acute Recurrent and Chronic Pancreatitis as Initial Manifestations of Cystic Fibrosis and Cystic Fibrosis Transmembrane Conductance Regulator-Related Disorders

Christina Baldwin, MD[*], **Melissa Zerofsky, PhD**[†], **Meghana Sathe, MD**[*], **David M. Troendle, MD**[*], **Emily R. Perito, MD**[†]

[*]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Texas Southwestern, Dallas, TX;

[†]Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Francisco, San Francisco, CA.

Abstract

Objectives: Recurrent pancreatitis is considered a rare manifestation of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction; this case series highlights that pancreatitis can be a presenting symptoms of cystic fibrosis (CF) or a CFTR-related disorder (CFTR-RD).

Methods: Retrospective review of patients younger than 30 years diagnosed as having acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) and subsequently diagnosed as having CF or CFTR-RD.

Results: Among 18 patients, median time from diagnosis of ARP/CP to diagnosis of CF was 0.4 years (range, 0–33 years). Eight were classified as having CF by elevated sweat chloride testing (SCT). Five had intermediate SCT (30–59 mmol/L) with 2 pathogenic mutations. Five had CFTR-RD with intermediate SCTand 0 to 1 pathogenic mutations. Eight patients (44%) had exocrine pancreatic insufficiency, and pancreatic fluid collections were more common in this group. Based on the *CFTR* mutation, 6 patients were eligible for CFTR potentiator therapy, although none received it during the study period. Nine of the 18 had ≥1 other likely CF manifestations, including sinusitis (33%), nasal polyps (11%), pneumonia (22%), and gallbladder disease (22%).

Conclusions: Cystic fibrosis or CFTR-RD can present as ARP/CP. Complete diagnostic testing for CFTR-RD in patients with ARP/CP will broaden treatment options and help to identify comorbid illness.

Address correspondence to: Emily R. Perito, MD, Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Francisco, 550 16th St, 5th Floor, Box 0136, San Francisco, CA 94143 (emily.perito@ucsf.edu).

The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the NIH or the Cystic Fibrosis Foundation. These data were presented previously as a poster at North American Society for Pediatric Gastroenterology, Hepatology and Nutrition 2018 meeting.

The authors declare no conflict of interest.

Keywords

cystic fibrosis; acute recurrent pancreatitis; chronic pancreatitis; CFTR-related disorder

Cystic fibrosis (CF) is increasingly recognized as a heterogeneous disease with significant variability in organ-specific manifestations between patients. A diagnosis of CF can be delayed in patients who lack classic symptoms such as pancreatic insufficiency, malnutrition, or respiratory disease. Advances in genetic sequencing technology of the CF transmembrane receptor (CFTR) and increased availability of CFTR functional testing have also led to the expanded diagnosis category of CFTR-related disorders (CFTR-RD).[1] Cystic fibrosis transmembrane receptor– related disorders are associated with CFTR dysfunction that does not fulfill diagnostic criteria for CF.[2] As treatment options have improved, diagnosis of CF or CFTR-RD has become increasingly key to achieving optimal clinical outcomes.

Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are described as relatively rare manifestations of CF. They have been associated with minimal or mild respiratory disease and pancreatic sufficiency.[3] However, particularly in children and young adults, CFTR-RD may be a relatively common contributor to ARP and CP. In the largest pediatric ARP/CP cohort, *CFTR* mutations were recently reported in 34% and 23% of ARP and CP patients, respectively.[4]

Establishing CFTR dysfunction as a cause of or contributor to ARP and CP is critical to adequately caring for these patients and understanding the systemic scope of their disease, and potentially for increasing their access to treatments.

This case series describes 18 patients who first presented with ARP or CP and were subsequently diagnosed as having CF or CFTR-RD. Our main objectives for this case series are to highlight CF and CFTR-RD as causes for ARP/CP and to illustrate the phenotypic spectrum of CFTR dysfunction in these patients.

MATERIALS AND METHODS

Research study staff (M.Z. and C.B.) reviewed retrospective medical records of children and young adults followed for ARP or CP at 2 tertiary care institutions and identified those who were diagnosed between 2007 and 2017 with ARP/CP who were subsequently diagnosed as having CF or CFTR-RD by sweat test and/ or genetic testing. Patients included were diagnosed as having ARP or CP at less than 30 years of age. Clinical symptoms, imaging, histology, and treatments were extracted from medical records. The Committees for Human Research at the University of California San Francisco (no. 17–21962; approval date: April 20, 2017) and University of Texas Southwestern (no. STU 052017–048; approval date: May 19, 2017) approved this study.

Definitions

Pancreatitis and Pancreatic Function—Acute recurrent pancreatitis and CP were defined using the *I*Nternational *S*tudy *G*roup of *P*ediatric *P*ancreatitis: *I*n Search for a Cu*RE*

(INSPPIRE) guidelines.[5] The diagnosis of ARP required at least 2 distinct episodes meeting 2 of 3 criteria: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal, and (3) imaging findings characteristic of AP. Chronic pancreatitis required imaging findings of chronic pancreatic damage and at least one of the following: (1) abdominal pain compatible with AP, (2) exocrine pancreatic insufficiency (EPI), and (3) endocrine pancreatic insufficiency. Features of chronicity were defined by using the diagnostic criteria provided by the 2014 American Pancreatic Association.[6] The EPI was defined as the presence of abnormal fecal elastase (<100 μg/g from stool). Endocrine pancreatic dysfunction was defined by random glucose >200 mg/dL and/or if hemoglobin A1c was >6.5%. For patients who underwent oral glucose tolerance testing (n = 6), results were defined by the CF Foundation guidelines: normal glucose tolerance is fasting glucose <100 mg/dL and 2-hour <140 mg/dL; impaired glucose tolerance is fasting glucose 100 to 125 mg/dL and/or 2-hour glucose 140–199 mg/dL. Insulin-dependent diabetes was defined by abnormal hemoglobin A1c or glucose tolerance testing and requirement of insulin for glucose control.

Diagnosis of CF and CFTR-RD—Using 2017 guidelines from the CF Foundation, a diagnosis of CF was based on a positive sweat chloride test (SCT; ≥60 mmol/L) with clinical manifestations such as pancreatitis or chronic sinusitis,[1] or clinical manifestations, an indeterminate SCT (30–59 mmol/L), and 2 CF-causing mutations. A diagnosis of CFTR-RD was applied to individuals who had a monosymptomatic clinical entity of CFTR dysfunction, that is, pancreatitis, but with intermediate SCT (30–59 mmol/L) and fewer than 2 pathogenic *CFTR* mutations in trans.[1]

Genetic Testing—Patients underwent comprehensive genetic testing for *CFTR*, along with additional 4 gene testing for hereditary pancreatitis including *CTRC*, *PRSS1*, and *SPINK1*. Depending on availability of testing at the time of diagnosis, if less than 2 pathogenic mutations for *CFTR* in the presence of abnormal sweat testing, additional testing with *CFTR* gene deletion/duplication analysis (165 variant panel including intronic variants) was performed. Mutations were interpreted with the assistance of CFTR2 database.[7]

Anthropometric Data—Patients' body mass index (BMI) percentiles were calculated for sex, age, height, and weight at the time of ARP or CP diagnosis and Centers for Disease Control and Prevention standard growth charts.[8] For our pediatric patients, nutritional categories were based on BMI percentile: nutritional failure (<10th), at risk (10th–25th), acceptable (25th–49th), optimal (>50th).[9,10] Our adult patients' nutritional status was defined as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obese (BMI >30.0 kg/m^2).[8]

Lung Function—Lung function was evaluated at the time of CF diagnosis by clinical history of pulmonary disease and evaluation of pulmonary function testing, including percent of forced expiratory volume in 1 second (FEV_1) and forced vital capacity. Appropriate lung function was defined as FEV_1% predicted greater than 80%.

Abnormal Imaging Findings—We reviewed reports of chest imaging (computed tomography or chest x-ray). Abnormal findings included bronchial wall thickening,

bronchiectasis, atelectasis, pulmonary nodules, or findings consistent with pneumonitis or emphysema.

Pancreatic fluid collections (PFCs) were classified based on duration and presence of necrosis. Acute peri-PFCs were defined as pancreatic or peripancreatic fluid seen within 4 weeks of pancreatitis onset without signs of necrosis.[11] Pancreatic pseudocysts were classified as clearly defined, walled-off fluid collections, without signs of necrosis, typically after 4 weeks of onset. If necrosis was noted on imaging after 4 weeks of PFC development, fluid collections were described as walled-off necrosis, which requires presence of necrosis after 4 weeks of onset with signs of a walled-off collection.[11]

RESULTS

Demographics and Presentation With Pancreatitis

We identified 18 patients who presented with ARP/CP and were subsequently diagnosed as having CF or a CFTR-RD. Eight patients qualified as CF based on elevated SCT (>60 mmol/L), and 5 patients qualified as CF based on an intermediate SCTwith 2 disease-causing mutations. Five were classified as having a CFTR-related disorder. Fifteen were diagnosed as children (8–17 years) and 3 as young adults (21–27 years; Table 1). The median age at ARP/CP diagnosis was 15.0 years. Among the 15 diagnosed as children, only 2 (13%) had low BMI percentiles (9th and 13th). Both of these patients had intermediate sweat tests and 2 disease-causing mutations. The 3 adult patients were all overweight or obese at ARP/CP diagnosis (Table 1).

Diagnosis of CF and CFTR-RD

As stated, 8 (44%) patients qualified as CF based on elevated SCT (>60 mmol/L) and 5 (28%) patients based on an intermediate SCT with 2 disease-causing mutations. The remaining 5 (28%) were classified as having a CFTR-RD. The 2 patients without SCT each had 2 pathogenic *CFTR* mutations. The median time from diagnosis of ARP/CP to diagnosis of CF was 0.4 years (range, 0–33 years). Newborn screens for CF were not available for any of the patients.

Six (33%) patients in our cohort had *CFTR* mutations eligible for treatment with CFTR modulator therapy, specifically ivacaftor (Table 1). No patients were treated with a CFTR modulator during the study period.

Pancreatic Function at Diagnosis

Eight (44%) of our patients had EPI at ARP/CP diagnosis. Five (28%) of these also had impaired glucose tolerance. Of the 3 (17%) insulin-dependent patients, 2 were diagnosed as having type 2 diabetics before detection of CFTR dysfunction and one was insulin dependent after total pancreatectomy with islet autotransplantation (TPIAT). The 2 patients who were diagnosed as having adult-onset type 2 diabetes mellitus were also diagnosed as having recurrent pancreatitis as adults, at age 26 and 27 years, respectively. They also both had a BMI >30 kg/m^2 at the time of ARP/CP diagnosis.

Several patients were discordant with regards to pancreatic endocrine and exocrine function. Of the 11 with normal endocrine function at ARP/CP diagnosis, 3 (27%) had exocrine insufficiency. Conversely, 3 (30%) of 10 patients with normal exocrine function had abnormal endocrine function.

Of the 8 exocrine-insufficient patients, 4 (50%) had a pathogenic *CFTR* mutation; of the 10 exocrine sufficient patients, 3 (30%) had a severe *CFTR* mutation (Table 1). Two patients also had *SPINK1* mutations; both had EPI at ARP/CP diagnosis.

Treatment and Course of Pancreatitis

Documented episodes of pancreatitis per patient during the follow-up period ranged from 1 to >10. Pancreatic fluid collections were particularly common among patients with pancreatic insufficiency at diagnosis (63%; n = 5), as compared with those who were pancreatic sufficient (10%; n = 1). Thirteen (72%) patients underwent endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic or therapeutic purposes. Of these, 31% (4/13) had PFCs and 77% (10/13) had imaging features of chronicity.

The therapeutic options available to our patients included endoscopic and surgical interventions, including ERCP and TPIAT. Two of the patients underwent TPIAT. The other patient, who also underwent identical genetic testing, was found to have one pathogenic and the most common *CFTR* mutation, *c.1521_1523del*, and another *CFTR* mutation that, when combined with another pathogenic mutation, can cause CF.[7] This patient did have a complex course with features of chronicity on imaging as well as pancreatic pseudocyst, exocrine insufficiency, and elevated glucoses.

Other CF Manifestations

There was a low prevalence of significant lung impairment, with only 4 patients having FEV_1% less than 80% predicted. The values of SCT for these patients ranged from 38 to 104 mmol/L; their genetic testing was also quite variable. Of the 4 patients with FEV_1% <80, only one had history of pneumonia. This patient had the highest SCT of the 4, at 104 mmol/L, but had only 1 severe (class I) mutation detected (Table 1). Nine of the 18 patients had at least one other organ system with disease suggestive of CF, including sinusitis (33%), nasal polyps (11%), history of pneumonia (22%), and gallbladder disease (22%).

DISCUSSION

This is one of the largest reported series of patients who presented with acute recurrent or CP and were subsequently diagnosed as having CF or CFTR-RD. It highlights the challenges of diagnosis and treatment in these patients (Table 2). This diverse group of patients varied in respect to age of diagnosis, nutritional status, CFTR genotype, and pancreatic function. However, at least 50% of our patients had at least one other symptom or finding supportive of CFTR dysfunction.

Previous case reports[12–26] have described similar patient presentations consisting of single patients or smaller groups of patients with recurrent pancreatitis and detected *CFTR* mutations (Table 2). To date, the most comprehensive data on risk factors associated with

pediatric recurrent or CP come from the INSPPIRE consortium data. In that cohort of children 18 years or younger at ARP/CP diagnosis, 34% of the 155 ARP patients and 23% of the 146 with CP were positive for at least one *CFTR* mutation. Mutations in CFTR were most common among patients with ARP. In addition, 6 (33.9%) of the 155 ARP patients and 2 (1.4%) of the 146 CP patients were diagnosed as having CF as determined by having 2 disease-causing mutations and/or abnormal SCT.[4] This demonstrates the importance of CFTR functional testing and genetic analysis in pediatric patients with recurrent pancreatitis or a severe episode of pancreatitis particularly if they have endocrine or exocrine dysfunction, chronic changes on imaging, or a PFC.

The original paradigm of CF as a disease of chronic respiratory failure and malnutrition is evolving as we discover the spectrum of CFTR dysfunction and its manifestations. In our cohort, most of our patients had normal BMI or BMI percentiles for age. Furthermore, most of our patients, despite having significant pancreatic disease, had mild respiratory disease. However, a few patients did have unexpectedly significant pulmonary disease. Evaluation for sinopulmonary disease should be done at least at baseline in patients with pancreatitis and CFTR dysfunction, with pulmonary function testing and chest imaging. Chest imaging can detect early pulmonary disease in patients who may not have any clinical symptoms or have normal pulmonary function testings.[27]

Early case reports, even before identification of the *CFTR* gene, described the relationship between a delayed diagnosis of CF and recurrent attacks of pancreatitis, concluding that CF patients who develop pancreatitis are typically diagnosed later in life and do not present with pancreatic insufficiency,[28] a contributing feature of CF diagnosis. However, our series and smaller ones previously published suggest that there is an underdiagnosed population of patients with a spectrum of CFTR dysfunction. These patients may not present with classical symptoms of CF; thus, there may be low clinical suspicion for CF evaluation.

Characterization of *CFTR* mutations and their translational effects have advanced our understanding of and ability to treat CF, but our ability to predict disease phenotype from genetics remains limited because of multiple factors, including other genetic modifiers and environmental factors.[29] In our patient population, we detected several notable patterns. Our patients, who all had recurrent pancreatitis, were overall well nourished and had adequate lung function. In addition, patients who had findings of chronic damage on pancreatic imaging were more likely to already have been EPI at the time of discovery of CP. Patients who were older at the time of diagnosis of CP tended to develop insulin dependence. Several patients in our series were diagnosed as having chronic pancreatic structural changes on imaging and exocrine insufficiency even at first presentation of pancreatitis. Patients with less severe CFTR dysfunction and a milder CF phenotype are associated with pancreatitis as well EPI. In this series, patients with EPI had greater than 10 episodes of pancreatitis reported before testing, chronic features of pancreatitis, or PFCs near the time of fecal elastase testing. This emphasizes the importance of functional screening even in early on after diagnosis of CP.[3] In addition, patients who meet the criteria for CF or a CFTR-RD but who have normal exocrine and endocrine pancreatic function at the time of diagnosis should be monitored for loss of pancreatic function due to continued pancreatic inflammation and damage over time.

In regard to initial screening for CF in infancy, the patients in this series were not identified, despite widespread newborn screening for CF.[1] Given the expanding options for preventative therapy and treatment in CF, testing guided by clinical suspicion remains critical for diagnosis. In states that perform both blood testing for elevated immunoreactive trypsinogen and genetic screening, the mutations screened for are limited to the most common.[30]

Six of 18 patients had a *CFTR* genotype predicted to be responsive to CFTR modulators based on available genetic testing information. During the duration of the study period, no patients were started on modulatory therapy. Genetic sequencing and expanded characterization of *CFTR* mutations give providers the opportunity to use gene-specific therapy and preserve respiratory and pancreatic function, with CFTR modulators, such as ivacaftor. Modulator efficacy has been studied in CF patients with pancreatitis and showed not only improvement in FEV% but also decreased episodes of pancreatitis and elevation in fecal elastase.[31,32] Providers should take caution when considering modulator use, as there is a theoretical risk that, by improving exocrine secretion by means of a modulator, enzyme activity would also be increased in the duct and worsen pancreatitis. These agents have also been suggested to be effective in other scenarios such as reversing the negative effects of cigarette and ethanol within the pancreas.[33,34]

If CFTR dysfunction is detected early through genetic testing, revealing mutations eligible for modulator therapy, then there may be greater potential for preservation of pancreatic function in ARP and CP patients, a population with currently extremely limited therapeutic options.

This study was limited by its retrospective nature, limiting available data. Another limitation was the varied type of *CFTR* testing and testing for hereditary pancreatitis (*SPINK1*, *CTRC*, and *PRSS1*). Larger, prospective cohort studies, like that of the INSPPIRE consortium, may provide additional insight on genotype-phenotype correlations and disease progression. Prospective studies are still needed to assess the impact of interventions on changing the progression of disease and to limit the variability in methods of diagnosis and management.

Timely diagnosis of CF or CFTR-RD in these patients could provide therapeutic options for maintaining function and health in the pancreas and other organs. A diagnosis of CF should be considered early when a young patient presents with ARP or CP. Clinical history must include inquiry about other manifestations of CF in these children. Although larger and prospective studies remain critical to fully understanding the role of CFTR in pediatric ARP and CP, our series highlights the utility of screening individuals for CF to optimize treatment of their pancreatic disease and overall health.

Acknowledgments

This work is supported by the National Institute of Health (NIH)–National Institute of Diabetes and Digestive and Kidney Diseases K23 (DK0990253-A101 [E.R.P.]), NIH–National Institute of Diabetes and Digestive and Kidney Diseases U01 (DK108328–02S1 [D.M.T.]), and the Cystic Fibrosis Foundation.

REFERENCES

1. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. J Pediatr. 2017; 181S:S4–S15.e1. [PubMed: 28129811]
2. Bombieri C, Claustres M, De Boeck K, et al. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros. 2011; 10 Suppl 2:S86–S102. [PubMed: 21658649]
3. Ooi CY, Durie PR. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in pancreatitis. J Cyst Fibros. 2012;11:355–362. [PubMed: 22658665]
4. Kumar S, Ooi CY, Werlin S, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. JAMA Pediatr. 2016;170:562–569. [PubMed: 27064572]
5. Morinville VD, Husain SZ, Bai H, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr. 2012; 55:261–265. [PubMed: 22357117]
6. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association practice guidelines in chronic pancreatitis evidence-based report on diagnostic guidelines. Pancreas. 2014;43:1143–1162. [PubMed: 25333398]
7. The Clinical and Functional Translation of CFTR (CFTR2). Available at: http://cftr2.org. Accessed May 1, 2018.
8. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. Vital Health Stat. 2002;11:1–190.
9. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008;108:832–839. [PubMed: 18442507]
10. Borowitz D, Baker RD, Stallings V, et al. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2002; 35:246–259. [PubMed: 12352509]
11. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–111. [PubMed: 23100216]
12. Conklin L, Zeitlin PL, Cuffari C. Cystic fibrosis presenting as recurrent pancreatitis in a young child with a normal sweat test and pancreas divisum: a case report. J Med Case Reports. 2008;2:176.
13. Koyano S, Hirano Y, Nagamori T, et al. A rare mutation in cystic fibrosis transmembrane conductance regulator gene in a recurrent pancreatitis patient without respiratory symptoms. Pancreas. 2010;39:686–687. [PubMed: 20562583]
14. Tomaiuolo AC, Sofia VM, Surace C, et al. Relationship between CFTR and CTRC variants and the clinical phenotype in late-onset cystic fibrosis disease with chronic pancreatitis. J Mol Diagnostics. 2015;17:171–178.
15. Montagnani M, Cazzato S, Mutignani M, et al. A patient with pancreas divisum, recurrent acute pancreatitis, and homozygosity for the cystic fibrosis transmembrane regulator–associated protein 5T allele. Clin Gastroenterol Hepatol. 2013;11:579–581. [PubMed: 23416327]
16. Volkan B, Islek A, Uygun DF, et al. Delayed diagnosis of chronic pancreatitis with cystic fibrosis and pancreas divisium. Med Sci. 2017;6: 557–559.
17. Conway SP, Peckham DG, Chu CE, et al. Cystic fibrosis presenting as acute pancreatitis and obstructive azoospermia in a young adult male with a novel mutation in the CFTR gene. Pediatr Pulmonol. 2002;34:491–495. [PubMed: 12422349]
18. Dray X, Fajac I, Bienvenu T, et al. Association of pancreas divisum and recurrent acute pancreatitis with the IVS8–5T-12TG allele of the CFTR gene and CFTR dysfunction. Pancreas. 2007;35:90–93. [PubMed: 17575549]
19. Sinha A, Akshintala VS, Afghani E, et al. A novel mutation in the cystic fibrosis transmembrane conductance regulator gene in an Indian patient with idiopathic chronic pancreatitis: a case report. Pancreas. 2014;43: 146–147. [PubMed: 24326373]
20. Masaryk TJ, Achkar E. Pancreatitis as initial presentation of cystic fibrosis in young adults—a report of two cases. Dig Dis Sci. 1983;28:874–878. [PubMed: 6617400]

21. Fierbinteanu-Braticevici C, Hodina AC, Oprea G, et al. Case report on a 21 years old female patient with acute pancreatitis in cystic fibrosis. Gastroenterol Pancreatol Liver Disord. 2014;1:1–3.
22. Gross V, Schoelmerich J, Denzel K, et al. Relapsing pancreatitis as initial manifestation of cystic fibrosis in a young man without pulmonary disease. Int J Pancreatol. 1989;4:221–228. [PubMed: 2656888]
23. Vanderbruggen K, De Waele K, Van Biervliet S, et al. Cystic fibrosis: an unusual cause of chronic pancreatitis. Acta Gastroenterol Belg. 2003;66: 260–262. [PubMed: 14618962]
24. Kopp BT, Pastore MT, Sturm AC, et al. A novel exon duplication of the cystic fibrosis transmembrane conductance regulator in a patient presenting with adult-onset recurrent pancreatitis. Pancreas. 2011;40:773–777. [PubMed: 21673536]
25. Brunson JM, Bridges D, Anderson R, et al. Cystic fibrosis diagnosed at age 45 based on symptoms of acute pancreatitis. Proc (Bayl Univ Med Cent). 2009;22:13–15. [PubMed: 19169392]
26. Villalona S, Glover-López G, Ortega-García JA, et al. R248G cystic fibrosis transmembrane conductance regulator mutation in three siblings presenting with recurrent acute pancreatitis and reproductive issues: a case series. J Med Case Reports. 2017;11:42.
27. Ernst CW, Basten IA, Ilsen B, et al. Pulmonary disease in cystic fibrosis: assessment with chest CT at chest radiography dose levels. Radiology. 2014;273:597–605. [PubMed: 25057981]
28. Shwachman H, Lebenthal E, Khaw KT. Recurrent acute pancreatitis in patients with cystic fibrosis with normal pancreatic enzymes. Pediatrics. 1975;55:86–95. [PubMed: 1110867]
29. Salvatore F, Scudiero O, Castaldo G. Genotype-phenotype correlation in cystic fibrosis: the role of modifier genes. Am J Med Genet. 2002;111: 88–95. [PubMed: 12124743]
30. Ross LF. Newborn screening for cystic fibrosis: a lesson in public health disparities. J Pediatr. 2008;153:308–313. [PubMed: 18718257]
31. Carrion A, Borowitz DS, Freedman SD, et al. Reduction of recurrence risk of pancreatitis in cystic fibrosis with ivacaftor: case series. J Pediatr Gastroenterol Nutr. 2018;66:451–454. [PubMed: 29045347]
32. Kounis I, Lévy P, Rebours V. Ivacaftor CFTR potentiator therapy is efficient for pancreatic manifestations in cystic fibrosis. Am J Gastroenterol. 2018; 113:1058–1059. [PubMed: 29887601]
33. Freeman AJ, Ooi CY. Pancreatitis and pancreatic cystosis in cystic fibrosis. J Cyst Fibros. 2017;16(suppl 2):S79–S86. [PubMed: 28986028]
34. Hegyi P, Wilschanski M, Muallem S, et al. CFTR: a new horizon in the pathomechanism and treatment of pancreatitis. Rev Physiol Biochem Pharmacol. 2016;170:37–66. [PubMed: 26856995]

TABLE 1.

Participant Characteristics.

Ethnicity	Sex	Pancreatitis Diagnosis Age, y	Pancreatic Function at Pancreatitis Diagnosis		Sweat Cl, mmol/L	No. Pancreatitis Attacks	Imaging		Interventions	Abnormal Chest Imaging (CT, XR)	Mutation
			Exocrine	Endocrine			Chronic Features	Presence of PFC			
Patients with CF diagnosis based on SCT >60 mmol/L											
Hispanic	M	10	PS	Normal	71	2	N	N	None	No imaging	No mutations
White	F	12	PI	Normal	68	1	Y	N	ERCP	No imaging	c.3773dupT, c.5T-TG12
White	M	12	PS	Normal *	69	>5	N	N	None	CT + CXR	12TG; C.1408A > G (also *NOD2* mutation)
Hispanic	M	16	PI	Impaired	65	>5	Y	PFC	ERCP, celiac plexus block, TPLAT	Normal	c,1521_1523del; c. 617T>G †
White	F	16	PI	Normal	104	2	N	PFC	ERCP	CT + CXR	C.178G > T
African American, Asian	M	16	PS	Normal *	62	4	Y	N	ERCP	Normal	No mutations detected
Hispanic	M	20	PS	Normal	103	6	Y	N	ERCP	Normal	c.1521 1523del; c. 2657 + 5G > A †
White	M	26	PS	Insulin	95	4	N	2 PFC	None	Normal	No mutations
Patients with CF diagnosis with 2 disease-causing mutations and intermediate sweat test (30–59 mmol/L) or no sweat test											
Hispanic	F	8	PI	Normal	38	1	Y	WON	ERCP	CT + CXR	c,1521_1523del; 12TG-5T ‡
White	F	13	PI	Normal *	38	6	Y	2 PFC	ERCP	No imaging	c3140–26A > G; c. [350G > A;1210–12T[7] †
White	M	14	PS	Impaired *	52	>10	Y	N	ERCP	Normal	c.1521 1523del; c. 3208C > T;7 T/9 T †
White	M	21	PS	Normal *	N/A	4	Y	N	ERCP	CT + CXR	c,1521_1523del; c. 350G > A †
White	F	27	PI	Insulin	N/A	>10	N	N	ERCP	CT	c.350G > A; c, 1657C>T †
Patients with CFTR-RD (intermediate sweat test and 0–1 disease-causing mutation)											

Ethnicity	Sex	Pancreatitis Diagnosis Age, y	Pancreatic Function at Pancreatitis Diagnosis		Sweat Cl, mmol/L	No. Pancreatitis Attacks	Imaging		Interventions	Abnormal Chest Imaging (CT, XR)	Mutation
			Exocrine	Endocrine			Chronic Features	Presence of PFC			
White	F	9	PS	Normal	47	2	N	N	None	No imaging	c.3162T > A; 5T
Hispanic	F	10	PS	Impaired	57	>10	N	N	ERCP	Normal	(TG)l 1–5T; (TG)l 1–7T
White	F	10	PI	Impaired	57	4	Y	N	ERCP, TPLAT	No imaging	No mutations detected[≠]
Hispanic	M	16	PS	Normal	41	1	Y	N	ERCP	No imaging	(TG)l 1–5T
Hispanic	M	17	PI	Impaired[*]	43	3	N	2 PFC	None	No imaging	c.601G > A

[*] Oral glucose tolerance test performed.

[†] Accepted for ivacaftor use.

[≠] Positive *SPINK1* mutation.

CT indicates computed tomography; CXR, chest x-ray; F, female; M, male; N/A, not available; PI, pancreatic insufficient; PS, pancreatic sufficient; WON, walled-off necrosis.

TABLE 2.

Literature Review of Patient Cases Describing Individuals Who Were Diagnosed as Having Pancreatitis Before CF and Their Respective Manifestations

Reference	Cases: Age/Sex/ Ethnicity	Age at Pancreatitis Diagnosis, y	Pancreatic Function at Pancreatitis Diagnosis		Age at CF Diagnosis, y	Time From Pancreatitis to CF Diagnosis, y	Highest SCT Result	Other CF Manifestations	*CFTR* Mutation, If Known
			Exocrine	Endocrine					
Conklin et al[12]	4/F/White	4	N/A	N/A	6	2	WNL	Abnormal nasal potential difference	delF508; L997F
Koyano et al[13]	14/F/Asian	6	N/A	N/A	14	8	23.2 mEq/L	Low pancreatic bicarbonate	D924N, 5T
Tomaiuolo et al[14]	9/M/White	9	PS	N/A	11	2	78 mmol/L	None	delF508, G91G
Montagnani et al[15]	17/M/Wliite	13	PS	N/A	17	4	84 mEq/L	None	HomozygousIVS8 5T-12TG
Volkan et al[16]	14/M/White	14	N/A	N/A	14	0	110 mmol/L	Recurrent cough	D110H; 2789 + 5G > A
Conway et al[17]	23/M/White	17	PS	WNL	23	6	25 mmol/L	Infertility, bilateral absence of vas deferens	Homozygous, del1123Glu; intron 8 homozygous 7T
Dray et al[18]	17/F/N/A	1: 17	N/A	N/A	1: 17	0	1:11 mmol/L	1: Asthma	1: R31C; IVS8–5T-12TG
	22/F/N/A	2: 22			2: 22		2: 81 mmol/L	2: nasal polyps, bronchitis, salivary litliiasis	2: delF508;IVS8–5 T-12TG
Sinha et al[19]	29/M/Asian	18	PI	WNL	29	11	N/A	Underweight	c.3125A > G
Masaryk and Aclikar[20]	20/M/White	1: 20	N/A	N/A	1: 20	1: 0	1: 143 mEq/L	1: Sibling with CF	N/A
	22/M/White	2: 22			2: not reported	2: not reported	2: 85.4 mEq/L	2: Azoospermia	
Fierbinteanu-Braticevici et al[21]	21/F/White	21	PS	WNL	21	0	78 mmol/L	Bronchiectasis	2183AA > G
Gross et al[22]	21/M/Asian	21	PI	N/A	26	5	92 mEq/L	Azoospermia: bronchitis	N/A
Vanderbruggen et al[23]	38/M/White	23	PI, postpancreatectomy	Required insulin postpancreatectomy	38	15	86 mEq/L	Asthma, azoospermia	delF508; R117H
Kopp et al[24]	30/F/White	25	PI	N/A	30	5	106 mmol/L	Recurrent sinusitis, GERD, cholelithiasis	*CFTR*: G551D; duplication of exon 19 and 7T/7T *SPINK1*: IVS3 + 184T > A

Reference	Cases: Age/Sex/ Ethnicity	Age at Pancreatitis Diagnosis, y	Pancreatic Function at Pancreatitis Diagnosis		Age at CF Diagnosis, y	Time From Pancreatitis to CF Diagnosis, y	Highest SCT Result	Other CF Manifestations	*CFTR* Mutation, If Known
			Exocrine	Endocrine					
Brunson et al[25]	45/F/White	45	N/A	WNL	45	0	N/A	Recurrent pneumonia; nasal polyps	Compound heterozygote: delF508, D1152H
Villalona et al[26]	39/M/White	N/A	N/A	N/A	1: 32	N/A	1:47 mEq/L	1: Congenital bilateral absence of vas deferens	1, 2, 3 (siblings): novel mutation, *R248G*, in trans with *N1303K*
	32/F/White				2: 25		2: 40 mEq/L	2: Infertility	
	29/F/White				3: 22		3: 42 mEq/L	3: Pneumonia	

F indicates female; GERD, gastroesophageal reflux disease; M, male; N/A, not available; PI, pancreatic insufficient; PS, pancreatic sufficient; WNL, within normal limits.