Chronic pancreatitis: A proposal for mechanism definition.

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Background: A definition of chronic pancreatitis (CP) is needed for diagnosis and distinguishing CP from other disorders. Previous definitions focused on morphology. Advances in epidemiology, genetics, molecular biology, modeling and other disciplines provide new insights into pathogenesis of CP, and allow CP to be better defined.
Methods: Expert physician-scientists from the United States, India, Europe and Japan reviewed medical and scientific literature and clinical experiences. Competing views and approaches were debated until a new consensus definition was reached.
Results: CP has been defined as 'a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function'. Focusing on abnormal morphology makes early diagnosis challenging and excludes inflammation without fibrosis, atrophy, endocrine and exocrine dysfunction, pain syndromes and metaplasia. A new mechanistic definition is proposed—'Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.' In addition, "Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia." This definition recognizes the complex nature of CP, separates risk factors from disease activity markers and disease endpoints, and allows for a rational approach to early diagnosis, classification and prognosis.
Conclusions: Initial agreement on a mechanistic definition of CP has been reached. This definition should be debated in rebuttals and endorsements, among experts and pancreatic societies until international consensus is reached.

Keywords: Chronic pancreatitis, pancreatitis.

Introduction

In 1995 a "Medical Progress: Chronic Pancreatitis" feature in the *New England Journal of Medicine* correctly summarized the state of understanding of chronic pancreatitis (CP) with the following statement, "Chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment."(1) Shortly thereafter, a series of scientific advances and clinical studies began revealing that CP is a group of complex disorders with overlapping features with no clear common denominator (2–8). Thus, CP cannot be considered a simple disorder with well-defined clinical features, a uniform etiology, and a stereotypic pathologic mechanism.

European Pancreatic Club (EPC) - International Association of Pancreatology (IAP) Meeting for June 24 – 28, 2014, in Southampton, UK and to provide a manuscript of the proceedings. The presentation was to include an assessment of whether there is agreement, controversy or inadequate evidence on the important management points. After reviewing the literature and consulting with domain experts, it was concluded that there was no consensus on the definition of CP and the diagnostic criteria.

Historically, the framework for medicine in the 20th century emerged from the germ theory of disease where one, and only one factor could be the primary cause of a disease syndrome by fulfilling Koch's postulates (9, 10). Application of this theory, with standardization of the "scientific method", disease taxonomy, criteria for diagnosis, evidence based medicine and a curriculum for medical education

defined Western medicine for a century and resulted in huge advances in simple infectious disease control and public health (11–13). However, like many other chronic disorders, CP is complex and no single factor is causative among patients. Therefore, it is not surprising that the traditional definition(s), diagnostic criteria and classification systems developed for CP using the germ theory paradigm fail to provide insights into etiology and meaningful clinical advances. The old framework is also proven to be inadequate when attempting to predict the natural history of the disease in individual patients or attempting to apply new molecular and genetic discoveries to the clinic. No consistently effective treatments for patients diagnosed with CP have been developed using the traditional approaches with the exception of supportive therapies or radical surgical procedures such as partial or total pancreatectomy, with or without islet autotransplantation.

Recent discoveries on complex gene-environment interactions in large subsets of patients with CP dictate that a germ theory-based model must be rejected and replaced by a new paradigm that provides insights into individual patients. The concepts of personalized, or precision medicines must be applied to CP (3, 9). A new approach must begin with a new mechanistic definition of CP that defines pathogenic processes in contrast to normal processes involving inflammation and fibrosis, and distinguishes CP from other diseases with overlapping features. It must also provide structure to assist in managing multiple types of information related to risk, disease activity and outcomes. Clear, robust definitions are also required, as disease models with predictive features are developed to provide useful guidance to physicians as they work to minimize human disease rather than treat the consequences of an enigmatic process.

Methods

A systematic literature review of major consensus reports, invited expert reviews, systematic reviews, and landmark papers that were published between 1965 and 2014 on recurrent acute pancreatitis (RAP) and CP was performed by DCW and JBG. Various consensus statements were organized and viewed from a historical perspective to understand the basis for recommendations or their attempt to revise previously published recommendations. Summary information was circulated among authors from India [PKG] Italy [LF]), Germany [AS], the United States of America [DY] and Japan [TS] to provide addition information, experiences, perspectives, comments and recommendations to address gaps in current knowledge and debate perspectives and approaches. The final draft is a consensus proposition.

Results

The working group chose to present highlights from key historical conferences/consensus meetings focused on CP to provide the framework of the current clinicopathologic-based definition. Second, the limitations of a clinicopathologic definition are presented. Third, the rationale for the framework of a mechanistic definition of CP is provided. Fourth, a conceptual model of the process of CP, extending from risk to end-stage disease is outlined. In addition to the proposed definition statements, a series of discussion questions are listed for ongoing discussion.

Historic definition of chronic pancreatitis

The definition of CP serves as the foundation for early detection, diagnosis and distinction from other syndromes with overlapping features. While there are many proposed definitions, seven important perspectives developed by expert consensus groups are given for historical perspective and further discussion.

Marseille:

The initial efforts for a consensus definition of CP were conducted in Marseille and Rome in 1963, 1984 and 1988 (14–16) (reviewed in Etemad and Whitcomb (17)). Although the morphological, functional and clinical criteria were carefully described in the Marseille conferences, the primary distinction between acute and chronic pancreatitis was the resolution of symptoms in acute pancreatitis (AP) versus the permanent changes in histology, and often (but not always) associated with persistent clinical and functional impairment in CP.

Cambridge:

An independent group of experts met in Cambridge, England in March 1983 to improve on the Marseille classification, and proposed the Cambridge Classification of pancreatic severity (18). The Marseille classification was criticized because there were no acceptable criteria for ‘irreversible morphological change’ or ‘loss of function’, and because it was unclear as how to classify RAP (18). Further, it was recognized that there may be lasting morphological changes in the pancreatic parenchyma years after a single episode of AP, as recently confirmed with more advanced techniques (19). The workshop members therefore defined CP as “a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function.” Other groups have adopted this, or similar

definitions, including the recent Italian consensus guidelines (ICG)(20) and Spanish recommendations (SR)(21, 22).

Japan:

From 1991–1994 the Japanese Pancreas Society met to defined CP. They concluded that CP was "a chronic clinical disorder, pathologically characterized by the loss of exocrine and endocrine pancreatic parenchyma, irregular fibrosis, cellular infiltration, and ductal abnormalities" (23, 24). They also noted that, "in general, these lesions do not resolve and show various levels of deterioration." They also recognized the progressive nature of CP, and recommended that treatment should start *prior* to the diagnosis of CP and during the early phases defined as "probable CP."

Zürich:

A workshop of experts met in Zürich, Switzerland in 1996 to develop a clinically based classification system for alcoholic CP (Zürich Workshop) (25). CP was designated as a "classic disease without a clinically valid, generally recognized definition". The focus was on alcoholic CP (ACP), which was divided into a "Probable ACP", a pre-CP phase lasting about 5 years and defined by RAP and a history of excessive alcohol intake (e.g. >80 grams per day in men), and "Definite ACP " the presence of CP features such as pancreatic calcifications, ductal changes and exocrine insufficiency. The recommendations were limited because the effects of smoking and genetic factors that alter the clinical severity of CP were not known.

United States:

The North American Pancreatitis Study Group (NAPSG) steering committee modified the Cambridge workshop definition of CP for the North American Pancreatitis Study II (NAPS2) in 1999. CP was defined as a "syndrome of destructive, inflammatory conditions that encompasses the many sequelae of long-standing pancreatic injury" (17). This definition was developed to be inclusive of all morphological, clinical and functional variants, with the intention of then classifying patients by etiologies and by the major features or outcomes (e.g. atrophy, fibrosis, episodic or continuous pain, quality of life, pancreatic exocrine insufficiency, diabetes mellitus, cancer), since these complications are not surrogates of each other (e.g. the degree of fibrosis does not predict the degree of pain or presence of diabetes mellitus). It also allowed for the inclusion of RAP, which was distinguished from CP in the NAPS2 program by the absence of features of irreversible morphologic changes on abdominal imaging, and of "minimal change" pancreatitis, in which the irreversible features were more functional than morphologic. Thus, it captured the concepts of the Japan Pancreas Society and the Zurich Workshop of "probable" CP, but framed it as beginning with AP that progressed to RAP (Sentinel Acute Pancreatitis Event [SAPE] model (3)).

Germany:

A multi-national working group organized by the German Association of Digestive and Metabolic Diseases (German Clinical Practice Guidelines, GCPG (26)) defined CP in 2013 as "a disease of the pancreas in which recurrent episodes of inflammation lead to replacement of the pancreatic parenchyma with fibrotic connective tissue". The advantage of this definition is its simplicity and the ability to make the diagnosis using abdominal imaging, but limits the consequences of pancreatic inflammation to fibrosis, thereby excluding atrophy and minimal change disease as being CP. The English version of the S3-Leitlinie Chronische Pankreatitis consensus guidelines (27) reported strong consensus on a more extensive definition, "Chronic pancreatitis is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of pancreatic parenchyma by fibrous connective tissue. This fibrotic reorganisation of the pancreas leads to a progressive exocrine and endocrine pancreatic insufficiency. In addition, characteristic complications arise, such as pseudocysts, pancreatic duct obstructions, duodenal obstruction, vascular complications, obstruction of the bile ducts, malnutrition and pain syndrome. Pain presents as the main symptom of patients with chronic pancreatitis. Chronic pancreatitis is a risk factor for pancreatic carcinoma. Chronic pancreatitis significantly reduces the quality of life and the life expectancy of affected patients." This remains a useful descriptive definition of a progressive disorder.

American Pancreatic Association Practice Guideline:

The APA guidelines, published in 2014 (5) largely followed the Cambridge definition in characterizing CP as a syndrome of chronic progressive pancreatic inflammation and scarring, irreversibly damaging the pancreas and resulting in loss of exocrine and endocrine function. The pathologic section went on to characterize CP by atrophy and fibrosis of the exocrine tissue with or without chronic inflammation.

Limitations to the historic approach to defining CP by pathologic criteria alone:

The working group remains impressed with the thoughtfulness of the previous consensus groups in defining CP using the information and concepts at the time of their development. In general, most groups appeared to take a pragmatic approach beginning with end-stage disease and working backwards to early signs and symptoms. In many cases, key foundational information on the role of genetics and complex gene-environmental interactions was unknown or genetic information was handled as rare Mendelian disorders.

Fibrosis as a surrogate for CP pathology:

A limitation of the CP definitions since the Cambridge definition in 1983 is the sizable reliance on structural changes related to fibrosis. Conceptually, this approach could be justified if structural, functional and clinical signs and symptoms were tightly linked, and could be used as surrogates of each other. However, this assumption fails clinical testing, as fibrosis dose not correlate with pain (28, 29) and morphologic images or histology do not correlate highly with pancreatic function test results (5, 30–33). Furthermore, issues of proximal causality, rather than the inflammatory response leading to fibrosis, are not adequately addressed. This issue also becomes important for addressing the problem of reverse causality where distinctions should be made between long-standing diabetes mellitus (DM) causing atrophy and/or fibrosis and CP causing DM, or pancreatic ductal adenocarcinoma (PDAC) causing pancreatic fibrosis rather than CP predisposing to PDAC (34).

The Role of Etiology:

With the exception of heavy alcohol use and rare Mendelian disorders, the issue of etiology and mechanism of disease are generally lacking. The exception is the APA Practice Guidelines that recommend using the TIGAR-O classification system of risk (35) for further classification (5), although this recommendation was not further developed.

CP defined as an outcome:

Each of the earlier consensus groups defined CP by pathologic criteria, although the Japanese Pancreas Society, Zürich Workshop, the NAPS2 steering committee and APA Practice Guidelines participants recognize the importance of early pathogenic processes that could not be defined or diagnosed using existing (morphologic) methods. Physicians recognize that something abnormal develops that eventually leads to morphologic changes that meet their diagnostic criteria for CP, and that this process continues to drive fibrosis and other complications of pancreatic inflammation to end stage disease. In this regard, it is important to decide whether the term “chronic pancreatitis” should be used to define a pathogenic process, a pathologic state, or an irreversible pathologic outcome resulting from chronic inflammation. While all three approaches are similar in end-stage disease, early diagnosis become challenging and arbitrary when the amount of fibrosis to qualify as definite CP is established (especially considering autopsy studies), or when abnormal function is detected, since most biological systems have significant adaptive processes and physiologic reserve that must be exhausted before significant dysfunction (e.g. statistically outside normal variation) is detected. A mechanistic definition is attractive because it focuses on the pathogenic process that can be predicted prior to the onset of pathology, can be monitored in multiple ways, and can be targeted with therapeutic and preventative approaches. However, such a definition does not yet exist.

Toward developing a mechanistic definition of CP:

A mechanistic definition should begin with an understanding of normal development, physiology, and response to common types of stresses or injury with an inflammatory response followed by reprograming and regeneration of cells with a return, over an interval of time, to a normal state. Thus, both conceptual and functional models of pancreatic biology are needed, with appropriate attention to the component parts. The mechanistic definition should be holistic, recognizing that multiple parts are interconnected and contribute in various ways to the whole. The mechanistic definition must also link clinical terms and disease mechanisms, since specific mechanisms determine the prognostic and therapeutic directions. Multiple pathological pathways and outcomes characterize CP, and all appropriate features and combinations should be considered. In some cases, clinical experience determines important aspects of pancreatic disease that are not intuitive from the study of simple models, and both heuristic and reverse engineering approaches may be needed to understand the underlying mechanisms so that the condition can be classified, modeled, detected early and managed.

The idea of “Probable CP” and “Definite CP” advanced by the Japan Pancreas Society, the Zurich Workshop and others represents mechanistic ideas of disease progression and these clinical ideas should be captured and explained in a mechanistic definition of CP or within diagnostic approaches. The definition needs to be broad enough to encompass all forms of pancreatic inflammation and its consequences, yet be

distinct from AP, DM and PDAC. Whether there is utility in defining the type of inflammatory cells, cytokines or biomarkers within the pancreas at defined time points to distinguish CP from AP, DM and/or PDAC should also be considered in subsequent diagnostic and management discussions. This approach has been applied to autoimmune pancreatitis Type 1 and Type 2 (36, 37) as a method to better define this type of pancreatitis from other pancreatic conditions, with implications for aggressive treatment.

Within the broad mechanistic definition of CP, the implications for diagnosis and disease classification must be considered. Examples include cystic fibrosis, hereditary pancreatitis, autoimmune pancreatitis, Shwachman-Diamond syndrome, metaplastic conditions, atrophy and others. Attention must be given to differentiate the cause of injury and stress, the character and magnitude of the response, factors that modify the response, and the regeneration process. Clear descriptions and methods of classifying pathogenic gene-environment interactions must be developed.

The term “pancreatitis” should be used to describe inflammation and should not be confused with “pancreatic fibrosis”, “pancreatic exocrine insufficiency”, “pancreatogenic diabetes mellitus”, or “pancreatic pain.” “Alcoholic Pancreatitis” is a clinical term but does not adequately describe the etiology or underlying mechanisms and can be associated with various pancreatic parenchymal changes that may or may not be true CP-associated changes. “Minimal change CP” (MCCP) should refer specifically to minimal morphologic changes in the presence of inflammation-associated pancreatic disease and be diagnosed within a mechanistic CP disease model.

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