Gastrointestinal complications therapy

Pancreatitis in cystic fibrosis

Code: 161 **Updated:** January 21, 2025

Background

Generally a combination of genetic, environmental, and metabolic factors contribute to the development of acute, recurrent and chronic pancreatitis in children, including biliopancreatic structural/obstructive causes (Suzuki M et al, 2021). Demographic and risk factors for pediatric recurrent acute pancreatitis have been postulated (Gariepy C et al, 2021).

New strategies are needed to determine their contribution to pathogenesis of pancreatitis (Whitcomb DC et al, 2013). In infancy pancreatitis has different clinical manifestations (Uc A and Husain SZ 2019).

Recent longitudinal studies showed that acute recurrent pancreatitis (ARP) may predispose to chronic pancreatitis (CP) in presence of genetic mutations ((Poddar U et al, 2017). Mutations/polymorphisms in at least 1 gene were identified in the majority of children enrolled from 2015 to 2018 including SPINK1 in 41.9%, PRSS1 (rs10273639) in 58.2%, CTRC in 25.6%, CTSB in 54.9%, CLDN2 in 72.9%, and CFTR in 2.3% (Nabi Z et l, 2020). In CF CFTR IVS8-5T has been demonstrated to be a risk factor in patients with CP, especially in the European population (Jiang Min et al, 2020).

A retrospective study of INSSPIRE -2 group (Sellers ZM et al, 2025) showed that mild-moderate hypertriglyceridemiain children with AP, ARP or CP was not associated with increased pancreatitis frequency, nor increased development of CP, but was associated with increased pancreatitis complications and disease burden (.

The project INSSPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure consortium)(Liu QY et al, 2019) determined the rate of progression from acute recurrent pancreatitis (ARP) to chronic pancreatitis (CP) in children assessing evolution to exocrine pancreatic insufficiency, and diabetes as risk factors. Hence, patients with ARP should be kept on regular follow-up to detect CP. Recently (Freeman AJ et al, 2024) the INSSPIRE-2 consortium assessed a retrospective cohort study, including children with pancreatic-sufficient ARP or CP , in order to evaluate the use of PERT. Clinical outcomes were compared for those receiving vs not receiving PERT, as well as frequency of AP before and after PERT. Main results showed that among 270/356 PS subjects and ARP, 60 (17%) received PERT. Among those on PERT, 42% did not have a subsequent AP episode, during a mean 2.1 years of follow-up. Children with a SPINK1 mutation ($P = 0.005$) and those with ARP (compared with CP, $P = 0.008$) were less likely to have an AP episode after starting PERT. After initiation of PERT, the mean AP annual incidence rate decreased from 3.14 down to 0.71 ($P < 0.001$). These results suggested the efficacy of PERT among children with ARP or CP.

In cystic fibrosis patients are at increased risk of acute (AP) and chronic (CP) pancreatitis, and their complications. A spectrum of pancreatic abnormalities occurs in CF patients especially in those bearing CF mutations with variable clinical consequences. In the past (Ooi CY, 2011) it was demonstrated that patients with pancreatitis were more likely to have genotypes associated with mild (70%) than moderate-severe (30%) disease based on the pancreatic insufficiency prevalence (PIP) score. This finding was recently suggested in adults with CF and pancreatic sufficiency (Gaitch N et al, 2016). PIP score, pancreatic status and normal/borderline sweat chloride levels could be applied to predict pancreatitis development in subjects with CF (Terlizzi V et al, 2014).

Pancreatitis is an uncommon complication in CF with a variable estimated prevalence and rarely occurs in patients with pancreatic insufficiency.The mild-variable mutations may account for the residual pancreatic function that is requested for pancreatitis.The extent of remaining healthy pancreatic parenchyma determines the risk of developing future episodes of pancreatitis, as well as pancreatic exocrine or endocrine insufficiency. Either single or recurrent acute episodes can occur and they occasionally may follow a protracted course with relentless destruction of the pancreas. Symptomatic pancreatitis occurs nearly to 20% of patients with CF and pancreatic sufficiency. AP and recurrent AP are managed with intravenous fluid hydration and pain control, in addition to early refeeding and treatment of complications. With the use of modulator therapy in CF, pancreatic function may be restored to some extent. CP related pain is managed with analgesics and neuromodulators, with surgery if indicated in specific situations. Long-term sequelae of CP in patients with CF include exocrine pancreatic insufficiency, fat-soluble vitamin deficiencies and associated metabolic complications such as bone disease/osteoporosis, diabetes, and less commonly, pancreatic cancer (Milano RV et al, 2024).

Issues

a. To define the prevalence of pancreatitis in patients with CF both with pancreatic sufficiency and insufficiency.
b. To show any relationship with genotype, age, gender, or other factors.
c. To perform guidelines mainly in relation to prevention of complications, clinical and radiological diagnosis, as well as to nutritional and medical intervention.

What is known

Regarding issue a and b the “International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium” (

Morinville VD et al, 2012), the largest multi-center prospective cohort study in pediatric patients with ARP or CP, has been formed to standardize definitions, develop diagnostic algorithms, to investigate disease pathophysiology, and design prospective multicenter studies on acute pancreatitis, acute recurrent pancreatitis, and chronic pancreatitis in children.

The INSPPIRE-2 (Uc A et al, 2022) showed that of 689 children, 365 had ARP (53%), 324 had CP (47%) CP was more commonly associated with female sex, younger age at first acute pancreatitis (AP) attack, Asian race, family history of CP, lower BMI%, genetic and obstructive factors, PRSS1 mutations and pancreas divisum. CFTR mutations, toxic-metabolic factors, medication use, hypertriglyceridemia, Crohn disease were more common in children with ARP. Constant or frequent abdominal pain, emergency room (ER) visits, hospitalizations, medical, endoscopic or surgical therapies were significantly more common in CP, episodic pain in ARP. A total of 33.1% of children with CP had exocrine pancreatic insufficiency (EPI), 8.7% had diabetes mellitus. No difference in race, ethnicity, age at first AP episode, age at CP diagnosis, duration of disease, risk factors, prevalence of EPI or diabetes between boys and girls was demonstrated. Multivariate analysis revealed that family history of CP, constant pain, obstructive risk factors were predictors of CP.

Regarding issue b 48 patients affected by CF complicated by RP/CP and, as controls, 35 patients with CF without pancreatitis and 80 unrelated healthy subjects were tested for a panel of 8 genes involved in the IPAT, i.e. *PRSS1, PRSS2, SPINK1, CTRC, CASR, CFTR, CTSB* and *KRT8* and 23 additional genes implicated in the PSP. Mutations in 12 genes of the PSP were found in 11/48 (22.9%) patients with CF and ARP/CP. Overall, 19/48 (39.6%) patients with CF and RP/CP showed one or more mutations in the genes involved in the IPAT and in the PSP, while such figure was 4/35 (11.4%) for patients with CF without pancreatitis and 11/80 (13.7%) for healthy controls (p <?0.001). This trans-heterozygous association between *CFTR* mutations in genes involved in the pathways of pancreatic enzyme activation and the pancreatic secretion may be suggested as risk factors for the development of recurrent or chronic pancreatitis in patients with CF (Sofia VM et al, 2018).

Regarding issue c 1 study (Obideen K et al, 2006) was performed in a group of patients with adult-onset CF (N=9) who were referred to CF care Centre for recurrent abdominal pain and pancreatitis. Nocturnal hydration was able to significantly reduce the frequency and the severity of abdominal pain, as well as the amount of pain medication and the number of emergency room visits and hospitalizations for recurrence of pancreatitis.

Recently (Carrion A et al, 2018) the use of ivacaftor was associated with a reduced frequency and recurrence rate of pancreatitis in patients with CF.

Very recently (Sadras I et al, 2023) two cases of pancreatic-insufficient CF patients presented acute pancreatitis shortly after commencing elexacaftor/tezacaftor/ivacaftor modulator therapy. The Authors suggested that modulator combination therapy may restore additional pancreatic acinar activity, resulting in the development of acute pancreatitis in the interim until ductal flow is improved.

Unresolved questions

No CDSRs are available about this topic.

Genetic factors that affect pancreatic cells and systems could lead to etiology-based therapies rather than treatment of symptoms in CF.

Further epidemiological studies are needed to define incidence, prevalence, etiology and diagnosis of pancreatitis, as well as the better therapeutic intervention for controlling symptoms and recurrence of pancreatitis in CF.

Further longitudinal studies will confirm whether the early treatment with modulator therapies will prevent acure recurrent pancreatitis.

Keywords

Pancreatic Diseases; Pancreatitis;