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Pathogenesis and managenent of pain in chronic pancreatitis

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INTRODUCTION

Of the three cardinal manifestations of chronic pancreatitis-pain, diabetes mel litus and steatorrhea, it is pain that brings the patient to the physician and is the most difficult to manage. The intractabale pain that is quite debilitating disrupts lifestyle and leads to functional incapacity, drug and alcohol dependency, and a drug-see king behavior that occasionally might push the desperate patient to suicidal ten d ency. Painless CP is an exception that has been observed in nearly 5% to 10% of patients with all forms of chronic pancreatitis. Lack of pain is also a feature of the late onset idiopathic CP.

CHARACTERISTICS OF PANCREATIC PAIN

The pain of pancreatitis is steady and agonizing, is felt in the epigastrium, so metimes in the left upper quadrant with radiation to the back between T12 and L2 or to the left shoulder. Typically pain is postprandial in nature suggesting a gastric lesion. Colicky pain is unusual in CP. Associated nausea and persistent vomiting that does not relieve the pain are in contrast to the pain of gastritis or pyloric obstruction. The pain may be accompanied by flushing and shortness of breath. The severity of pain varies greatly in defferent patients and indeed in the same individual in different episodes, for no obvious reason. The onset of the persistent abdominal pain 12 to 48 h after a drinking bout or "on the afternoon after the night before" is said to be characteristic of alcoholic pancreatitis, but exacerbation of pain may occur even during abstinence from alco hol with no identifiable cause. At times of pain patients bend forward to the so-called "pancreatic position" or lie in the knee-chest position on their ri ght or left side. The duration of pain-free intervals is unpredictable and may last from weeks to many months, making it difficult to assess the value of dif ferent modalities of pain therapy. As the disease advances, the postprandial rel ationship is lost and pain becomes steady and unrelenting[1].

Recently Ammann *et al* reported characteristics of pancreatic pain in 207 pat ients with alcoholic chronic pancreatitis[2]. They identified two patter ns of pain Type A and B based on natural history. In Type A pain in nearly 44% o f patients, who never, who never needed surgery for pain relief the duration of pain was short usually less than 10 days. In contrast Type B pain occurred in 56% of patients who had episodes of constant pain defined as prolonged periods of daily persistent pain, occurring 2 or more days per week for at least 2 months. All these patients underwent surgery. The two types of pain noted by Ammann in S witzerland has not been observed in other series[3]. What Ammann has not ed in his Zurich patients based on the natural history of pain in chronic pancre +atitis as "burning out of the pancreas" and pain relief after 10 or more years is also not seen in many other countries[4-6]. Although it is not clear why geographical differences occur in the natural history of chronic pancreatit is, one observation is that the different studies quoted include patients with a lcoholic and non-alcoholic pancreatitis while Ammann's group is exclusively of alcoholic pancreatitis.

PATHOGENESIS OF PAIN IN CP

Pain in CP is multifactorial in pathogenesis[1]. The current thoughts in clude (a) increased intraductal pressure, (b) increased pancreatic tissue pressure (interstitial-hypertension), (c) pancreatitis-associated neuritis, (d) pa ncre atic ischemia, and (e) ongoing pancreatic injury. Complications of CP, such as pseudocyst, common bile duct obstruction, and associated gastroduodenal diseases (e.g., peptic ulcer), may contribute to the pain. Pancreatic cancer may mimic CP and may be a complication in some patients with CP.

Intraductal hypertension

Increased intraductal pressure is the most important cause of pain. Intraoperative ductal pressure measurements, direct measurements through endoscopic approach , and studies on surgical and autopsy specimens of pancreas have substantiated the concept.

The normal intraductal pressure, depending on the

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methodology used in the unstim hulated pancreas, is about 7 mmHg, and it is markedly increased in CP. DuVal in 1 958 measured the pancreatic duct pressures in nine patients with CP using a smal l-caliber Foley catheter inserted into the distal pancreatic duct at pancreatic ojejunostomy and in four patients with cutaneous pancreatic fistulae who served as controls [1]. In those with CP the intraductal pressure was invariably higher. Hi stopathological studies reveal that strictures of the ducts and ductules, obstru ction by calculi in major ducts or its branches are the essential features of CP and could all cause pre-stenotic intraductal hypertension.

Interstitial hypertension

The pathogenesis of interstitial or tissue hypertension is the same as intraduc tal hypertension[7]. Even minimal obstruction to the ductules can lead to tissue fluid hypertension. Indeed, interstitial hypertension can theoretically occur much before intraductal hypertension and ERCP changes of ductal morphology are detectable. In the so-called minimal change chronic pancreatitis, the severe pain cannot be explained with the above[8].

Pancreatic pain maybe ischemic in nature analogous to the pain in compartment sy ndromes. High interstitial pressure could greatly increase vascular resistance and reduce pancreatic blood flow. Karanjia *et al* have shown in their cat mode l of CP that the blood flow to the pancreas was 40% lower than in normal pan creas, whereas secretory stimulation of the pancreas further decreased the blood flow[9]. Decompression of the obstructed pancreatic duct reversed all these changes. Increase in ductal or interstitial pressure has been questioned in a few studies and no correlation has been found between ductal morphology and pain[10]. In those with normal ERCP findings, one cannot rule out the poss ibility of interstitial hypertension.

Ongoing pancreatic injury

Kloppel hypothesizes that the dynamics of the disease rather than the end result are possible factors for pain [11]. During progressive scarring the pancreatic nerves and ducts become irregularly entrapped in fibrotic tissue. Recurrent tissue necrosis causes pain in early stages, whereas the persistent pain in a dvanced CP is a result of incomplete obstruction of the ducts.

The role of pancreatic stellate cells in this regard is notable. Pancreatic stel late cells are perivascular and derived from Vitamin A-containing cells. These cells because of their contractile potential and perivascular location could cause microvascular ischemia and pain[12].

Inflammatory mass

Nearly 30% of patients with painful chronic pancreatitis have enlargement of the pancreatic head caused by inflammation[13]. The inflammatory mass cause d pain by involving pancreatic nerves and producing obstruction of bile duct, pancreatic duct or duodenum[14,15]. Operations have been devised to remove inflammatory masses[16, 17]. The studies of Ammann *et al* did not find these inflammatory masses in the head of the pancreas[2].

Neuronal changes

Keith *et al* (1985) studied pancreatic tissue obtained from 50 patients who underwent pancreatic resection or decompression[18]. They found perineur al accumulation of inflammatory cells, predominantly eosinophils correlating with severity of pain and alcoholism-scores, but not with ductal morphology, indic ating a role of these inflammatory cells in the causation of pain.

It is well known that eosinophils are toxic to nerve tissue. The mean diameter of nerves in the pancreas of CP patients is significantly greater than in controls[19]. The perineural sheath is altered such that it no longer provides a barrier be tween the surrounding connective tissue and the internal neural components. The absence of the normal barrier provided by the perineurium exposes the nerves to activated eczymes, plasma components, and bioactive materials released from infl a mmatory cells. Increased mean diameters of nerves argue against an old thought that pain is caused by strangulation of nerves by fibrosis. The weakness of the n euronal theory of pain lies in its failure to explain the relief of pain with the cessation of pancreatic function when it shows the same histologic changes in nerves, as in painful pancreatitis. It also does not explain the relief of pain with surgical procedures that reduce intraductal pressure but do not alter the neuronal changes.

NATURAL HISTORY OF PAIN IN CP

Pain in CP as the disease progresses to pancreatic exocrine and endocrine insuff iciency is unpredictable in an individual case. Levra *et al* (1970) reporting on a longitudinal study of 113 patients followed for 4 years, observed that the pain decreased in 42%, was stable in 32%, and worsened in 26%[20]. The often quoted study of Amman *et al* (1984) from Switzerland concluded that 85% of patients obtained lasting relief from pain at a median of 4.5 years from the onset of disease accompanied by a marked increase in pancreatic dysfunction and calcifications suggesting a relation between pain and the onset of pancreatic insufficiency.

Although there seems to be no consensus with regard to the perce ntage of patients who get spontaneous relief, some observers have confirmed a fi nal pain-free stage in the natural history of CP in 30% to 50% of patients. How ever, in an individual case no one can predict how long it will take to reach a pain-free stage of CP or whether that individual will ever get a “burned out pancreas”. Surgical management cannot be delayed hoping that spontaneous relief would ever occur.

The study of Ammann *et al* quoted earlier is relevant here[2]. Nearly 44% of patients had only intermittent pain

and had a favorable course without invasive therapy. In evaluating various treatment modalities the group of patients who underwent the therapy has to be clarified. An endoscopic therapy of clearing stones from the pancreatic duct by a group claimed that the best predictor of pain-free int erval after therapy was infrequent attacks before therapy[22]. One might criticize studies with similar results as expected response even without the therapy.

MANAGEMENT OF PAIN IN CP

Management of pain in CP is to be approached by a team of physicians that includes a gastroenterologist, surgeon, radiologist, and a psychiatrist. It is difficu lt to assess the severity of pain in patients with CP since many of them are add icted to alcohol and/or narcotics. Equally important is to recognize that in pat ients with alcoholic pancreatitis it is not uncommon to see malingering or a drug-seeking behavior in the form of exaggerated complaints of pain. The available modes of therapy in the management of pain are tabulated. Bef ore the initiation of therapy, treatable complications such as pseudocysts, bile duct abstructions, and peptic ulcer disease should be ruled out.

Table 1 Management of pain in chronic pancreatitis

Medical (conservative)	Abstinence from alcohol
	Analgesics (nonopioid and opoid NSAIDs)
	Tricyclics
	Pancreatic enzyme supplements
	Parenteral nntrition
	Octreotide
Endoscopic therapy	Sphincterotomy, stone extraction, extracorporeal shock wave
	Lithotripsy (ESWL) of pancreatic calculi
	Septotomy+
	Stent placement
Neurolytic therapy	Drainage procedures
	Surgical therapy
	Resections
	Denervation procedures
Experimental	Dissolution of calculi with oral medications
	Direct chemical dissolution of calculi
	Duct injection to cause complete obstruction (prolamin, acrylate, latex)

Abstinence from alcohol

The help of a psychiatrist or an alcoholics anonymous group is often necessary. The rate of pain relief is usually higher in abstinent patients, and deteriorati on of pancreatic function is slower. The importance of alcohol abstention thus cannot be overemphasized. Considerable time should be spent in discussing with the patient and making him or her understand the inevitable progression of disease if alcohol use is continued.

It is difficult to interpret the results of studies showing no correlation betwe en abstinence from alcohol and abdominal pain. It is likely that the clinical stage of the disease alters the effect of alcohol or pain. In the early stages, with well-preserved pancreatic function, secretagogoues such as alcohol may exagg erate pain, whereas in advanced stages they may have very little stimulatory effect on the fibrotic pancreas[21].

Diet

The goal is to provide rest to the pancreas or avoid excessive stimulation while maintaining adequate nutrition. The conventional diet is one that is low in fat and small in quantity. In some patients hospitalization, total cessation of oral intake of food, and short-term use of partial or total parenteral nutrition may be needed for urgent management of severe pain. The diet is also determined by the fact whether there is associated diabetes and/or steatorrhea. Supplement ation with oral antioxidants is reported to reduce the intensity and frequency of pain.

Antioxidant supplementation

The basis of antioxidant therapy was the hypothesis that CP is a disease caused by unopposed free radical (FR) injury[23,24]. Banks and colleagues in their attempt to prevent generations of FR used allopurinol 300 mg/d. There was no significant reduction in pain.Despite a definite proof for FR injury in relation to CP or clinical trials conf irming the use of antioxidants, there is widespread enthusiasm for the therapy. Antioxidant therapy is inexpensive and harmless. For a disease with no better substitute for treatment the simplicity of antioxidant therapy is attractive.

Cigareete smoking is noted to be an associated factor in the pathogenesis of CP, it is prudent to advise against smoking[25,26]. Most alcoholics who develop CP are heavy cigarette smokers.

Analgesics

The first step is to try nonopioid analgesics, such as acetaminophen, salicylate s and nonsteroidal anti-inflammatory drugs (NSAIDs) with or without antidepress ants. However, most patients need opiod analgesics for symptomatic relief, and the initial doses should be low and administered less frequently. Small doses of codeine derivatives with acetaminophen are the usual drugs of choice. The use o f an H_2 receptor antagonist or a proton pump inhibitor to suppress gastric acid production, reduce destruction of orally administered pancreatic enzymes and theoretically reduce pancreatic stimulation is advocated. As an adjunct to the therapy, a small do se of an antidepressant may be helpful. If a potent narcotic is needed to offer pain relief, surgery should be considered as early as possible before the developme nt of narcotic addiction.

Pancreatic enzyme therapy

The basis for oral enzyme therapy for pancreatic pain is as follows. Secretory status of exocrine tissues and obstruction to outflow determine intraductal pressure. Deficiency of proteases (trypsin, chymotrypsin) within the duodenal lum en causes release of cholecystokinin from the mucosa,

leading to enhanced stimulation of the exocrine tissues [27-29]. Experimental evidence indicates that the presence of intraluminal proteases in the proximal small intestine inhibits the release of cholecystokinin and thereby stimulation of the exocrine parenchyma.

To effect feedback inhibition of pancreatic secretion, it is important to admini ster large doses of commercially available pancreatic enzymes. One should choose the type of preparation that increases the intraduodenal proteases[28]. The ideal patient for enzyme therapy is a female with idiopauhic pancreatitis with normal fecal fat excretion. Individuals with large dilated ducts tend not to respond to enzyme therapy. Enzyme therapy is simple, easy to initiate, but some what expensive. However the cost of enzyme therapy cannot be considered high when the alternative is major pancreatic surgery. The selection of an enzyme prepar ation is to be based on the protease concentration within the preparation, the s tability of the enzyme in withstanding gastric acidity, and the timely release of the enzyme from capsules in the proximal intestine. The inconvenience of taking l arge doses of enzyme preparations is justified if the preparations relieve painor reduce the need for analgesics. Hence, it is worth trying enzyme therapy in all patients with painful CP for at least 6 to 8 weeks.

If there is no pain relief with a nonenteric coated preparation, addition of an H_2 receptor antagonist or sodium bicarbonate (650 mg) before and after each do se of pancreatic enzymes to protect them from gastric acid is a consideration.

The side effects of enzyme therapy are few. Pancreatic extracts from insoluble comple xes with folic acid, as a result folic acid deficiency can develop. Hyperuricemi a and hyperuricosuria are described in cystic fibrosis patients treated with large doses of pancreatic extracts. Allergic reactions to the porcine proteins in extr acts may occur. There is a valid criticism that studies supporting response to enzyme therapy are few and have used only a small number of patients.

The vast majority of patients with CP are those with longstanding history of alc oholism, more often men, with large duct disease. Even the protagonists of enzyme therapy do not consider the above group as ideal patients to obtain relief with oral pancreatic enzymes. It appears that at this time the majority of gastroen terologists are not quite enthusiastic about enzyme therapy for pancreatic pain[30]. The role of enzyme therapy is limited despite its wide populari ty which is so lely based on its simplicity and the fact that it appears to be a non-invasive form of therapy compared to endoscopic therapy or surgery.

Somatostatin and octreotide

Somatostatin is a naturally occurring hormone that inhibits pancreatic secretio n. Octreotide is a synthetic long-acting analogue of somatostatin that inhibits cholecystokinin release and both basal and oral stimulated pancreatic secretion . The duration of action of octreotide is longer than that of somatostatin, but it increases the contractability of the Sphincter of Oddi while somatostatin dec reases it. One multi-center randomized study of 91 patients with CP showed promising results [31]. At a dose of 200 mg TID octreotide offered good pain relief especially in those with constant pain. Another recent study by Mal fertheiner *et al* however did not show any benefit[32].

Endoscopic therapy in CP

Endoscopic therapies are based on the premise that the most important, mechanism of pain in CP is impairent of outflow of pancreatic secretion by strictures or calculi in the main pancreatic duct[33-36]. The attractive feat ure of endoscopic drainage procedures is that it offers an alternative to surgic al forms of drainage. The optimistic belief that these methods may achieve the same results as surgical drainage but without its operative morbidity (20% to 40%) or mortality (2% to 5%) rates is attractive.

The forms of endoscopic procedures currently available include sphincterotomy, internal drainage of pancreatic cysts, extraction of stones from the pancreatic duct, guidewire-catheter dilation of strictures, and placement of pancreatic stents. Endoscopic intervention can be considered in the following situations: (1) biliary strictures, (2) pain or recurrent pancreatitis associated with a dominant s tricture at the proximal end (head), (3) recurrent pancreatitis with pancreas divisum, (4) pancreatic cysts, (5) pancreatic stones, and (6) Sphincter of Oddi dys function.

Lithotripsy

Although it is controversial whether stones or calculi directly cause pain it is logical to assume that removal of stones would relieve intraductal hypertensi on. Although endoscopically it is possible to remove one or two stones in the head end of the pancreas, it is only after fragmentation by shock wave or laser li thotripsy that the more proximal innumerable stones can be drained. Some studies have noted excellent pain relief[35-38]. In a series of 123 patients with pancreatic calculi ESWL was helpful in 122. After ESWL the pancreatic duct could be completely cleared with endoscopic papillotomy in 595 of patients [37]. Adamack and group recently (1999) studied 43 patients who were success fully treated with ESWL [38]. The only feature associated with treatment success was the presence of a single stone rather than multiple stones. Successfully treated patients achieved some degee of reduction in pain. The factors favoring stone removal and clinical response include three or less stones, absence o f multiple strictures, stones confined to the head of the pancreas, stone diameter of <10 mm and absence of impacted stones[35]. Lithotripsy with stone removal is not yet a well accepted form of therapy for pain relief in chronic pancreatitis. Lack

of expertise, a skepticism generated by lack of adequate well controlled trials and the theoretical opinion that removal of stones is only cosmetic to the total histology of the pancreas have dampened the enthusiasm for this form of therapy in the U.S. among academicians.

Sphincterotomy

The best indication for endoscopic sphincterotomy is when the patient has a soli tary ductal stone in the head of the pancreas without any evidence of proximals tricture. Relief of pain can be predicted if a postsphincterotomy pancreatogram demonstrates immediate reduction in size of the main pancreatic duct.

Stenting

Another procedure used in the treatment of pain is endoscopic stenting of the ma in pancreatic duct after sphincterotomy. The stents have side holes at approxima tely 1-cm intervals that permit better drainage of pancreatic juice from side b ranches. Plastic stents have been noted to be inferior to self-expandable metallic stents (Wallstent), which provide better dilation of the stricture and do not clog as often. Cremer's group noted that in addition to pain relief marked im provement in nutritional status of patients occurred as a result of better delivery of bile and pancreatic secretions in the duodenum helping digestion[37]. Excellent improvement in pain has been reported. Prolonged symtomatic impr ovement even after the stent has been removed is observed. This unexpected result may be explained by the fact that before or during stenting, many small calculi are removed, eliminating small ductular obstructions.

The risk of pancreatic stenting is beginging to be appreciated[33,39,40,41]. A number of complications are reported after stent placement:(1)clogging o f the endoprosthesis is frequent, and it must be changed every 4 to 6 months; (2) migration of the prosthesis may be serious problem (3) the stent can be passed spontaneously without any adverse effect; (4) migration, clogging, and occlusion of the stent may lead to pancreatic abscess formation or infect a pseudocyst th at is in communication with the main pancreatic duct; (5)duodenal erosion may be caused by improper positioning of the stent; (6) pancreatitis may be induced by stent placement but is usually mild and self-limiting; and (7) ductal changes mimicing CP may develop even after stent placement.

Celiac ganglion blocking

It is reasonable to expect that pharmacologic denervation of the celiac plexus w ill result in pain relief. Celiac plexus blocking is technically difficult; the pain relief is transient and sometimes lasts only a few days. It is also associa ted with complications such as hypotension, epidural or intraperitoneal hematomas, and sexual dysfunction. Neurolytic block is thus considered a last resort the rapy.[41] Recent reports on celiac ganlion blocking using endoscopic ultr asound guidance offer much hope[42,43].

A variant of celiac block is intrapleural analgesia achieved by instilling local anesthetic into the pleural space[44]. Dramatic pain relief lasting for 4 months has been reported. Diffusion within the interpleural space seems to block several intercostal nerves. The scientific explanation is that pancreatic pa in is transmitted along afferent fibers from the pancreas to the splachnic nerve s and also by the lower intercostal nerves, which innervate the peritoneum.

Acupuncture and transcutaneous nerve stimulation (TENS)

A pilot study showed that 3 patients with chronic pain responded well to both el ectroacupuncture and TENS [45]. In 23 patients with chronic pancreatitis with daily pain for 3 minths the efficacy of TENS was studied. In two prospectiv studies with cross over design active acupuncture was compared with sham acupun cture and TENS of the segemental points of the pancreas with sham treatment.Neit her acupuncture nor TENS brought about pain relief that could substitute for or supplement medical treatment (Ballegaard, et al. 1985). This small study con ducted in an institution not specializing in acupuncture should not discourage experts in the field from trying it. In the absence of an effective therapy for pain in CP, there is a great need to look at alternate medicine for possible answers. The expertise of the Chinese is greatly needed here.

Surgery for pain in CP

Surgery is a consideration when pain is severe enough to interfere with day-to-day life and when it cannot be managed safely with medical treatment alone. Re cent review articles well describe the surgical aspects of CP[46,47] Eva luation for surgery must be individualized and the following should take into co nsideration: frequent hospitalizations, disruption of employment and social life, nutritional status, depression of other psychiatric manifestations, and drug d ependence. Preoperative assessment should include abdominal computed tomography, ERCP, and if appropriate, psychiatric evaluation.

The operative candidates can be divided into two broad groups: those with dilated pancreatic ducts (who more likely benefit from ductal drainage) and those normal size ducts (who may need pancreatic resection or a denervation procedure).

Drainage procedures Many authors recommend longitudinal pancreaticojejunostomy or lateral pancreaticojejunostomy (modified Puestow precedure) when the pancreatic ducts are large enough for anastomosis[46]. Long-term pain relief is achieved in more

than two thirds of patients with CP and a dilated (more than 7 mm diameter) pa ncreatic duct. Pain relief is immediate in 80% to 90% of patients, although there is an unpredictable recurrence rate in some of them. Some 60% to 75% of patien ts are pain free for 5 to 6 years. Recurrence of pain after an initially success ful longitudinal pancreaticojejunostomy suggests stricture formation and may indicate the need for reoperation.

The operative mortality rate averages about 4%, and diabetes, does not result fr om the procedure. However, many patients may go on to become insulin-requiring diabetics because of continual destruction of the pancreas as a result of CP.

Pancreatic resection Resection is the procedure of choice in a pancreas whose ducts are not dilated, when a previous drainage procedure has failed, or if pathologic changes predomin antly involve a particular area of the gland. Resection offers good pain relief that tends to be more permanent than that after pancreaticojejunostomy. Resectio ns generally involve one of the following procedures: (1) pancreaticoduodenecto my, (2) local resection of the head of the pancreas, and (3) subtotal or distal pancreatectomy. However, exocrine and endocrine insufficiency is a major drawback with resections.

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