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Pancreatic insufficiency in Cystic Fibrosis

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Abstract

Pancreatic insufficiency (PI) affects about 85% of the cystic fibrosis population. Although most are PI soon after birth, some will have pancreatic sufficiency (PS) for some or all of their life. Understanding the clinical presentation, diagnosis, and management of PI is crucial to the care of people with cystic fibrosis.

Keywords: Pancreas; Pancreatic insufficiency; Pancreatic enzyme therapy; Fat soluble vitamins; Pancreatitis

1. Background

Although we think of cystic fibrosis (CF) as a disease of the lungs, it was initially recognized as a cause of failure to thrive in infants. CF was distinguished from celiac disease by Dorothy Andersen in 1938, as a form of lethal malabsorption with an abnormal pancreas on autopsy [1,2]. From the beginning, pancreatic insufficiency has been a key characteristic of CF. Cystic fibrosis is generally characterized as "pancreatic insufficient" (PI) or "pancreatic sufficient" (PS), based on whether the person has enough pancreatic function to grow and maintain health without supplemental pancreatic enzyme therapy (PERT). In general, about 85% of the CF population is PI early in life (before the age of 1 year) [3]. Pancreatic insufficiency correlates closely with the specific mutation of the CFTR genes found in the individual with CF [4]. Individuals with 2 severe CFTR mutations (classes I, II, III, and VI) tend to have early PI, often being PI at birth, while those with 2 mild CFTR mutations (classes IV and V) or with one severe and one mild mutation tend to be PS at birth [3].

Individuals with CF have evidence of pancreatic disease beginning in fetal life [5]. Autopsy studies of infants with CF demonstrated deficiency in development of pancreatic acinar tissue compared to age-matched controls [6]; it should be noted that these autopsy studies predate both careful assessment of exocrine pancreatic sufficiency status and CF gene mutation analysis. It is thus likely but not confirmed that the tissue studied came from individuals destined to be PI. The loss of acinar tissue was progressive, with older infants deviating more from their age-matched controls. Fibrosis was common, as was variable duct dilatation. It has been thought that the injury to the pancreas is the result of secretory material collecting within the ducts, creating obstructive destruction of acinar tissue [7]. In the CF pig model, similar in utero changes were seen, with active inflammation limited to the pancreas [8]. Expression of pro-fibrotic, pro-inflammatory, and complement cascade genes are increased in CF compared to non-CF pigs [9]. In summary, in CF, substantial injury to the pancreas occurs early in life. The extent of injury is variable, as evidenced by the variable degree of exocrine insufficiency at birth [10].

The approximately 15% of individuals with CF who are PS have adequate exocrine pancreatic function to digest and absorb food and grow normally [3]. Generally, CF patients who are PS have milder pulmonary disease and longer lives than those born PI [11]. However, they do not have completely normal pancreatic function [3]. Their pancreatic function may deteriorate over time, with or without the complicating effects of pancreatitis.

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Compared to the early damage to exocrine pancreatic tissue, endocrine tissue is relatively preserved in early in life, but in many PI individuals islets cells are gradually destroyed [12]. Approximately 20% of adolescents and up to 50% of adults develop cystic fibrosis-related diabetes (CFRD), a unique form of diabetes with similarities to both type 1 and type 2 diabetes [13]. Some PS patients will also develop CFRD [14]. The pathophysiology of CFRD is complex, with early evidence of disordered glucose regulation, and evidence of diabetes generally developing after age 6 years [12]. The level of a biomarker for pancreatic sufficiency, circulating immunoreactive trypsinogen, measured in newborns, was inversely correlated with the risk of later CFRD [15]. This suggests that worse exocrine pancreatic disease in infancy predicts CFRD at an older age.

In summary, while pancreatic insufficiency was described early in the history of CF, it is recognized that not all people with CF begin life PI, and that some people with CF born PS will become PI through their lifespan. PI is the result of obstructive destruction of exocrine tissue, beginning early in life for those with 2 severe CFTR mutations. Importantly, individuals with CF born PS may become PI at any age, and without symptoms initially, emphasizing the importance of constant monitoring.

2. Clinical presentation and differential diagnosis

The classic symptoms and signs of exocrine pancreatic insufficiency include weight loss, gas, bloating, dyspepsia and loose foul-smelling oily stools that can be difficult to flush (steatorrhea). It should be noted that these signs and symptoms do not help to differentiate pancreatic from non-pancreatic causes of malabsorption (Table 1). Exocrine pancreatic insufficiency may develop without symptoms, or may be characterized by failure to thrive in the infant and child or unexplained weight loss in the adult.

Differential diagnosis for PI is quite broad. It is important to consider CF when symptoms of PI are present. Newborn screening has reduced sensitivity to the possibility of CF as a cause of failure to thrive or weight loss, but there are reports of missed diagnosis of CF in CF newborn screening [16,17]. Older children and adults may have been born before the institution of newborn screen for CF in the state of their birth; older individuals with PS CF may develop PI over time, sometimes without knowing they have CF. Thus, despite the use of newborn screen for CF in most developed countries, a sweat chloride should be an early step in the differential diagnosis of pancreatic insufficiency or malabsorption. Other diseases that may mimic PI CF include other causes of pancreatic insufficiency, other causes of intestinal malabsorption, and some behavioral problems (see Table 2). A general guide to the evaluation of malabsorption is available [18]. The initial evaluation should include a careful history and physical exam, which will guide the selection of laboratory, imaging studies, and procedures.

Table 1
Non-pancreatic causes of malabsorption.

Celiac disease
Crohn's disease
Zollinger-Ellison syndrome
Small intestinal bacterial overgrowth
Gastroparesis
Gastric bypass surgery
Short bowel syndrome

3. Diagnostic workup

3.1. Tests for pancreatic insufficiency

Two problems complicate the diagnosis of exocrine pancreatic insufficiency. First, there is no gold standard for the diagnosis or degree of severity of pancreatic exocrine insufficiency. Second, available tests are positive only when the exocrine pancreatic function is severely impaired [19]. There are multiple indirect and direct tests of pancreatic exocrine function. The indirect tests include laboratory evaluations of blood and stool as well as breath tests. Because of methodological problems, blood and breath tests are not in common use and will not be discussed. The direct tests involve the collection of secreatogogue-stimulated pancreatic fluid in the duodenum through a Dreiling tube or an

Table 2
Differential diagnosis of pancreatic insufficiency.

Age	Class	Disease
Infant	Pancreatic insufficiency	Schwachman-Diamond
		Pearson's Pancreas-Marrow
		Johanson-Blizzard Syndrome
		Pancreatectomy
Child		Schwachman-Diamond
		Pancreatectomy
		Pearson's Pancreas-Marrow
Adult		Schwachman-Diamond
		Chronic pancreatitis
		Pancreatectomy
Infant	Intestinal malabsorption	Short bowel
		Congenital malabsorption syndromes [a]
		Infection
		Cholestasis
Child		Infection
		Short bowel
		Celiac disease
		Cholestasis
		Crohn's disease
Adult		Infection
		Celiac disease
		Cholestasis
		Gastric bypass surgery
		Crohn's disease
		Zollinger-Ellison Syndrome
		Short bowel
Infant	Behavioral	Neglect/abuse
		Munchausen by proxy
Child		Neglect/abuse
		Munchausen by proxy
		Anorexia (use of purges)
Adult		Anorexia (use of purges)

[a] Including abetalipoproteinemia, hypobetalipoproteinemia, intestinal lymphangectasia.