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The Challenge of Chronic Pancreatitis Pain

Chronic pancreatitis is a progressive and potentially fatal disease caused by persistent unresolved inflammation and necrosis of the pancreas. The initial chief complaint of patients is severe upper abdominal pain, which may extend around the back and may be accompanied by nausea, vomiting, weight loss, diarrhea, and oily stools.[1]

Pain reportedly occurs in up to 94% of patients with chronic pancreatitis. The pain is burning, intermittent, and shooting, suggesting that it has both inflammatory and neuropathic components. The pain is caused by sustained peripheral sensitization secondary to both inflammatory and neuropathic damage to nerve endings in the pancreas, as well as central sensitization. Pancreatic fibrotic strictures and calcifications develop, increasing ductal and interstitial pressure. The pathology promotes premature trypsin conversion within the pancreas, causing autodigestion, a prime activator of intense pancreatic pain. Recurrent activation of the innate immune response (stellate) cells resident in the pancreas, as well as cellular necrosis, promote cytokine release and inflammatory cell invasion.

Persistence of pancreatic inflammation, particularly in those with an identified genetic predisposition combined with continued high-risk behaviors (alcohol abuse, smoking, and a high-fat diet), can produce irreversible chronic pancreatitis (Fig. 1). Pain can abate if the high-risk behaviors cease. While some patients do not experience pain, in others the pain can be severe and unrelenting, sometimes leading to suicide. Chronic pancreatitis can be accompanied by diabetes and weight loss brought on by insufficiency in production of digestive enzymes such as insulin, glucagon, trypsin, and amylase, as well as pancreatic bicarbonate.[1]

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Clinical Burden

Direct and indirect costs for the treatment of pancreatitis in the United States were estimated at $3.56 billion in 2010.[5] Pancreatitis can be difficult to diagnose, and persisting abdominal pain is the cardinal symptom. Both acute and chronic pancreatitis can be fatal conditions, brought on by alcohol abuse in more than half of patients. Because many patients with chronic pancreatitis have a history of alcohol abuse, they are often labeled as addicts seeking narcotics.[6–8] Other contributory factors include hereditary gene mutations, smoking, and poor dietary primary symptom. In many cases, pain management, metabolic problems associated with diabetes, disability, and prevention of progression to pancreatic cancer are difficult clinical issues that impair quality of life.[1,2] In the United States, pancreatitis was reported as the 11th leading cause of death from digestive disease in 2004, with a 62% rise of pancreatitis-associated hospital discharges between 1988 and 2004,[3] concurring with an estimated 210,000 hospital admissions each year.[4]

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Treatment for chronic pancreatitis includes pain medication, intravenous fluids, a low-fat, nutritious diet, and enzyme supplements, thus requiring a team of health professionals. Recent surgical and endoscopic therapeutic advances to remove ductal blockage and necrotic tissue have been important in reducing pancreatic pain as a

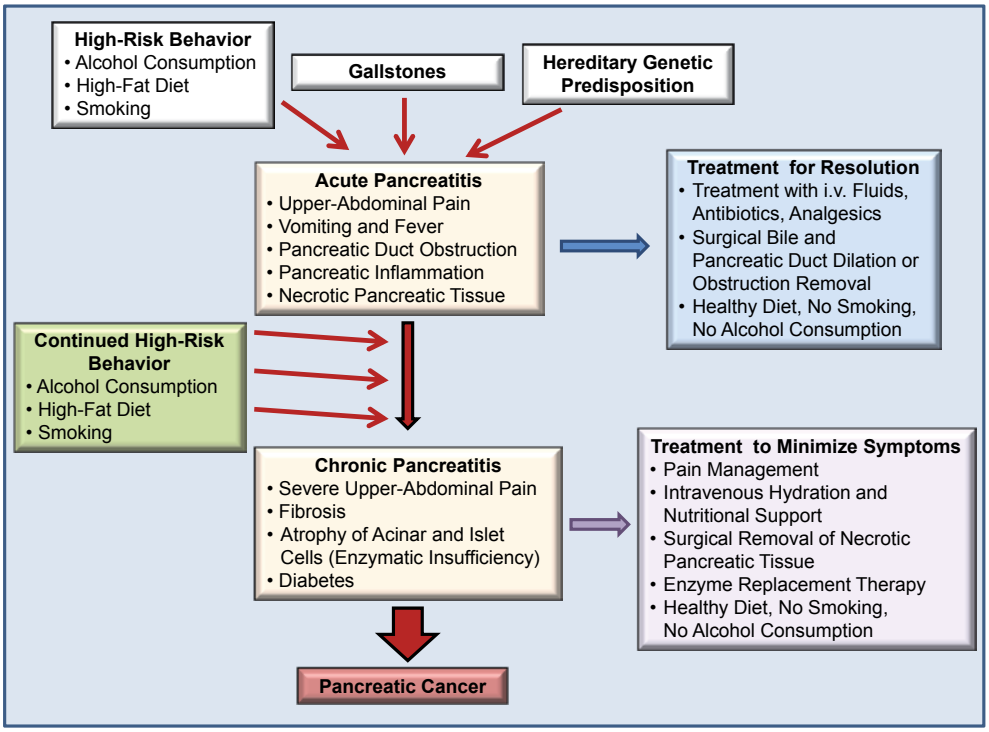

Fig. 1. A combination of hereditary genetic susceptibility factors interacting with environmental factors can result in the development of pancreatitis or cause a shift from acute to chronic pancreatitis. Recurrent acute pancreatitis develops predominantly in patients with non-gallstone-related pancreatitis, although it can develop in patients with gallstone-related pancreatitis when cholecystectomy has been delayed or refused. Continued high-risk behavior may cause the disease to progress to chronic pancreatitis and even pancreatic cancer.[1,2,4,5,7–9]

choices resulting in hypertriglyceridemia and gallstones.[1,2,9] The prevalence of both acute and chronic pancreatitis increases with age.[2]

Biological and Molecular Mechanisms of Pancreatitis Pain

The multifactorial pathophysiology of pain associated with alcoholic chronic pancreatitis and pancreatic cancer is not clearly understood, but significant progress has been made (Fig. 2).[10] Human pathology studies report striking neuroplastic changes in the pancreas of patients with chronic pancreatitis and pancreatic cancer compared to the normal pancreas.[11] In particular, unmyelinated nerves are proliferated and edematous, with evidence of inflammatory cell invasion and disruption of the protective perineural sheath. Reported phenotypic alterations include upregulated substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide, and growth-associated protein 43.[12]

Alcohol produces harmful breakdown products that damage the cells of the pancreas. Alcohol metabolites and chemicals released by damaged cells activate and sensitize pancreatic nerves, causing pain. Ethanol, acetaldehyde, and oxidative stress have been shown to activate pancreas cells via three intracellular pathways mediated by mitogen-activated protein kinase: extracellular signaling kinase pathways (ERK1/2), p38 kinase, and c-jun amino terminal kinase.[13] Alcohol and its acetaldehyde metabolites also activate inositol triphosphate and protein kinase C. Many other cellular signaling pathways have been described for functional changes initiated by ethanol-induced tissue damage. Alcohol produces acute inhibitory effects on lipoprotein lipase activity. Furthermore, alcohol disrupts hepatic fatty acid metabolism.[14] Damage, hypoxic ischemia, gallstones, infection, and ductal stenosis create a physiological imbalance, unleashing a multitude of highly ordered physiological processes and complex cellular signaling cascades that produce tissue necrosis and affect primary afferent endings, ultimately causing pain.

Chronic alcohol abuse can impair alcohol dehydrogenase, an enzyme that catalyzes the oxidation of alcohol. Reduced activity of alcohol dehydrogenase results in nonoxidative metabolism of alcohol, which produces arachidonic acid. Arachidonic acid itself functions as a signaling molecule and is converted by cytochrome p450 epoxygenase into epoxyeicosatrienoic acid, an agonist for transient receptor potential vanilloid 4 (TRPV4) ion channels found on both pancreatic cells and spinal sensory neurons.[15–16] Pancreatic stellate cells, local innate immune cells, have inducible TRPV4 receptors that are activated in response to alcohol metabolites, including arachidonic acid, the

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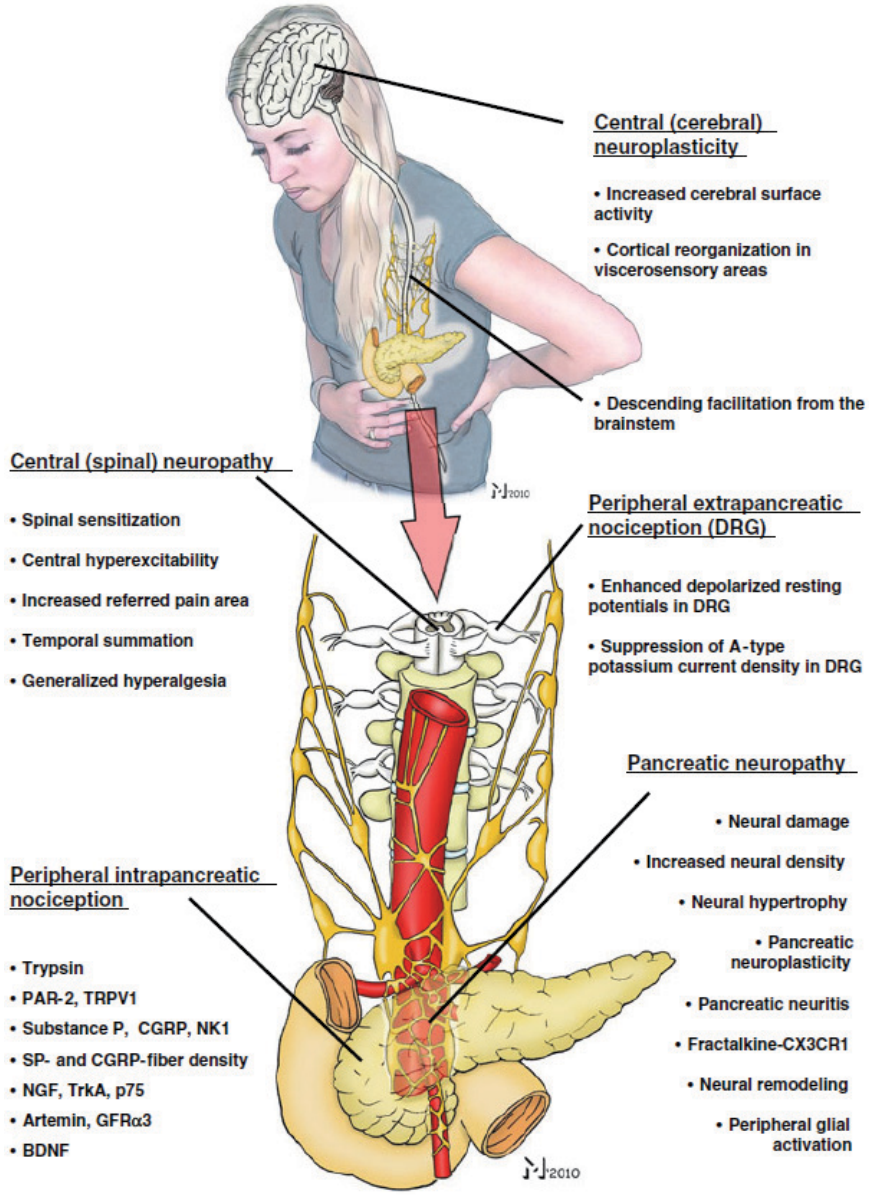

Fig 2. The main causes of pain in chronic pancreatitis. Neuropathic pain in chronic pancreatitis patients involves numerous molecular and morphological alterations at intrapancreatic (peripheral) sites and extrapancreatic sites including the nervous system (dorsal root ganglia [DRG], spinal cord, brainstem, and cerebrum). Increased presence of nociceptive signals in the periphery, mediated by neurotransmitters and neurotrophic factors, is paralleled by prominent neural damage and numerous intrapancreatic neuropathic and neuroplastic alterations. At the same time, peripheral sensory neurons, DRG neurons, and spinal cord neurons exhibit a hypersensitive state that is subject to modulation by the brainstem through descending facilitation. Finally, the cerebral cortex adapts to these caudal alterations by increasing its basal activity and changing its spatial conformation in viscerosensory areas. From: Demir et al.[10]

lipid second messenger phorbol ester 4α-phorbol 12,13-didecanoate, and the hypoosmotic conditions present in the pancreas during inflammation.[17] Activation of the protease-activated receptor 2 (PAR2) by prematurely released trypsin results in an influx of cations, calcium and sodium cations by TRPV4. This influx can activate neurogenic inflammation, an autocrine loop that ultimately increases pancreatic cell damage, inflammation, pain, and pancreatic tissue necrosis.[16] In rodent models of pancreatitis, pain-related behaviors and inflammation are markedly diminished by administration of TRPV1, TRPV4, and TRPA1 antagonists, or in animals genetically modified to lack these ion channels.[16,18,19] Other neuroactive molecules implicated in pancreatic pain include substance P, CGRP, and nerve growth factor (NGF).[11,16,20,21]

Knowledge acquired in recent years indicates that mechanisms active in relaying information about acute pain are different from and can even be the opposite of chronic pain mechanisms. Thus, successful development of pharmacological approaches depends on chronic pain models. Future studies may increase our understanding of the mechanisms that cause chronic pancreatitis pain and how it contributes to the pathogenesis and pathobiology of this disease and its potential to progress to other clinical conditions with significant pain—diabetes and pancreatic cancer. Such research will provide a better understanding of how to prevent the progression of pancreatic inflammatory disease to diabetes and cancer.

Incidence

Combined risks, including alcohol abuse and smoking, can continue to amplify pain and inflammation of the pancreas and can eventually progress to diabetes and pancreatic cancer. A large percentage of patients with pancreatitis and pancreatic cancer suffer from mild to severe pain. Immediate cessation of smoking and alcohol consumption is recommended.[1,2] However, cessation of alcohol intake is difficult for chronic alcoholic pancreatitis patients, particularly because alcohol may be able to relieve the pain caused by nerve damage. When surveyed, 32% of chronic pain patients reported a willingness to try any new therapy for relief. Surgery to remove part of the pancreas may be necessary to resolve pancreatic inflammation and associated pain, but reoccurrence of pain after surgery is

common in 50% of patients at a 10-year follow-up.[3–5]

Intractable pain contributes to the high suicide rate among patients with chronic alcoholic pancreatitis. In patients with pancreatitis and pancreatic cancer, the level of pain experienced is directly linked to the decrease in pancreatic function, the increased length of hospitalization, and disease progression.[1,11] When diabetes also develops, the pain typically abates. However, with continued hyperglycemic and hypoxic conditions, a second painful condition referred to as painful diabetic neuropathy often develops in the extremities. The risk of progression to pancreatic cancer is reportedly 50% for newly diagnosed chronic pancreatitis patients in the U.S. Veterans Affairs system. Although many different treatments are available, pain management, improvement in quality of life, recovery of pancreatic function, as well as prevention of progression to pancreatic cancer remain challenging.[2,7,8,22] Thus, there is an urgent need to pursue novel pain relief strategies for chronic pancreatitis and to inhibit progression to diabetes and pancreatic cancer.

Diagnosis

Sequential assessment is required to diagnose chronic pancreatitis, including laboratory testing and imaging with computerized tomography, endoscopic ultrasound, and magnetic resonance cholangiopancreatography (Fig. 3).[1,23] Diagnosis of chronic pancreatitis is difficult because blood values of digestive enzymes (lipase, amylase) may be normal.

Therapeutic Approaches

General Principles

Pain due to chronic pancreatitis can be one of the most challenging chronic pain conditions to treat because of the combination of severe relapsing and remitting pain, the burden of chronic disease, and the inherent risk of drug abuse related to the risk for having the disease itself, particularly alcohol abuse and smoking. Strong pain medications, notably opioids, are often needed, especially during exacerbations, when pain can be extremely severe. Over time, it may become difficult to wean the opioid between exacerbations, so that opioid use becomes chronic, and the likelihood of abuse increases. There is a role for interventions in selected cases, but the mainstay of treatment remains behavioral and pharmacological.

Interventions: Surgical Versus Endoscopic Approaches

A survey of pain in patients with chronic pancreatitis is reported by Lankisch, who found that 50% of alcoholics and 62% of nonalcoholics still reported pain

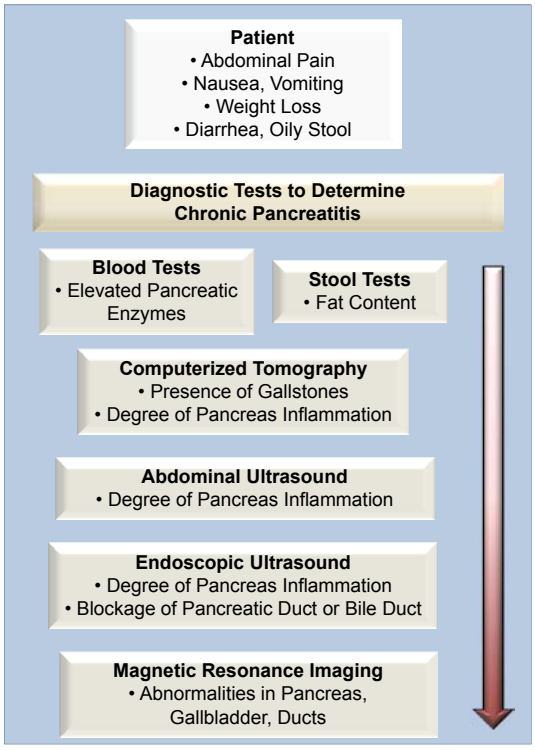

Fig. 3. A diagnostic algorithm for chronic pancreatitis.

attacks after 10 years with chronic pancreatitis.[24] A recent consensus review from Sweden provides significant recommendations for treatment of chronic pancreatitis and the accompanying pain, highlighting guidelines from Australia, Germany, Italy, and a recent Cochrane review citing a collection of more than 1,000 clinical cases.[25,26] The recommendation of the Swedish review is that a multidisciplinary team of expert physicians knowledgeable in pain, endoscopy, gastroenterology, and surgery should tailor an individualized therapeutic approach for each patient.

While hereditary pancreatitis in young patients may best be treated with nonsurgical approaches, the Cochrane review suggests that early surgical intervention provides significant immediate pain relief and improved pancreatic function. However, there was no significant difference in morbidity and mortality between endoscopic and surgical approaches. While demonstrating that endoscopic ductal decompression therapy offers pain relief in two-thirds of all patients when it is used as the only form of treatment, the Cochrane revoew found that a quarter of those patients eventually still have to undergo surgery.[27,28] In cases treated with extracorporeal shock wave lithotripsy in conjunction with endoscopy, the result was additional costs with no improvement in outcome for patients with chronic pancreatitis pain.[28]

Extracorporeal shock wave lithotripsy with or without endoscopic retrograde cholangiopancreatography provided equal results regarding pain control. Worldwide comparisons from the literature reviewed by Lankisch[24] included reports claiming that 48–85% of patients could become pain free for five years with both procedures, while the remaining patients had relapsing pain attacks. With the observation time extended to 10 years after initial treatment, 53% of patients reported having relapsing pain attacks. Long-term duration of pain is particularly prominent in early-onset pancreatitis in patients 35 years of age and younger.

Groups in Switzerland and South Africa have reported that pain decreases as pancreatic function declines, while reports from Germany and Denmark found the opposite, using different measures of pancreatic insufficiency. In Germany, the annual incidence for chronic pancreatitis in 2013 was reported as 23 per 100,000 persons, more than twice the rate in the United States.[2,24] In the German report, more than half of the patients (59%) with severe endocrine sufficiency reported pain.

After surgical procedures, 24–100% pain relief is reported in the short term, but later on, the pain may get worse again, and complications may develop.[24] In two prospective randomized clinical trials comparing endoscopic versus surgical therapy for the treatment of pain, the long-term outcome statistics were markedly in favor of surgical procedures, with 75% of patients showing clinical improvement compared with 32% of those treated with endoscopy.[29,30] After endoscopy, in many cases surgery is eventually required at a later date, suggesting that surgery is the more cost-effective treatment.[31]

Given that pancreatic pain is closely tied to pancreatic dysfunction, the consensus statement published in June 2013, which provides a new classification for acute pancreatitis based on severity, is of great importance.[32] This report provides results from a global web-based survey of surgeons, gastroenterologists, internists, and radiologists active in the clinical care of patients with acute pancreatitis. The new classification is the result of a consultative process among specialists in pancreatic diseases from 49 countries spanning North America, South America, Europe, Asia, Oceania, and Africa. Concise, up-to-date definitions of all the main entities pertinent to classifying the severity of acute pancreatitis in clinical practice and research are provided in the report. The goal was to provide a classification that is based on local and systemic determinants of severity to be used in a uniform manner throughout the world.

Pharmacotherapy

The basic principles of managing chronic pain due to pancreatitis are similar to those of any other chronic pain condition. Wherever possible, pain should be managed with weak analgesics before progressing to opioids.[33–35] Adjunct treatments such as counseling, cognitive-behavioral treatment, group therapy, and complementary approaches such as acupuncture or guided imagery are helpful both for disease management and coping, as well as for pain management.

Although the use of chronic opioid therapy may be unavoidable in advanced cases, the risk of developing or exacerbating substance abuse can be minimized by using "universal precautions."[36] These precautions include regular assessments, frequent prescriptions, urine toxicology screening, and checking of prescription monitoring data where available. Use of extended-release or long-acting opioids, either alone or in combination with immediate-release opioids, is debatable in the treatment of chronic pancreatitis pain. Ideally, between exacerbations, clinicians should either discontinue opioids or prescribe and monitor extended-release opioids, reserving immediate-release preparations (including intravenous patient-controlled analgesia) for exacerbations.

Tricyclic antidepressants, selective serotonin reuptake inhibitors, and gabapentinoids are suitable adjuvant agents.

In a study of 64 patients with chronic pancreatitis, pregabalin given at a stable analgesic dose (75 mg b.i.d., titrated up to 300 mg b.i.d.) was compared to placebo.[37] Improved pain reduction was reported at three weeks in the pregabalin-treated group compared to the placebo group (36% versus 24%), but side effects were more common in the pregabalin group.

Reportedly, high-dose naproxen treatment (40 mg/kg, p.o.) aggravated the pancreatic fibrosis that produced ductal constriction and pain in a rat pancreatitis model, suggesting a potential risk for long-term use of nonsteroidal anti-inflammatory drugs as analgesics in clinical practice.[38]

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