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Journal of Cystic Fibrosis 11 (2012) 355 – 362

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Review

Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations in pancreatitis

Chee Y. Ooi [a, b,*], Peter R. Durie [c, d, e]

[a] *School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, Australia*
[b] *Department of Gastroenterology, Sydney Children's Hospital Randwick, Sydney, Australia*
[c] *Physiology and Experimental Medicine, Research Institute, the Hospital for Sick Children, Toronto, Canada*
[d] *Department of Paediatrics, Division of Gastroenterology, Hepatology and Nutrition, the Hospital for Sick Children, Toronto, Canada*
[e] *Department of Pediatrics, the University of Toronto, Canada*

Received 4 April 2012; received in revised form 4 May 2012; accepted 4 May 2012
Available online 2 June 2012

Abstract

Background: The pancreas is one of the primary organs affected by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. While exocrine pancreatic insufficiency is a well-recognized complication of cystic fibrosis (CF), symptomatic pancreatitis is often under-recognized.
Results: The aim of this review is to provide a general overview of *CFTR* mutation-associated pancreatitis, which affects patients with pancreatic sufficient CF, CFTR-related pancreatitis, and idiopathic pancreatitis. The current hypothesis regarding the role of CFTR dysfunction in the pathogenesis of pancreatitis, and concepts on genotype–phenotype correlations between CFTR and symptomatic pancreatitis will be reviewed.

Symptomatic pancreatitis occurs in 20% of pancreatic sufficient CF patients. In order to evaluate genotype–phenotype correlations, the Pancreatic Insufficiency Prevalence (PIP) score was developed and validated to determine severity in a large number of CFTR mutations. Specific *CFTR* genotypes are significantly associated with pancreatitis. Patients who carry genotypes with mild phenotypic effects have a greater risk of developing pancreatitis than patients carrying genotypes with moderate–severe phenotypic consequences at any given time.
Conclusions: The genotype–phenotype correlation in pancreatitis is unique compared to other organ manifestations but still consistent with the complex monogenic nature of CF. Paradoxically, genotypes associated with otherwise mild phenotypic effects have a greater risk for causing pancreatitis; compared with genotypes associated with moderate to severe disease phenotypes. Greater understanding into the underlying mechanisms of disease is much needed. The emergence of CFTR-assist therapies may potentially play a future role in the treatment of *CFTR*-mutation associated pancreatitis.

Keywords: Cystic fibrosis; Cystic fibrosis transmembrane conductance regulator; Pancreatitis; Pancreatic insufficiency; Pancreatic sufficiency; Cancer

Contents

* Corresponding author at: Sydney Children's Hospital Randwick, School of Women's and Children's Health, High Street, Randwick, New South Wales, Australia 2031. Tel.: +61 2 93821752; fax: +61 2 93821787.
E-mail address: keith.ooi@unsw.edu.au (C.Y. Ooi).

1569-1993/$ -see front matter
doi:10.1016/j.jcf.2012.05.001

1. Introduction

Cystic fibrosis (CF), termed after the autopsy findings of "cystic fibrosis of the pancreas" in malnourished infants [1], is caused by mutations in the gene that encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein [2]. The CFTR protein functions on the apical surface of epithelial cells as a cyclic AMP-dependent chloride channel, a bicarbonate channel and as a modulator of other ion channels [3–8]. CFTR is located in the apical membrane of secretory and absorptive epithelial cells of the pancreas, intestine, liver, airway, vas deferens and sweat glands. Absence or defective function of the protein product is directly or indirectly responsible for disease pathogenesis in CF-affected organs. The manifestations of CF generally arise when ductal or glandular obstruction occurs due to an inability to hydrate macromolecules within affected ductal lumens.

Functionally, the pancreas can be divided into its exocrine and endocrine components. The former is comprised of pancreatic acinar and ductular cells, while the latter is primarily composed of pancreatic islet cells. Although CFTR is predominantly expressed in the pancreatic ductal epithelium, both exocrine and endocrine components of the pancreas are affected, to varying degrees, in CF. In health, the human pancreatic ductal epithelium secretes large volumes (1–2 L/day) of alkaline fluid made of sodium chloride and bicarbonate, as well as other cations (e.g. potassium) [9,10]. The pancreatic secretion is physiologically intended to flush digestive enzymes secreted by pancreatic acinar cells down the pancreatic–biliary tree and into the duodenum. The alkaline solution also functions to alkalinize acidic chyme emptied from the stomach into the duodenum, and to provide the optimal pH milieu for pancreatic digestive enzyme activity. In CF disease, exocrine pancreatic damage in its severe form is known as pancreatic insufficiency (PI). Pancreatic damage begins in utero and continues into infancy or early childhood when complete loss of pancreatic acinar tissue occurs [11,12]. Only 1–2% of residual pancreatic reserve is required to maintain pancreatic sufficiency (PS). In contrast to PI CF, patients with PS CF have sufficient exocrine pancreatic function to maintain normal nutrient digestion without the use of pancreatic enzyme supplements. In CF, pancreatic secretions have lower fluid volumes and increased acidity within the pancreatic lumen which leads to precipitation of the protein rich secretions, causing plugging of small ducts, obstruction, and progressive damage to the pancreas (Fig. 1). Despite the progressive destruction of the acinar pancreas by inflammation and fibrosis the vast majority of PI individuals have no clinical manifestations of pancreatitis in early life.

Among all the different organ systems affected, the exocrine pancreas is the most reliable phenotypic barometer of CFTR function [13,14]. Most CF patients carrying functionally severe mutations on both alleles have a PI phenotype [13–16]. A small proportion of patients carrying severe mutations on both alleles are PS at diagnosis, but most progressively transition from PS to PI state. Patients who carry a mild mutation on at least one allele, which confers some residual ion channel function, usually have sufficient exocrine pancreatic function to allow normal digestion of nutrients. Thus, mutations that confer the pancreatic sufficient phenotype do so in a dominant fashion. PS CF patients are often diagnosed at an older age, notably in adolescence and adulthood and present with more subtle disease manifestations and lower sweat chloride concentrations than PI CF patients [14,17].

2. Pancreatitis in CF and CFTR-related disorder

Symptomatic pancreatitis is a well known but uncommon manifestation in CF disease because it occurs exclusively in PS CF patients and not in patients with PI CF [15,16,18,19]. This is not surprising since the presence of a "critical mass" of pancreatic acinar tissue is necessary for symptomatic pancreatitis to occur and considering that the majority of CF patients (85–90%) who carry functionally severe *CFTR* mutations on both alleles have PI. Therefore, the vast majority of individuals with severe mutations on both alleles do not develop symptomatic pancreatitis. Approximately, 20% of PS CF patients develop pancreatitis, while the rest do not [15,16,19].

In addition, to PS CF patients, individuals with so-called "idiopathic" recurrent-acute or chronic pancreatitis have an

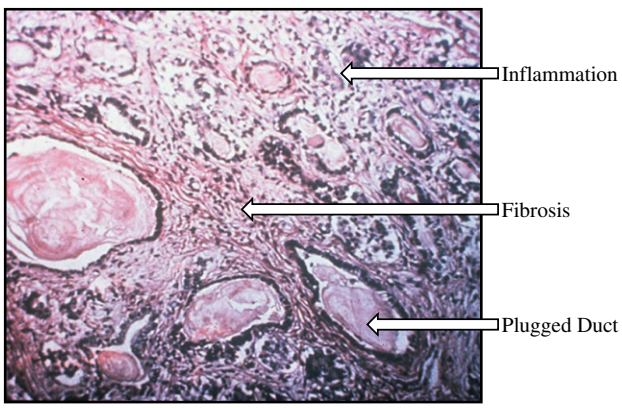

Fig. 1. Histopathological features of chronic pancreatitis in CF.