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Complications of chronic pancreatitis in Children

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Abstract

Purpose of Review: In children, chronic pancreatitis (CP) is infrequent but may be associated with serious complications, including severe pain that limits activities, exocrine and endocrine pancreatic insufficiency and malnutrition. Investigation into pediatric chronic pancreatitis has transitioned from single center reports to multicenter, protocol driven studies. As a result, we now have information on much larger numbers of children with CP, allowing a more reliable understanding of the complications of chronic pancreatitis.

Recent Findings: A high percentage of children with CP use opioids frequently to control pain. About a quarter of children with CP have exocrine pancreatic insufficiency, and about 6% have pancreatogenic diabetes. Mild malnutrition and low bone density are both common in children with CP.

Summary: Large multicenter and single center observational studies have allowed us to more accurately assess complications of CP in children. These studies demonstrate the need for examination of therapies for these complications in children.

Keywords

exocrine pancreatic insufficiency; pancreatogenic diabetes; opioid

Introduction

Chronic pancreatitis (CP) is an uncommon but devastating disease in childhood. Prevalence of CP in children was 5.8/100,000 in a database of privately insured children[1]. The most common consequences of CP include pain and endocrine and exocrine pancreatic

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Conflicts of Interest

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insufficiency. In children this may result in loss of time in school, loss of opportunity to socialize with friends and play sports, and repeated hospital admissions[2].

In the last decade large multicenter observational studies of pediatric pancreatitis have replaced single center studies of the disease. Multicenter studies allow a large number of patients to be amassed for study, improving the understanding of the true frequency of complications in pediatric CP. Multicenter studies are less likely to be biased in reporting risk factors or effective treatments because larger studies include more geographic regions and larger numbers of patients. One of the first such multicenter study of chronic pancreatitis was INSPPIRE 1 (**IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE)**, which began in 2009 and initially included 18 centers, including sites in the United States, Australia, Israel and Canada[3]. In 2015 INSPPIRE became part of a larger study of CP in adults and children, the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC), as INSPPIRE 2[4]. The project is currently funded by the National Institutes of Health. INSPPIRE 2 encompasses 22 centers, with a diverse regional and cultural/ethnic mix. INSPPIRE 1 and 2, and other similar studies worldwide (for example, the Analysis of Pediatric Pancreatitis (APPLE) of the Hungarian Pancreatic Study Group[5]) have been important in advancing our understanding of CP in children and in offering a large enough population of children with chronic pancreatitis to make interventional studies possible. At the same time, some single centers see large enough populations of children with CP to provide important additions to the literature.

In this article we will review recent progress in understanding CP in children, focusing on multicenter and large single center studies in the literature over the last two years. These articles lay the foundation for further inquiry and exploration. We will summarize information on complications of CP, including pain and pain management, endocrine and exocrine pancreatic insufficiency and malnutrition. This highlights the power of large multicenter, collaborative studies to investigate diseases that are relatively infrequent. Pediatric gastroenterologists at many centers will see very few children with CP in their careers and may thus profit from the knowledge generated by the work of INSPPIRE and similar studies.

Pain in pediatric chronic pancreatitis

Pain is the most common symptom of CP in children and drives a substantial amount of the disease burden for children with the disease and their families. Pain may be the initial symptom alerting providers to pancreatitis; many children have pain for months or years before pancreatitis is recognized. Almost 40% of children with CP report constant pain, with 70% of those in constant pain also suffering intermittent pain exacerbations. Another 33% have episodic severe pain[6, 7].

A cross-sectional analysis of opioid use in the baseline enrollment data for in the INSPPIRE cohort included 194 children. Providers and patients reported opioid use independently. Among children with CP, 65% reported “frequent” opioid use (defined as daily or a few times a week). Interestingly, close to 40% of providers reported those same children as using opioids infrequently alerting to the fact of a discrepant physician awareness of their patient’s opioid use. Risk factors for needing daily or weekly opioid pain medications in

the cohort included CP (vs. acute recurrent pancreatitis), older age at diagnosis, being in constant and/or severe pain, and having exocrine pancreatic insufficiency[6]. Genetic mutation and pancreas divisum were not associated with frequent opioid use. Of those children taking opioid pain medications frequently, almost 80% reported that their pain interfered "quite a bit" or "very much" with their school participation, day-to-day activities, ability to concentrate, and enjoyment of life. These children also reported significantly more missed school days, hospitalizations, and emergency room visits in the past year than children who did not take opioids daily or weekly[6].

The impact of pain on the lives of children with CP highlights the need for safe, targeted pain management interventions to improve their functioning and quality of life. Although guidelines exist for adults[8], there are no evidence-based or consensus "best practice" guidelines for outpatient pain management in children with acute recurrent pancreatitis or CP. This is particularly critical because the risk factors associated with pediatric CP are different from those of adult CP[7], with pediatric CP associated with genetic and obstructive risk factors and adult CP associated with tobacco and alcohol. Medical therapy for the pain in these two groups may require different approaches. A dearth of interventional studies in children is a major barrier to developing best practices. There are no large, randomized, well-constructed published studies of analgesic medications, antioxidants or other supplements, dietary modification, integrative medicine or other wellness interventions, or regional nerve blocks to mitigate pain in children with CP.

Available evidence and expert consensus support the use of endoscopic retrograde cholangiopancreatography (ERCP) to treat pain in select children with chronic pancreatitis[9]. However, systematic prospective studies of exactly which patients will benefit most from ERCP are not available. ERCP appears to be most beneficial for treating pain in children with pancreatic duct stones that can be removed during the procedure, and possible those with pancreatic duct strictures that can be dilated. The benefit of repeated ERCPs remains unclear, and therapy is best tailored to the individual patient by a team experienced in both pediatric CP and ERCP. For children with intractable CP pain, large, retrospective, single-center studies consistently suggest that total pancreatectomy with islet cell auto-transplant (TPIAT) decreases pain, opioid use, and hospitalizations in at least 75% of children – with more robust improvements in children than adults[10, 11]. Pain improvement has also been reported after other drainage procedures (e.g. Puestow lateral pancreaticojejunostomy) but if pain recurs and requires completion TPIAT, islet yield is low with less favorable diabetes outcomes[12].

As we better understand the risk factors for chronic pain and its sequelae in children with CP, developing therapeutic interventions to successfully manage that pain has been a central focus of INSPPIRE. Currently underway is a web-based cognitive-behavioral therapy (CBT) intervention that aims to reduce pain severity and pain-related disability in children with ARP and CP[13]; this is the first multi-center, randomized controlled trial of any therapeutic intervention in children with CP.

Exocrine pancreatic insufficiency in pediatric chronic pancreatitis

Exocrine pancreatic insufficiency (EPI) is a long-term complication of CP and in some cases it may be the only clinical symptom of CP[14, 15]. In the INSPPIRE cohort, EPI was diagnosed in about 26% of children with CP at baseline, which was similar compared to the prevalence of EPI in adults with CP[7]. Development of EPI is associated with risk of malnutrition as documented in about 30% of children with CP in a Polish cohort[16]. The consequent need for pancreatic enzyme supplementation not only interferes with the daily life, but also significantly increases the individual health costs by around $4,000 per year and patient as per cost-analysis performed in the INSPPIRE cohort[17]. Thus, better understanding of how to disrupt this sequela of acute recurrent pancreatitis – chronic pancreatitis to end organ failure leading to EPI would have significant impact on the health outcomes as well as health costs.

EPI results when a significant loss of enzyme producing acinar cells occurs in consequence to a chronic fibroinflammatory process resulting in fibro-fatty replacement of the pancreas. Earlier studies correlated the pancreatic enzyme output to fecal fat excretion in patients with CP and found that the threshold for steatorrhea and thus the clinical manifestation of EPI is achieved when the pancreatic enzyme output is reduce to 10%[18]. EPI affects fat maldigestion and fat malabsorption twofold. One is the direct loss of fat, protein and carbohydrate digestive enzymes, mainly lipase and co-lipases. Secondly, loss of bicarbonate secretion into the small bowel impairs micelle generation since this requires an alkaline environment, which further impairs fat digestion and absorption.

So far there is little data to identify children with CP at imminent risk of EPI. The INSPPIRE study has shown that the development of EPI was independent of the age of onset of CP[19]. Furthermore, obese children were less likely to develop EPI probably associated with their lower association with CP[20]. This means that all patients with CP need to be regularly monitored for signs of impaired growth and malnutrition. This should also include monitoring for signs of micronutrient deficiency such as fat-soluble vitamin levels (25-hydroxy-vitamin D, Vit A and E), magnesium and zinc [15, 21]. While EPI is thought to reflect irreversible pancreas end organ damage, there are cases of transient EPI with consequent recovery of pancreas function as observed in children with autoimmune or fibrosing pancreatitis[22, 23]. Therefore, for children with these specific sub forms of chronic pancreatitis continuous assessment of pancreas function is recommended to identify resolution of EPI.

Measurements of elastase-1 in stool is commonly used in clinical practice to screen for EPI[24] with a fecal elatase-1 < 100 μg/g stool being diagnostic for EPI, 100-200 μg/g stool indicating borderline and >200 μg/g stool indicating normal pancreatic function. Other tests to assess pancreas function either indirectly by measuring percent of fat lost in stool or directly by measuring level of pancreatic enzymes collected during an endoscopy are available[25] and employed in specialized centers. Recently a large case-control study showed that serum trypsin levels can indicate acinar mass loss in CP and thus identifies those at risk for EPI[26]. Serum trypsin levels can also support a diagnosis of CP.

Once a diagnosis of EPI is established children should be started on pancreatic enzymes replacement therapies (PERT) to treat fat maldigestion, aiming to achieve normal growth in children and adolescents with CP. Similarly fat-soluble vitamins should be supplemented[21]. EPI is commonly observed in patients with cystic fibrosis who require PERT from early infancy onwards. Dosing and adjusting PERT in CP patients has therefore been adapted from this expertise gained from cystic fibrosis patients[27] and is mainly based on clinical symptoms of steatorrhea and achievement of normal growth.

Endocrine pancreatic insufficiency in pediatric chronic pancreatitis

Few published studies evaluate the risk for pancreatogenic diabetes during childhood. Data from nearly 400 children with recurrent acute or chronic pancreatitis in INSPPIRE suggested a 6% prevalence of diabetes, excluding those children who had undergone total pancreatectomy with islet autotransplant (where risk for diabetes is much higher)[28]. These findings were similar to other series from India showing a 5-9% prevalence of pancreatogenic diabetes in children with CP[29, 30]. However, the risk for diabetes is progressive over time, and those children not developing diabetes during childhood remain at risk into adulthood. For hereditary pancreatitis, the cumulative risk for diabetes approaches 50% by 50 years of age[31].

Data on mechanisms underlying the development of pancreatogenic diabetes are entirely extrapolated from adult studies. In adults, diabetes development is driven largely by insulin secretory defects resulting from loss of islets secondary to pancreatic fibrosis and beta cell dysfunction from chronic pancreatic inflammation[32-35]. However, impaired insulin sensitivity, pancreatic polypeptide deficiency, and possibly dysregulation of incretin hormones may also play a role[32, 36-39]. Increased odds for diabetes have been observed with pancreatic atrophy and pancreatic calcifications, supporting the hypothesis that more severe pancreatic damage and fibrosis results in islet loss and defective insulin secretion[28-30]. Concomitant exocrine insufficiency was also more common with diabetes in children followed in INSPPIRE, present in 37% of children with pancreatogenic diabetes[28]. However, hypertriglyceridemia and other autoimmune diseases were also associated with increased odds of diabetes, with beta cell autoantibodies found in 5 of 13 patients tested. The latter findings suggest potential contributions of metabolic syndrome and autoimmune diabetes (type 1) respectively[28].

Because of the elevated risk for diabetes, children with CP should be monitored yearly for glycemic control. At minimum, a fasting plasma glucose and hemoglobin A1c (HbA1c) are recommended[4, 40]. An oral glucose tolerance test can be considered to increase sensitivity to detect diabetes, particularly if fasting blood glucose or HbA1c suggest pre-diabetes (FPG 100-125 mg/dL or HbA1c 5.7-6.4%). Diabetes is diagnosed based on standard American Diabetes Association criteria, based on two lab tests confirming diabetes (FPG ≥126 mg/dL, HbA1c ≥6.5%, 2 hour OGTT glucose ≥200 mg/dL) or by a random glucose is ≥200 mg/dL with classic symptoms of diabetes[41].

There are no clinical trials to establish treatment standards for pancreatogenic diabetes. However, most children diagnosed with pancreatogenic diabetes are treated with insulin[28]. Insulin is a logical first-line medication since insulin deficiency is the primary defect.

In addition, very few non-insulin medications are approved in children, further limiting pharmacologic options. Metformin is FDA approved for use in children 10 years of age and older and might be considered in an obese child with signs of insulin resistance[42]. Although glucagon like peptide-1 agonists have more recently been approved for use in type 2 diabetes in children, the controversial potential association of these agents with *de novo* acute pancreatitis and pancreatic cancer suggest a potential contraindication to their use in children with underlying CP[42].

Children with pancreatitis and diabetes are recommended to see a dietitian at least once a year[40]. Lifestyle modifications are introduced as needed to maintain a normal body mass index. All children with pancreatogenic diabetes should be assessed for EPI, and treated, when needed, with PERT[40, 43]. Because insulin is often dosed based on food intake, malabsorption from under- or untreated EPI may contribute to glycemic variability[44]. In addition, some data in adult populations suggest an improved incretin hormone (glucagon like peptide-1) response to a meal when pancreatic enzyme therapy is administered in EPI patients[39].

Malnutrition in pediatric chronic pancreatitis

In children with CP several factors may increase risk of malnutrition, including poor appetite, opioid use leading to nausea, depression, and EPI. In a single center study of children with CP, anthropometry, vitamin levels, and bone mineral density were systematically examined[45]. The study included 83 children with CP, 84.1% with EPI by measurement of fecal elastase-1. At enrollment, only 15.6% were on PERT. By anthropometry, 43.4% had mild malnutrition; only 1 child had severe malnutrition. By dual energy X-ray absorptiometry, 18.6% had low total bone mineral density (total body less head bone mineral density = <−2SD), but none had osteoporosis. Vitamin D levels were low in 84.3% of the children, but vitamin E and A levels were not measured.

Fat soluble vitamins levels were measured in children prior to total pancreatectomy, islet autotransplantation for CP in a single center study of 100 children[46]. Vitamin A was low in 7%, E in 17%, and D in 22%. There was no difference in vitamin levels between those receiving PERT and vitamin supplementation and those not receiving them. A longer period of CP was associated with vitamin D deficiency in multivariate analysis.

It seems clear that children with CP are at risk for malnutrition, poor bone mineral density and fat-soluble vitamin deficiency. Clinicians can use this information to screen children with CP aggressively for these problems[21].

Conclusion

CP is an uncommon in children but can be associated with severe complications that may impair their quality of life and prevent them from growing and developing normally. These complications include pain, exocrine pancreatic insufficiency, pancreatogenic diabetes, and malnutrition. Children with pain from CP frequently use opioids, the full extent of which is often unknown to their providers. There are few studies addressing pain in children with CP, severely limiting the ability to provide pain relief. Currently, limited data support ERCP in selected patients as a mode of pain relief, but many children with severe pain undergo

surgery, particularly total pancreatectomy islet autotransplantation for unmanageable pain. Approximately 25% of children with CP have exocrine pancreatic insufficiency; about 6% have pancreatogenic diabetes. Routine testing is necessary to allow early diagnosis of these complications. Finally, mild malnutrition, fat soluble vitamin deficiency, and low bone mineral density are common in children with CP. Regular monitoring is critical to maintain health and normal development in these children.

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have low bone mineral density, but no osteoporosis. Unrecognized pancreatic insufficiency may account for many of these problems.

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Key Points

- Chronic pancreatitis (CP) is an uncommon but devastating disease in childhood
- Complications of CP in children include pain, exocrine pancreatic insufficiency, pancreatogenic diabetes, and malnutrition.
- Children with pain from CP frequently use opioids, the full extent of which is often unknown to their providers
- Children with CP have exocrine insufficiency about 25% of the time and endocrine insufficiency about 6% of the time. Routine testing is necessary to allow early diagnosis of these complications.
- Mild malnutrition, fat soluble vitamin deficiency, and low bone mineral density are common in children with CP. Regular monitoring is critical to maintain health in these children.