Pancreatology 16 (2016) 218–224

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition

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ARTICLE INFO

Article history:
Available online 16 February 2016

Keywords:
Chronic pancreatitis
Genetic
Alcoholic
Fibrosis
Diabetes mellitus
Pancreatic cancer

ABSTRACT

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.

Propositional mechanistic definition of CP

> *"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, the following features of the CP syndrome may or may not be present in individual cases:

"Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and

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http://dx.doi.org/10.1016/j.pan.2016.02.001

strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia."

These propositional statements are structured to serve as a foundation for future work on reaching a consensus to a mechanistic definition, diagnostic criteria, and disease classification in terms of subtypes, severity and prognosis.

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.

In 2013 DCW was invited to present a "consensus of consensus guidelines" on CP at the combined 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 (List 1).

Historic definition of CP

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