The etiologic agent in nearly all instances is Clostridium difficile. The disease is caused by the two toxins of C. difficile, A and B (Dis Colon Rectum 1998; 41:1435-1449). About 75% of C. difficile isolates produce these toxins. Isolates that do not produce toxins do not cause colitis or diarrhea. Growth of the organism is promoted by poorly understood antibiotic-induced alterations in the normal intestinal flora. PMC is usually found in association with one or more underlying diseases, which especially involve the abdomen and require antibiotic therapy. Variations in the clinical severity of C. difficile infection in different patients are not solely-specific phenomena related to immunoblot type or to the production of cytotoxin or enterotoxin (Infect Immunol 1991; 59:2456-2462).

The incidence of PMC depends on the frequencies with which endoscopy and toxin tests on stools are performed to establish the diagnosis, on patterns of antimicrobial use, on antibiotic resistance patterns of the C. difficile isolates, and on epidemiologic factors favoring transmission of the organism (Infect Control Hosp Epidemiol 1995; 16:459-477).

C. difficile is now acknowledged to be the main cause of nosocomial diarrhea in USA as well as in Europe. Many observers have noted a steady increase in the number of cases over the past 15 years. The traditional association of PMC with exposure to clindamycin, a condition known as "clindamycin colitis", greatly reduced the use of this drug in the United Kingdom. During this same period of declining clindamycin use, C.difficile-associated diarrhea has increased, even in hospitals in which this drug is only rarely used. The chief risk factor for the disease is prior exposure to antibiotics. Nearly all antimicrobials have been implicated in PMC. Analysis of the available data suggests that use of second- and third- generation cephalosporins, clindamycin, ampicillin and amoxicillin is associated with the highest risk of C. difficile diarrhea. Quinolones, aminoglycosides, macrolides, vancomycin, and extended-spectrum penicillins are associated with lower risks, and trimethoprim, tetracycline, imipenem, and meropenem seem to carry an intermediate level of risk (N Eng J Med 1999; 341:1690-1691).

In the study of Johnson et al., treatment with clindamycin had a dual effect. It selected for the clindamycin-resistant epidemic strain of C. difficile, and the suppressive action of the drug on the patients' bowel flora facilitated overgrowth of the organism. The strain identified or a closely related one was responsible for outbreaks of diarrhea in geographically diverse hospitals in the USA and UK. The findings of the authors provide support to the earliest observations about the role of clindamycin in causing C. difficile diarrhea. There is no doubt about the reliability of the results because of use of high sensitive methods (PCR, dot blot hybridization) and positive and negative controls (N Eng J Med 1999; 341:1645-1651).

Several hospitals have noted an increase in the number of cases of C. difficile diarrhea after antibiotic restrictions were relaxed, thereby increasing access to newer antibiotics, including third-generations cephalosporins (Lancet 1997; 349:1176-1177). The literature is not definitive on the value of changing antibiotic policies, nor there is agreement on which drugs need to be restricted, since this varies depending on patterns of use. We need at least one large randomized trial comparing the epidemic strains of C. difficile which are responsible for outbreaks of diarrhea and their resistance to clindamycin and other antibiotics. However, altering antibiotic-prescribing patterns by instituting strict control measures is worthy of consideration when standard isolation and environmental policies are unsuccessful. Discontinuing all suspect antimicrobial agents is desirable especially when one confronts such situations as the epidemic of C. difficile diarrhea in hospitals. The problem to be solved is whether physicians are willing to make changes in their practices even if that means forsaking some of their favorite antibiotics (N Eng J Med 1999; 341:1690-1691).

EFI AGGELOPOULOU

The natural history of pain in alcoholic chronic pancreatitis

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According to the current literature, 27-67% of patients with alcoholic chronic pancreatitis (ACP), experience chronic pain severe enough to warrant surgical intervention. The choice of surgical procedure (drainage vs. resection) and its efficacy in relieving pain and maintaining pancreatic function are debated.

The main purpose of the study was to (1) characterize and classify the types of pain; (2) try to assess whether different types of pain may be related to events in the natural history of the disease process; and (3) characterize the pain profile in ACP in patients with and without surgery.

The diagnosis of ACP was based on a typical history of recurrent clinical acute pancreatitis; a daily alcohol intake of > 80g for at least 5 years and one or more of the following: pancreatic calcifications, moderate to marked ductal lesions, severe pancreatic exocrine insufficiency and typical pancreatic histology. Two typical pain patterns were identified. Type A pain pattern, typically observed in acute relapsing pancreatitis, is short lived pain episodes usually lasting <10 days and separated by long pain-free intervals of several months to 31 year. On the other hand, prolonged periods of persistent (daily) pain and/or clusters of recurrent severe pain exacerbations characterize type B pain. Persistent pain relief was assumed in patients with recurrent pancreatitis after a pain-free interval of 32 years. The following structural abnormalities were assigned as the presumptive cause of B-type pain: (1) pseudocysts; (2) symptomatic cholestasis; and (3) symptomatic large duct CP (presumptive high ductal pressure), i.e. pain associated with dilated main pancreatic duct. Two stages in the evolution of CP are distinguished: (1) early stage CP, i.e., no calcification and only minor or no exocrine insufficiency; and (2) late stage CP, i.e., with calcification and/or persistent exocrine insufficiency.

According to the authors' experience, ACP accounts for about 70% of all patients with CP; the rest is etiologically classified as idiopathic (24%) or due to rare causes. Since 1963, 207 patients with proven ACP were included in the study. 116 underwent surgery for B-type pain. 56 of the 116 patients died (14.7±5.7 years of the onset) and 6 were lost follow-up. The indication of surgery was usually determined by the authors' medical-surgical team. The average duration of ACP was approximately 17 years in both surgical and nonsurgical groups. Longitudinal pancreatic jejunostomy (LPJ) and/or cyst drainage were the most common surgical procedures.

The total number of annual hospitalizations was significantly higher in the surgical series.

Two thirds of procedures were performed for B-type pain associated with pseudocysts. Less than 14% of patients underwent surgery for symptomatic large duct CP and about 16% for B-type pain accompanied by persistent cholestasis (without pseudocysts). The data indicate that the first surgical procedure for B-type pain was performed in 75% of patients within 6 years of onset.

Pain recurrences occurred postoperatively in 65 patients. A second surgical procedure for B-type pain was performed in 39 of the patients. Hepaticojejunostomy for persistent cholestasis and/or jaundice or cholangitis was the most frequent second surgical procedure.

The interval between the onset of ACP and the realization of pain relief were similar in the surgical and the nonsurgical series. (´ 50% within 6 years and >80% within 10 years from onset of illness). Complete (permanent) pain relief was documented in the nonsurgical series for an average of 11 years and in the surgical series for an average of 10.9 years after the first and for 6.8 years after the second procedure.

The progression of endocrine and exocrine insufficiency in relation to the evolution of ACP were similar in both the surgical and the nonsurgical series.

The mortality rate was not statistically different in the surgical vs. nonsurgical series. The death rate was almost three times higher in the subgroup with continued alcohol abuse than the subgroup with reduced or ceased alcohol intake.

In conclusion, this study presents a clinically based staging system of pain in ACP during the evolution from onset to end-stage disease. Unfortunately, there is no standardized definition for severe pain in ACP and a pain score system, based on the long-term use of narcotics, jeopardizes the assessment of pancreatitis-related pain. The data indicate that complete (permanent) pain relief regularly occurs in late stage ACP either after selective surgical correction of local complications or spontaneously in uncomplicated ACP.

COMMENTS

Pain in alcoholic chronic pancreatitis is poorly understood and its management is controversial. There are two mechanisms of pain production. First, perineural inflammation, disrupted neural sheaths and exposure of unprotected nevres to bioactive substances, and second, increased pancreatic ductal and parenchymal pressure produce a compartment syndrome that induces ischemia (Gastroenterology 1998;115:765-776). At the beginning of disease it is present in approximately 75% of patients with alcoholic chronic pancreatitis. Overall, about 40% of the patients requires surgery to relieve pain. The remainder can be treated with medical, nonsurgical treatments. Pain eventually decreases in 75% of patients with

or without surgery (Gastroenterology 1999;116:1252-1257).

In this article, Amman et al report the characteristics of pain and associate them with underlying clinical causes and outcome (with or without surgery) in 207 patients with alcoholic chronic pancreatitis. They identified two pain patterns in their prospective longitudinal study. The first pain pattern (type A) was the only one in 44% of patients and was characterized by short episodes of pain, usually less than 10 days duration, that were separated by pain free intervals of months to years. None of these patients underwent surgery for pain relief. By contrast, 56% of patients had constant pain (type B) defined as prolonged periods of persistent (daily) pain. All of these patients underwent surgery and most of them had a complication (pancreatic pseudocysts or cholestasis) that was amenable to surgical correction that induced pain relief. Sixty-six percent had a cyst(s) and 16% had biliary obstruction. Cysts were treated by a drainage procedure, lateral pancreaticojejunostomy or resection. The proportion of cysts in Amman's series is higher than reported by others (Gastroenterology 1994; 107:1481-1487, Gastroenterology 1998; 115:765-776). The first operation occurred within 6 years of onset of disease. Thirty-four percent of patients underwent a second surgical procedure; this was usually performed to relieve biliary obstruction.

In contrast to other studies, only 14% of patients who underwent the first surgical procedure did not have a correctable complication. Another surprising finding in Amman's series is the apparent absence of inflammatory masses as a cause of pain. Some investigators claim that the inflammatory mass causes pain by involving pancreatic nerves and producing bile duct, pancreatic duct or duodenal obstruction (Gastroenterology 1988; 94:1459-1469). Because of these findings, operations have been devised to remove inflammatory masses (Am. J Surg 1995; 169:65-70, Ann Surg 1994; 220:492-507). Amman's group performed none of these operations. Also, they only evaluated patients with alcoholic chronic pancreatitis, who were not addicted to narcotics.

Amman et al also reinforce their previous finding (Gastroenterology 1994; 82:820-828) that progression to pain relief occurred in all patients. They also emphasize that progression to diabetes or exocrine insufficiency is similar whether or not patients underwent surgery. And, the continuation of alcohol abuse was associated with higher mortality but not with pain reduction. All study groups agree that there is an inexorable march to calcification and exocrine and endocrine insufficiency. However, the association between the cessation of pain and onset of exocrine and endocrine insufficiency is controversial. As Amman et al now point out, the character of the pain is more important than this association in predicting natural history of pain. Fifty percent of patients with intermittent pain, without a pseudocyst or cholestasis, had pain relief within 6 years of onset of disease and >80% had pain relief within 10 years. Identical results were obtained for patients with chronic pain undergoing surgery, usually for these complications.

Amman's study has several important clinical messages. First, many patients with chronic pain caused by alcoholic chronic pancreatitis have complications that, if corrected, will produce pain relief. In addition, about 50% of patients with ACP had pain that was managed by nonsurgical treatment, finding that is in agreement with other studies (Gastroenterology 1994; 107:1481-1487). Cremer's group (Gastroenterology 1992; 102:610-620) noted that 7 (10%) of 70 patients undergoing extracorporeal shock wave and endoscopic removal of pancreatic stones never had pain and 40% had only one pain attack in the year before treatment.

One can suggests that the two patterns of pain are produced by different mechanisms. The intermittent pattern may be produced by the underlying chronic pancreatitis, whereas chronic pain may be caused by complications of chronic pancreatitis (pseudocysts and biliary tract obstruction).

But, the problem of understanding and treating the pain in ACP is more complicated. For example, is pain correlates with genetic predisposition? (N Engl J Med 1998; 339:645-652, N. Engl J Med 1998;339:653-658). Are pancreatic stellate cells (perivascular and derived from vitamin-A containing cells that thought to cause fibrosis in chronic pancreatitis) correlates with pain in ACP ? (Gastroenterology 1998; 115:491-493). It is not known also, if reducing secretion treatments are effective in amelioration of pain (Gastroenterology 1998;115:765-776).

So, since there are many unanswered questions, one has to be careful in medical, early endoscopic or surgical intervention in pain relief of ACP, because of the many complications (Gastrointest Endosc 1996; 44:276-282).

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