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Surg Clin N Am 87 (2007) 1309–1324

SURGICAL
CLINICS OF
NORTH AMERICA

Pathophysiology of Chronic Pancreatitis

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Chronic pancreatitis (CP) is defined as the permanent destruction of the gland on a histologic level and a failure of the organ on a physiologic level. Inflammation and fibrosis of the pancreas eventually lead to destruction of acinar cells and the islets of Langerhans. Clinically, this process is associated with chronic abdominal pain in most patients, weight loss, steatorrhea, and diabetes. Economically, CP inflicts considerable damage in terms of lost wages, innumerable hospital visits, excessive medication (narcotic) usage, and the need for operative and nonoperative intervention. The diagnosis carries with it a higher risk for early mortality and an increased risk for the development of pancreatic carcinoma. In the Western world, the cause of the disease remains primarily one of self-indulgence with alcohol, although CP only affects a minority (approximately 10%) of individuals using alcohol in excess. To attribute the cause and progression of CP to any one given mechanism would be oversimplification. It has become increasingly recognized that although the inciting event of CP may be consistent, the pathophysiology of the disease is multifactorial and likely includes environmental, nutritional, chemical, and genetic abnormalities. For example, a genetic predisposition to the disease has become a not uncommonly recognized phenomenon and may partly explain why the minority of individuals abusing alcohol develop CP. This article reviews new concepts in the pathogenesis of CP.

Incidence and natural history

Defining the exact incidence of CP is difficult because autopsy findings of fibrosis may be seen as part of the aging process and there is poor

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doi:10.1016/j.suc.2007.09.001 *surgical.theclinics.com*

correlation between histologic findings and either the symptoms of CP or evidence of organ dysfunction. The underlying cause of the disease varies, although most often alcohol is thought to represent the inciting event. Finally, definitions and diagnostic criteria used to define CP are variable. With these limitations in mind, CP is demonstrated in approximately 0.05% to 5% of autopsies, which most likely represents an overestimate [1]. The prevalence of the disease has been reported as high as approximately 1 per 830 in the orient and India, where tropical pancreatitis (TP) is common, to 27.4 per 100,000 in Scandinavia, where CP most commonly results from alcohol consumption [2,3].

Genetic abnormalities associated with CP include mutations of the cystic fibrosis transmembrane conductance regulator (CFTR), the Kazal type 1 serine protease inhibitor (SPINK1), and the protease serine 1 (PRSS1) genes. The incidence of one or more of these mutations in individuals who have CP varies from 0 to 100% depending on the cause of CP, as is discussed later in this article [4].

The natural history of CP is characterized by progressive pain and loss of glandular function. Pain, initially intermittent, becomes constant. Most often, exocrine and endocrine function is gradually lost, with endocrine dysfunction lagging behind that of the exocrine pancreas [5,6]. Evidence suggests that a progressive loss of pancreatic function with or without an increase in glandular calcification may lead to an alleviation of pain (pancreatic ''burnout'') [5,7]. In the study by Ammann and colleagues [5], 145 patients with alcoholic relapsing calcific pancreatitis were followed for a mean of 10.4 years. In this group, 85% of patients had lasting pain relief within a median time of 4.5 years. A gradual increase of pancreatic calcification and progressive pancreatic dysfunction was observed with increasing duration of disease. The observation of predictable nonoperative pain resolution given a certain disease duration remains controversial, and this conservative approach to the disease has not been universally followed [8]. Results in surgical series suggest that pancreatic ductal decompression not only relieves pain in most patients but also delays exocrine and endocrine dysfunction [9,10]. The impact of continued alcohol use on the progression of CP is also contentious. Some studies suggest that abstinence may decrease the severity and frequency of pain and reduce the progressive loss of pancreatic function [11,12]. In contrast, other studies have found that cessation from alcohol does not alter the course of the disease or that CP remains stable despite continued use [13].

The mortality rate associated with CP may approach 50% within 20 years of diagnosis, especially in persons whose disease is caused by alcohol abuse [5,6,11]. In this population, most deaths are caused by complications related to tobacco abuse, liver dysfunction, infection, and malnutrition. Approximately 20% of deaths are related to complications arising from CP itself, however. CP is a known risk factor for the development of pancreatic carcinoma. Approximately 3% to 4% of individuals who have CP develop