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EDITORIAL

Molecular Biology, Epidemiology, and the Elusive Nature of Pancreatitis

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The myriad of presentations of pancreatitis can cause confusion and controversy among clinicians affecting the diagnosis, treatment, and research of patients with these disorders. Although the disease is best thought of as a spectrum with classic presentations, the underlying pathophysiologic reasons for the differences in manifestations remains unknown. In this issue of the Journal, LaRusch and colleagues provide an elegant study combining epidemiology and molecular biology to explain why some patients with pancreatitis develop fibrosis chronic pancreatitis. The implications of the findings add to the growing request to support large multidisciplinary, combined genetic, and epidemiologic studies in pancreatic disease.
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Despite the high prevalence of gallstones and alcoholism, why do so few patients (<10%) develop acute pancreatitis (AP)? Why do some patients develop AP and others develop chronic pancreatitis (CP)? Why is the cause of pancreatitis not found in almost a third of patients presenting with the disease?

Despite intense basic and clinical research, the nature of causation and pathogenesis of pancreatitis remain largely unknown. More problematic, the myriad of presentations have clouded definitions leading to confusion and controversy. Experts cannot agree on the criteria for CP, idiopathic pancreatitis, and recurrent AP (RAP) as many findings and manifestations of the diseases are subject to various interpretations. It is not clear when RAP becomes CP. This led the International Classification of Diseases (ICD-9) to use the same code for both disorders, 577.1.

There is a general agreement on the classic presentations of pancreatitis. AP is an inflammatory process of the pancreas with or without the involvement of peri-pancreatic tissues or distant sites. It is clinically defined as the presence of two of the following three features: pancreatic type abdominal pain, and/or elevated serum amylase/lipase more than three times the upper limit of normal, and/or findings of AP with absence of the changes characteristic of CP on cross-sectional abdominal imaging.[1] CP is present when there is evidence of pancreatic duct changes, pancreatic stones, fibrosis, and/or calcification. There may be evidence of exocrine and endocrine insufficiency.[2] RAP is defined as more than one well-documented and separate attacks of AP that completely or nearly completely resolve with more than a few months between the attacks. Usually, the time between the attacks has to be known in order to be certain that the initial attack has resolved. If the patient with AP redevelops pain with elevated pancreatic enzymes within the month, it may be owing to some complication of the first attack of AP and not represent RAP.[3]

Despite these classic definitions, owing to the wide spectrum of the disease, strict adherence to these definitions will undoubtedly lead clinicians to make errors in the diagnosis and treatment, and lead to misclassification in research. Although the definition of AP has been best established, numerous problems still exist with this disorder. Some patients present with abdominal pain and elevations of amylase and/or lipase although they do not have AP, such as those who are diabetic suffering from another cause of abdominal pain. Some patients with CP present with AP, an acute attack, but have no evidence of CP either clinically or by imaging.

Consider the problem of AP in alcoholics. Does it really exist? In order for "acute" pancreatitis to develop in patients with alcoholism as the etiology, many years of heavy chronic alcohol consumption must pass before the first attack.[4] Binge drinking on a single or a few occasions does not lead to AP. Alcoholic AP is the manifestation of a chronic disease despite the term "acute". Yet, the majority of patients with alcoholic AP fail to meet the definition of CP. Few have clinical findings or imaging consistent with CP. Is alcoholic AP really a form of CP that does not meet the diagnostic criteria of CP? Alternatively, is alcoholic AP an acute exacerbation of CP? When recurrent attacks occur, is this RAP or CP with exacerbations of AP? Why do patients present so differently when the underlying cause, alcohol, is the same?

Some investigators have suggested that pancreatitis is best understood as a spectrum of a syndrome. The argument continues that the classic patterns of the disease described above exist only to assist clinicians superficially, and the true hetergenous nature of the disease should be seen as a complex interplay between environmental factors, genetics, and resultant differences in pathophysiology. It is becoming clear that environmental and anatomic factors such as alcoholism, tobacco, gallstones, pancreas divisum, etc. trigger disease only in susceptible individuals and the myriad of presentations are based on host susceptibility, controlled largely by genetic factors.

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Although the term "recurrent acute pancreatitis" was first used in the medical literature by Henry Doubilet in 1948,[5] it was not until 50 years later that Whitcomb and colleagues discovered the underlying genetic disorder of cationic trypsinogen mutations that explain the pathophysiology of this disorder. By combining epidemiology, genetics, and molecular biology, the underlying mechanisms of hereditary pancreatitis were illuminated.[6] In this disorder, mutations in a gene encoding trypsin lead to susceptibility for patients to develop AP and RAP, which progresses to CP. These patients develop a spectrum of pancreatic disease and have an increased risk of developing pancreatic adenocarcinoma. Although much of the underlying pathophysiology is still not understood, the major pathologic pathway envisioned in the Sentinel Acute Pancreatitis Event (SAPE) model appears to be the best way of understanding how many patients with AP and RAP progress to CP.[7] Identifying the underlying genetic factors that lead people who develop AP to become susceptible to CP, silently or through RAP, is needed. Only through a combination of understanding genetics, molecular biology, and epidemiology will advances in caring for patients with these diseases develop.

In this issue of the Journal, LaRusch *et al.*[8] advance our understanding of the underlying molecular mechanisms that may lead some patients to develop CP in the setting of AP and RAP. Through a combination of elegant epidemiology, genetic testing, and laboratory elucidation of pathophysiology, the authors demonstrate that a variant of chymotrypsin (CTRC) increases the risk of alcohol, smoking, or CFTR–serine protease inhibitor Kazal type 1 (SPINK)–associated CP. By using a well-designed epidemiologic database (North American Pancreatitis Study 2), the authors show that a highly significant difference in susceptibility to fibrosis exists with CTRC variants, but not for patients suffering from RAP. Their findings support the idea that CTRC variants do not increase susceptibility to trypsin activation as seen in patients with cationic trypsinogen mutations, but may drive stellate cells to produce fibrosis.

The discovery of cationic trypsinogen mutations, CFTR mutations, SPINK, and variants of CTRC have provided gastroenterologists a greater insight into the nature of pancreatitis. It is becoming clear that environmental factors, such as alcohol, and genetic factors, such as CTRC variants described by LaRusch *et al.*, are important in determining the susceptibility to the physiologic manifestations of the disease. Clinicians should look forward to a better understanding of pancreatitis in the future, a better understanding of causation, susceptibility, and even treatments that target these molecular differences.

When one considers the advancements that have occurred for the treatment of people suffering from diseases of the gastrointestinal tract, the medical treatment of pancreatic disease has failed to maintain a similar pace. The findings of this study represent an infancy in a field that will undoubtedly grow. The resources to enroll patients in studies, develop the epidemiologic databases, laboratory testing, and basic science understanding will be enormous in order to uncover the mechanisms of pancreatic disease and develop treatments that target these mechanisms. Unless the scientific community studying pancreatic disease is better funded, unless the support for similar multidisciplinary Centers for Pancreatic Disease grow, the natural history of pancreatitis will continue to be hidden and identification of novel treatments will be restrained.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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