

Chronic pancreatitis: faces, facets, and facts

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Only few diseases present with such a wide spectrum of clinical symptoms and therapeutic problems as chronic pancreatitis. This is due, first, to the particular combination of exocrine and endocrine functions provided by this gland, with production of both, digestive (ie aggressive) enzymes and several regulatory peptides crucial for metabolic control. Second, the not easily accessible anatomical location in the centre of various important viscous, parenchymal, vascular and neural structures is critical. Third, there is the typically progressive course of the disease, which may be characterised initially by painful inflammation but preserved function, or by steatorrhea and/or diabetes, with or without pain at any time during its course [1]. And fourth, the clinical picture and course is often dominated by local complications such as pseudocysts, infections, haemorrhage, or obstruction of adjacent structures.

This clinical and pathophysiological heterogeneity explains, why the differential diagnostic work-up as well as therapeutic strategy may be demanding in chronic pancreatitis. It illustrates also why, in contrast to other chronic diseases (such as inflammatory bowel diseases or chronic hepatitis) it has been difficult to design powerful prospective studies. Indeed, the striking scarcity of randomised controlled clinical trials in chronic pancreatitis, a disease with steadily increasing prevalence [2], explains, why much of the scientific evidence on which current management concepts are based is anecdotal.

In a timely and knowledgeable review published in the current issue of this journal [3], Ammann, who has contributed crucially to our present understanding of the clinical manifestation and natural history of chronic pancreatitis [4], has summarised important (including controversial) aspects of our current understanding of alcoholic pancreatitis, and touched several areas of discussion and unsolved problems beyond the role of alcohol.

Important breakthroughs include the discovery of mutations of trypsinogen, SPINK, or CFTR genes that cause, promote and/or modulate entities such as hereditary, idiopathic, and tropical pancreatitis. Moreover, they may help us to explain why only some, but not all individuals consuming alcohol develop pancreatitis. Current hypotheses

involve intriguing interrelationships to genetic diseases such as cystic fibrosis. The role of exogenous insults in addition to, or instead of alcohol, such as smoking as independent and likely potentiating causative factors is increasingly recognised. Moreover, the pancreas as an important target of autoimmunity has only recently been acknowledged [5]. On the other hand, while our understanding of the pathogenetic cascades leading to chronic pancreatitis has improved, it nevertheless is still limited, as a few examples might demonstrate.

Thus, it has been shown that mutations of the cationic trypsinogen gene may lead to autosomal dominant hereditary pancreatitis [6]. Other genetic alterations such as loss-of-function mutations of the pancreatic secretory trypsin inhibitor (SPINK1) [7] or a variety of CFTR gene mutations increase susceptibility to chronic pancreatitis [8, 9] but additional factors are needed for manifestation. Therefore, in the vast majority of patients, genetic mechanisms may be of importance but do not explain development of chronic pancreatitis and their exact role still needs to be defined.

Moreover, there is evidence that immunological alterations or diseases may cause or be associated with development of chronic pancreatitis. Most obviously, this has been demonstrated for autoimmune chronic pancreatitis, a disease entity that has been observed mainly in Japan, but is increasingly recognised in Western countries as well. Autoimmune pancreatitis shows specific clinical and morphological characteristics and is associated with other autoimmune phenomena, eg Sjögren's syndrome, autoimmune thyroiditis and ulcerative colitis [10]. It is particularly important to diagnose this disease early because steroid treatment does not only improve the patient's well-being dramatically but may also lead to restitution of morphological alterations [11]. Whether or not a related pathogenesis is responsible for the markedly increased association of pancreatic inflammation and/or insufficiency with inflammatory bowel diseases or celiac disease has remained speculative so far.

Immunologic alterations are not only potentially important aetiologic factors in chronic pancreatitis but also determine the progressive destructive inflammatory and fibrotic process that

ends in destruction of the organ. Some cytokines and growth factors at least partly exert their action by regulating activity of pancreatic stellate cells, which are of pivotal importance for development of pancreatic fibrosis [12]. Apart from activation via cytokines, direct activation of pancreatic stellate cells by ethanol via its metabolism to acetaldehyde and the generation of oxidant stress appears to be possible [13, 14]. These intriguing findings need to be expanded and further aspects of chronic pancreatic inflammation still need to be elucidated. Examples include the mechanisms that turn acute, reversible inflammation into a chronic destructive process and may eventually lead to pancreatic cancer. Such studies might help us to define the subgroup(s) of patients with chronic pancreatitis that are at high risk of developing malignancy.

Another unsolved question involves our difficulty to detect the disease in its initial stage. Early diagnosis of chronic pancreatitis is hampered by the lack of sensitive and widely available imaging and/or functional tests. Alterations of pancreatic ducts and tissue may be mild or even absent in patients with significant symptoms so that conventional diagnostic techniques such as abdominal ultrasound or CT are inconclusive. Thus, it has been a matter of debate whether ERCP or rather endoscopic ultrasound should be considered the golden standard for diagnosis of morphological alterations in chronic pancreatitis. Moreover, morphological changes may be absent in a subset of patients who present with loss of function only [15]. The role of (functional) MRCP as an alternative method has not been clarified convincingly so far.

With respect to pancreatic function testing the current situation is even more dissatisfying. Despite decades of research there is still no non-invasive pancreatic function test available that would allow reliable diagnosis of mild to moderate impairment of pancreatic exocrine function [16]. Indeed, our diagnostic armamentarium appears to be decreasing since tests like the Pankreolauryl® and PABA tests are no longer available. Potentially, ¹³C-breath tests may become important alternatives [17].

For the affected patient, optimisation of treatment modalities is of pivotal importance. Treatment should address typical symptoms of chronic pancreatitis such as flares of acute inflammation,

chronic pain and pancreatic exocrine and endocrine insufficiency as well as optimal handling of further complications. However, many relevant problems that challenge the clinical pancreatologist in his daily practice remain a matter of controversial discussion. For instance, while many clinicians would agree that there is a certain role of interventional endoscopic or extracorporeal shock-wave lithotripsy (ESWL) therapy approaches, neither their benefits and potential indications nor their limitations and long-term hazards have been demonstrated in prospective randomised trials. Similarly unclear is the optimal therapeutic strategy in patients with chronic pain in the absence of local complications, and widely different conservative and surgical concepts are discussed controversially. Another developing area is the treatment of pancreatic exocrine insufficiency [18], which has become clearly more effective since the introduction of acid-resistant pancreatin microgranules, compared with traditional preparations consisting of pancreatin powder or acid resistant capsules. However, even with excessive doses, normalisation of steatorrhea is not possible in a relevant proportion of patients. Thus, the ideal pancreatic enzyme supplement still needs to be developed [19].

Limitations and difficulties like the ones depicted above continue to challenge our pathogenetic concepts in chronic pancreatitis, and we should keep in mind that many of our management strategies continue to be based on individual experience and beliefs rather than on controlled studies. On the other hand, it is equally important to acknowledge and take into account the substantial improvement of our understanding of the complex disease mechanisms witnessed by the past decade, and, perhaps, to utilise it as groundwork for further progress.

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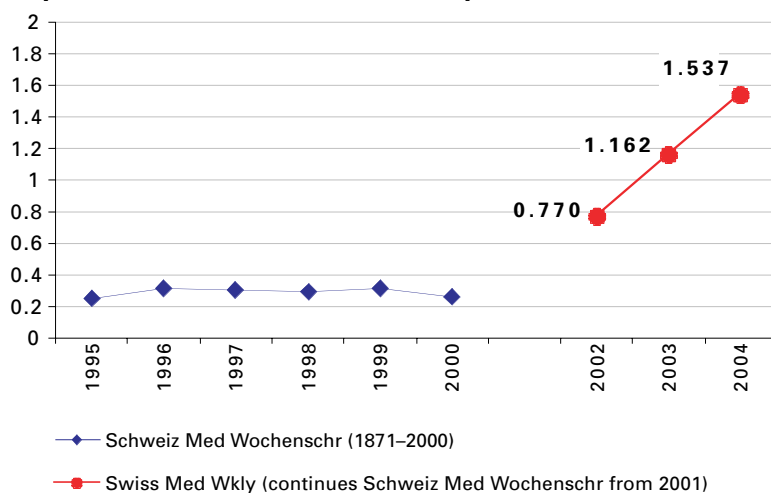
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