Risk Factors of Chronic Pancreatitis

Generoso Uomo^a Gianpiero Manes^b^aDepartment of Internal Medicine, Cardarelli Hospital, Naples, and ^bGastroenterology Unit, L. Sacco Hospital, Milan, Italy

Key Words

Chronic pancreatitis, risk factors • Alcoholic pancreatitis • Autoimmunity • Tobacco smoking • Pancreatic fibrosis • Genetic factors • Pancreatic stellate cells

Abstract

Chronic pancreatitis (CP) still remains a challenging clinical problem with many controversial issues regarding pathogenesis, outcome, and treatment. The disease comprises a spectrum of disorders that culminate as a final step in the destruction of the pancreas. Complex interaction does exist between genetic, environmental and immunologic factors leading to development of the disease. Multiple risk factors interact in a multiple-step model; the pancreatic injury may occur through different mechanisms with transition between an acute pancreatitis condition to recurrent pancreatitis and, finally, to CP. Most patients have multiple risk factors and the overall risk is a product of all risk factors in additive or multiplicative fashion. Susceptibility to develop CP in alcoholics depends on the expression of single gene mutation or is derived from complex genetic polymorphism; in addition, smoking habit can influence the risk of pancreatic calcifications and severity in alcoholic and idiopathic CP. Alteration of the immune response induced by gene mutations and/or environmental factors represents the main determinant of pancreatic fibrosis, the end-stage histologic feature from all CP etiologies.

Copyright © 2007 S. Karger AG, Basel

Chronic pancreatitis (CP), an inflammatory disease characterized by fibrosis leading to the destruction of pancreatic exocrine and endocrine tissue, still remains a challenging clinical problem with many controversial issues regarding pathogenesis, outcome, and treatment [1, 2]. Various predisposing factors have been identified over the last decades, but their impact on etiology and the natural disease course is still a matter of debate. In the Western world the disease is commonly associated with excessive consumption of alcohol. The etiological role of alcohol was strongly supported by epidemiological features rather than experimental data; nevertheless, excessive consumption of alcohol was thought to be the most common cause, accounting for 70–80% of all cases. About 20% of cases were considered idiopathic pancreatitis, while the remaining 10% included cases associated with duct obstruction, trauma, pancreas divisum, cystic dystrophy of the duodenal wall, hyperparathyroidism, hypertriglyceridemia, autoimmune pancreatitis, tropical pancreatitis and hereditary pancreatitis [3]. Other important epidemiological aspects emerging in the recent years are the role of cigarette smoking on CP evolution, the recognition that alcohol alone seldom causes CP and the discovery of pancreatitis-associated gene mutations [4]. In many studies, smoking has been found to be an additional risk factor in alcohol-induced or other types of CP, and experimental and clinical observations showed that smoking can damage the pancreas [5]. In

non-alcoholic idiopathic CP, smoking is associated with progression of the disease through an anticipation of pancreatic calcifications in the late-onset patients group [6]. In addition, smoking may increase the severity of alcoholic CP as verified by the occurrence of an earlier clinical diagnosis and a significant increase of the risk of pancreatic calcifications [7]. Recent knowledge clearly prompts us to consider that excessive alcohol consumption *alone* does not cause CP in animals or humans. It is observed that only a minority (3–7%) of heavy drinkers ultimately develop CP; therefore, alcohol should be considered a *cofactor* associated with pancreatitis only in conjunction with a specific trigger or other additional yet-to-be identified predisposing genetic or environmental factors [4]. Some genes and various gene polymorphisms (table 1) are able to increase susceptibility to develop CP in alcoholics through an increase of pancreatic progressive damage [8]. Such studies can help us to understand the reasons of the different epidemiologic results concerning the different degree of pancreatic damage in different populations with equal intake of alcohol or to understand why, within the same population, we can observe more frequently alcoholic liver disease rather than pancreatic disease [9].

Search for a Model of Multiple Risk Factors Interaction

CP represents a complex multi-step disease without a single etiology, even if the end-stage histology from all etiologies has identical phenotype features. The pancreatic injury may occur through different mechanisms with transition between an acute pancreatitis condition to recurrent pancreatitis and, finally, to CP [10]. Most patients have multiple risk factors and the overall risk is a product of all risk factors in an additive or multiplicative fashion. Recently, a three-domain model of CP was introduced in order to consider the interaction of multiple risk factors that had similar effects [11]. The *metabolic and environmental domain* comprises stressors as alcohol, smoking and other conditions able to give hyperstimulation of the pancreas (hypercalcemia, hyperlipidemia, renal failure and recurrent injuries). Factors in this domain may occur in patients who present mutations of PRSS1, SPINK1 and CFTR genes and who represent the main actors of the *inadequate injury protection domain*. This domain also encompasses some conditions which limit pancreatic duct flushing such as ductal obstruction, pancreas divisum, Oddi's sphincter stenosis/dysfunction. The area of over-

Table 1. Genes able to increase susceptibility to develop CP in alcoholics

α ₁ -Antitrypsin
Alcohol dehydrogenase
Cytochrome P ₄₅₀ -2E1
Glutathione S-transferase
Aldehyde dehydrogenase
HLA (human leukocyte antigen)
Genetic polymorphism
N-Acetyltransferase-2 → slow acetylator phenotype
Susceptibility genes involved in the:
a) Intra-acinar protection system against activation of
trypsinogen and trypsin-related damage
b) Regulation of immune response
c) Regulation of inflammatory response

lap between these two domains identifies the group of patients who will develop recurrent acute pancreatitis. The third domain is the *altered immune response domain*, which comprises other gene mutations inducing overexpression of cytokines and growth factors and environmental factors such as alcohol, smoking and, more rarely, medications. The pathologic process linked to this domain is mainly oriented to development of pancreatic fibrosis by means of the activation of pancreatic stellate cells. In a normal condition, pancreatic stellate cells, localized at the basal acinar level, are quiescent; factors like oxidative stress, alcohol, cytokines, pancreatic necrosis and others activate these cells with subsequent proliferation and transformation in myofibroblast-like cells, through a complex intracellular pathway involving the kinase system and growth factors [12]. The final product is the synthesis and secretion of type II collagen, leading to an irreversible and spreading pancreatic fibrosis. Development of CP requires an area of overlap of the three domains: metabolic and environmental stresses *plus* inadequate injury protection *plus* altered immune response. In other terms, it seems necessary that CP develops a complex interaction between genetic, environmental and immunologic factors. Risk assessment based upon this interpretation may help identify individuals who are likely to develop CP early in the disease course, and pursue a targeted policy to slow or prevent this illness in the future.

References

- 1 Steer ML, Waxman I, Freedman S: Chronic pancreatitis. *N Engl J Med* 1995;332:1482–1490.
- 2 Büchler MW, Friess H, Uhl W, Malfertheiner P (eds): *Chronic Pancreatitis: Novel Concepts in Biology and Therapy*. Oxford, Blackwell, 2002.
- 3 Etemad B, Withcomb DC: Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; 120:682–707.
- 4 Hanck C, Withcomb DC: Alcoholic pancreatitis. *Gastroenterol Clin North Am* 2004;33: 751–765.
- 5 Malfertheiner P, Scutte K: Smoking – a trigger for chronic inflammation and cancer development in the pancreas. *Am J Gastroenterol* 2006;101:160–162.
- 6 Imoto M, Di Magno EP: Cigarette smoking increases the risk of pancreatic calcifications in the late-onset but not early-onset idiopathic chronic pancreatitis. *Pancreas* 2000; 21:115–119.
- 7 Maissoneuve P, Frulloni L, Müllpaut B, Faintini K, Cavallini G, Lowenfels AB, Amman RW: Impact of smoking on patients with idiopathic chronic pancreatitis. *Pancreas* 2006; 33:163–168.
- 8 Burim RV, Canale R, Candolo Martinelli A, Satie Takahashi C: Polymorphisms in glutathione S-transferase GSTM1, GSTT1 and GSTP1 and cytochrome P₄₅₀ CYP2E1 and CYP1A1 and susceptibility to cirrhosis or pancreatitis in alcoholics. *Mutagenesis* 2004; 19:291–298.
- 9 Horie Y, Ishii H: What factors play a crucial role in the pathogenesis of alcohol-related chronic pancreatitis and liver cirrhosis? *J Gastroenterol* 2004;39:915–917.
- 10 Uomo G, Manes G, Rabitti PG: Role of hereditary pancreatitis and CFTR gene mutations in the aetiology of acute relapsing pancreatitis of unknown origin. How are they important? *JOP* 2001;2:368–372.
- 11 Whitcomb DC: Mechanisms of disease: advances in understanding the mechanisms leading to chronic pancreatitis. *Nat Clin Pract Gastroenterol Hepatol* 2004;1:46–52.
- 12 Talukdar R, Saikia N, Singal DK, Tandon R: Chronic pancreatitis. Evolving paradigms. *Pancreatology* 2006;6:440–449.