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Clinical Chronic Pancreatitis

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Abstract

Purpose of Review—To summarize observations in clinical chronic pancreatitis (CP) in the past year.

Recent Findings—A predisposing genetic mutation was identified in 67% of cases of pediatric chronic pancreatitis. A novel susceptibility gene involving a hybrid allele (CEL-HYB) is associated with idiopathic CP. ABO blood type B and FUT2 non-secretor status is associated with asymptomatic hyperlipasemia and chronic pancreatitis. Alcohol consumption impairs CFTR activity leading to decreased bicarbonate secretion and patients with susceptible CFTR mutations can develop clinical pancreatitis. CT imaging findings in CP correlate poorly with pain patterns. EUS features correlate poorly with fibrosis. Circulating epithelial cells are present in CP patients but not healthy volunteers. Surgery is superior to endoscopic treatment in providing durable pain relief (> 5 years). Repetitive pancreatic duct stent placements and chronic narcotic use are pre-operative predictors of poor outcome after total pancreatectomy with islet cell auto transplantation (TPIAT).

Summary—Novel genetic mutations for idiopathic chronic pancreatitis are being identified. Alcohol impairs CFTR activity and may explain a mechanism for pancreatitis. Current imaging modalities correlate poorly with clinical pain presentation and fibrosis in CP. Novel imaging modalities are needed. As TPIAT grows, rigorous outcomes analysis is needed to drive patient selection.

Keywords

chronic pancreatitis; pathophysiology; imaging; diagnosis; treatment

Introduction

Chronic pancreatitis (CP) is characterized by progressive inflammation and fibrosis of the pancreas. Clinically, it is challenging to encounter due to the various causes, the variable clinical presentations, the suboptimal correlation between available diagnostic imaging and functional testing and clinical symptoms, and the challenge in getting reliable and safe histological tissue. These factors, including the overall low prevalence of the disease, creates

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formidable barriers for advancing clinical care and research. Despite this, novel observations have been made in the past year to provide hope for better diagnostic and treatments.

Epidemiology

The estimated prevalence for adult CP is 42/100,000 persons with an etiological distribution of alcohol (44.5%), non-alcohol (26.9%), and idiopathic (28.6%). (1, 2) Little is known about pediatric CP. The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium have begun to provide important observations. In contrast to adults, a predisposing genetic mutation was identified in 67% of cases in their CP cohort and calcifications on imaging studies were uncommon. Similar to adult studies, there is significant disease burden manifested in missed school days (70% missed 1 day in the past month) with a median of 3 emergency room visits and 2 hospitalizations in the last year. (3) The proportion of cases from a predisposing genetic mutation will likely increase as better comprehensive diagnostic DNA tests become available. The low prevalence of calcifications fits our framework of this being a marker of advanced CP.

Pathophysiology

The low prevalence of CP suggests genetic susceptibility mutations as a key driver to CP development beginning with the discovery of PRSS1.(4) Novel mutations and new insights into previously recognized mutations have been described in the past year. One such novel susceptibility mutation, separate from the protease pathway, involves a hybrid allele (CEL-HYB) between carboxyl ester lipase (CEL) and its neighbor pseudogene (CELP). Described by Fjeld and colleagues, patients with this mutation demonstrate reduced lipolytic activity by impaired lipase secretion, increased intracellular accumulation of lipase and induced autophagy. They found this mutation in a higher proportion of non-alcoholic CP cases (14.1% vs. 1.0%) in a discovery series and validated it in a replication cohort.(5)

The clinical significance of asymptomatic hyperlipasemia remains uncertain. Weiss and colleagues performed an exploratory genome-wide association study (GWAS) on such a population and identified 2 single nucleotide polymorphisms (SNPs) involving the ABO blood group and Fucosyltransferase-2 (FUT2). In addition to replicating this in a validation cohort, they identified these associations in a pancreatitis cohort connecting ABO blood type B and FUT2 non-secretor status to asymptomatic hyperlipasemia and the development of CP.(6) If non-pancreatic causes of hyperlipasemia are excluded then, such patients may need to be clinically monitored for CP.

The vast majority of heavy alcohol abusers do not get CP. Therefore an underlying susceptibility mutation is thought to exist in patients with alcoholic CP. In a series of experiments, Maleth and colleagues linked CFTR function to alcohol consumption in pancreatitis by showing that sweat chloride concentrations increased in patients with acute alcoholic pancreatitis compared to normal healthy volunteers. Alcohol consumption can impair CFTR activity leading to decreased bicarbonate secretion. While patients with normal CFTR activity have compensatory reserves for this effect by alcohol, patients with impaired

CFTR activity can develop clinical pancreatitis.(7) This study nicely links genetic susceptibility mutations to environment factors in causing CP.

Several other studies related to genetic mechanisms in CP pathophysiology were published this past year. Two highlighted the importance of specific promoter variants in SPINK1 (8), and chymotrypsin C (CTRC) as a risk factor for CP. (9) Another reported on the importance of gene conversion events leading to phenotypes similar to established genetic mutation variants in PRSS1 (10). A validation genome wide association study (GWAS) of CP confirmed a protective effect of a PRSS1-PRSS2 SNP, and an increased risk in variants of the CLDN2-MORC2 loci in alcoholic CP. (11) These variants were observed equally by gender differing from an earlier report that reported a male preference in alcoholic CP.(12) Finally, a new genetic model of CP in mice based on impaired autophagy may provide further mechanistic insights into clinical chronic pancreatitis.(13)

Natural History

A critical research gap is to define the natural history of CP including its complications (type 3c diabetes, exocrine insufficiency, pancreas cancer and other potential adverse outcomes such as osteoporosis). Most studies to date have been retrospective evaluations confounded by inherent design biases. The Dutch Pancreatitis Study Group has initiated a prospective cohort since 2010 and described their preliminary results of recruiting 1218 patients. They have enrolled patients with recurrent acute pancreatitis (RAP), probable CP, and definite CP. Annual questionnaires that include validated pain and quality of life instruments are obtained with an impressive 80% response rate in the past 2 years. Imaging data is not standardized however, and outcomes are collected by medical chart review.(14) Recently, an NIH consortium to study chronic pancreatitis, diabetes and pancreatic cancer (CPDPC) has been formed with a primary goal of developing a longitudinal cohort of RAP, early CP, and established CP. A bio-specimen collection protocol is included for biomarker discovery and validation along with standardized imaging and function testing (http://cscpdpc.mdanderson.org).

Autoimmune Pancreatitis

Although there are 2 types of AIP defined by international consensus, it has been proposed that type 2 AIP be solely designated idiopathic duct centric pancreatitis (IDCP) because of the differences in histology and pathophysiology.(15, 16) To support this idea, a study by Mitsuyama and colleagues observed that neutrophil accumulation is uniquely elevated in inter-lobular pancreatic ducts in IDCP and that this correlated with elevated expressions of granulocytic chemotactic protein 2.(17) Biomarkers to differentiate type 1 AIP are needed. A small exploratory study of serum microRNA (miRNA) identified upregulation of miR-150-5p and miR-30-3p in type 1 AIP when compared to CP, pancreatic cancer, and healthy controls.(18) In another study, Prohibitin (PHB), a gene associated with various functions including mitochondrial function and transcriptional modulation, was identified as a possible auto-antigen.(19)

Imaging Update: Computed Tomography (CT)

Although insensitive for the detection of early CP, CT imaging is a common test for diagnosing parenchymal and ductal calcifications in advanced CP and pancreatic masses. Sinha and colleagues showed that a pre-operative CT with parenchymal calcifications correlated with higher rates of pain relief at 1 year (88% vs. 46%, p = 0.001) in 66 patients who underwent either a Whipple or Frey procedure for painful CP.(20) In another study however, Wilcox and colleagues performed a cross-sectional study of 518 patients with established CP and correlated CT image findings to pain patterns. Though the most common pain presentation was constant mild pain with severe exacerbations (45%), up to 15.6% reported no pain. Imaging findings were variable and correlated poorly with pain patterns. (21)

Imaging Update: Endoscopic Ultrasound (EUS)

EUS is considered the most sensitive modality to diagnose chronic pancreatitis. There are 9 defined features of CP by EUS, but the threshold for accurate diagnosis remains unresolved. Furthermore, small sample sizes and variable patient populations have limited studies that correlate these features to histopathology.(22–25) Trikudanathan and colleagues performed an important study in this regard. They reviewed 68 patients who had an EUS within 1 year of a total pancreatectomy with islet cell auto transplantation (TPIAT) for non-calcific chronic pancreatitis. Out of the 68, 12 (18%) had no evidence of chronic pancreatitis by histology. Among these 12 patients, 58.7% had ≥ 3 out of 9 EUS features. There was a poor correlation between EUS features and the Amman Fibrosis score (FS) (r=0.24). Using ≥4 EUS features provided the best balance of sensitivity (61%) and specificity (75%) for predicting a FS ≥ 2.(26) This study suggests that current EUS criteria are not adequate to diagnose non-calcific CP. Another question from this study is whether current selection criteria for TPIAT are adequate.

The value of EUS elastography remains an area active research. Dominguez-Munoz and colleagues have demonstrated that EUS elastography could be used to diagnose pancreatic exocrine insufficiency (PEI) in CP. They studied 115 CP patients, where 35 patients (30.4%) had PEI by a positive 13C-mixed triglyceride breath test. EUS elastography identified a significant difference between those with PEI (strain ratio 4.89: 95% CI: 4.36 – 5.41) from those without PEI (SR 2.99 95% CI: 2.82 – 3.16).(27) This study suggests that patients with more fibrosis, independent of calcifications, had a higher likelihood of having PEI. While this shows another potential use for EUS elastography, it remains unclear whether it will become part of routine practice.

Another common challenge where EUS currently plays an important diagnostic role is differentiating an inflammatory mass related to CP from pancreas cancer. Saftiou and colleagues evaluated whether the use of contrast enhancement agents during EUS (CEH-EUS) along with quantitative software programs that incorporate artificial neural networks (ANN) for classification could improve current diagnostic performance. In a multi-center study, they observed an incremental benefit in sensitivity to diagnose pancreas cancer from standard EUS-FNA (84%) to quantitative CEH-EUS (87.5%) and to use of an ANN (95%).

(28) Although an area of potential promise, the sensitivity in their study was much lower than reported in other studies where the sensitivity is ~95%.(29)

Novel Diagnostics

A key clinical challenge in CP management is 1) early and accurate diagnosis of CP and 2) early and accurate diagnose of cancer among CP patients. New approaches and refinements of current approaches are required. Referred to as a liquid biopsy, the concept of a cell signature in the peripheral blood has been made possible with novel sensitive technologies. Cauley and colleagues evaluated whether circulating epithelial cells (CEC) could distinguish benign, pre-malignant, and malignant pancreatic lesions. Although they did not identify any CEC's in healthy volunteers, 9 of 13 CP patients had CECs – 6 had CEC's that were malignant in appearance and 3 had CEC's suspicious of being malignant.(30) Despite several limitations, this study demonstrates as a proof-of-concept of liquid biopsies (present in the blood) in CP, particularly to diagnose pancreas cancer. Beyond conventional imaging, there have been studies describing the technological innovations with the capacity to map out the distribution and density of neural networks within an organ such as the pancreas.(31, 32) Such possibilities may provide significant insight toward understanding clinical pain patterns and pathophysiology in CP.

Medical Treatments

The benefit of anti-oxidants in treating pain remains unclear. Talukdar and colleagues have hypothesized that inappropriate selection and dose of anti-oxidants are responsible for mixed results. They undertook a systematic review and meta-analysis focusing on 8 studies that used methionine because of its role in donating methyl moieties to maintain the acinar trans-sulfuration pathway. Although there remained significant heterogeneity, they reported a significant reduction of pain score.(33) This may lead to further clinical trials on anti-oxidants. Trials that focus on non-opioid analgesics are needed for pain relief.(34) Juel and colleagues describe a double-blinded, placebo-controlled randomized clinical trial of 40 CP patients to S-ketamine versus placebo over 4 weeks.(35) S-ketamine is an anesthetic used since the 1960's with anti-hyperalgesic effects. As an NDMA receptor antagonist, it can treat central sensitization from chronic pain. With increasing appreciation of the microbiome in health and pancreatic disease, Rammohan and colleagues performed a single-blinded, placebo-controlled trial studying synbiotics (prebiotics plus probiotics) in 75 patients undergoing a Frey procedure for painful chronic calcific pancreatitis to prevent post-operative infectious complications. Patients took either treatment or placebo pills three times per day beginning 5 days before the surgery until 10 days after surgery. The treatment arm (N=39) had a lower post-operative infectious rate (12.8% vs. 39%, $p<0.05$) than placebo (N=36).(36)

Surgical Treatments

A Cochrane meta-analysis comparing endoscopic versus surgical intervention for painful obstructive CP found surgery to be superior for providing pain relief beyond 5 years of follow up.(37). This meta-analysis, however, included only 3 trials.(38–40) For patients with

refractory pain and no dilated duct, a meta-analysis demonstrated that a duodenum-preserving pancreatic head resection (DPPHR) provided similar pain relief, better quality of life and reduced PEI than a standard pylorus preserving Whipple.(41)

Interest in TPIAT programs appears to be growing and many centers are beginning to report their outcomes.(42–45) Some centers without islet isolation facilities have used remote or off-site isolation collaborations with a regional center with comparable outcomes.(46, 47) Some centers are offering it to patients who have had previous surgical resection for CP with comparable outcomes.(48) In response to this interest, findings from an NIDDK sponsored workshop were published this past year and several research gaps were identified.(49) Although the majority of patients appear to benefit, a substantial minority of patients do poorly. Chinnakotla and colleagues reviewed 581 cases and identified repetitive pancreatic duct stent placements and long standing narcotic use as predictors of unchanged pain after TPIAT and continued narcotic dependence at 1 year.(50)

Complications

Undiagnosed or undertreated exocrine insufficiency leads to fat-soluble vitamin deficiencies including vitamin D. Previous studies have shown an increased risk of osteoporosis and low trauma fractures in CP patients.(51–53) A prospective case-control study showed CP patients to have higher rates of osteoporosis (31% versus 6.9%), increased markers of higher bone turnover, higher inflammatory markers, and lower vitamin D levels.(54)

Conclusion

Research in the past year on chronic pancreatitis highlight novel genetic susceptibility mutations, limitations in CT and EUS imaging, the durability of surgery over endoscopic therapies for refractory pain in CP, the growth of total pancreatectomy with islet cell auto transplantation procedures, and the promise of future consortium-based prospective cohorts and clinical trials.

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**** outstanding interest with annotations**

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Key Points

- Approximately 67% of pediatric chronic pancreatitis is associated with a known predisposing genetic mutation
- A novel hybrid allele (CEL-HYB) mutation is associated with impaired lipase secretion, increased intracellular accumulation of lipase, induced autophagy, and is found in a higher proportion of non-alcoholic CP cases.
- Alcohol consumption can impair CFTR activity leading to decreased bicarbonate secretion and pancreatitis.
- Among 12 patients with no evidence of chronic pancreatitis by histology, 58.7% had ≥ 3 out of 9 EUS features and there was poor correlation between EUS features and the Amman Fibrosis score (r=0.24).
- Total pancreatectomy with islet cell auto transplantation is growing in the U.S. While reported outcomes have been promising, patient selection is paramount.