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Early Onset Idiopathic Chronic Pancreatitis: Is there a Role for Endoscopic Treatment?

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Layer *et al*. were the first to describe a different clinical course in patients with idiopathic chronic pancreatitis (ICP) as compared to those having alcoholic pancreatitis (AP) [1]. They found that patients with early onset ICP (onset before 35 years of age) have, initially and thereafter, a long course of severe pain but develop morphological and functional pancreatic damage slowly, whereas patients with late-onset ICP (onset after 35 years of age) have a mild and often painless course (pain absent in nearly 50% of patients) confirming the earlier observations of Ammann *et al*. [2]. Both forms differ from AP in their equal gender distribution and much slower rate of calcification. In contrast, Lankisch *et al*. [3] found that the clinical course is the same in alcohol- and non-alcohol- induced chronic pancreatitis. Even when they divided the non-alcoholic group into teetotallers and patients with little alcohol consumption, and compared their course of pain with alcoholics separately, there were no differences concerning pain among the three groups [4]. Probably, one of the reasons for the differences between the data of Layer *et al*. [1] and Lankisch *et al*. [3] is patient selection. To determine the specific and distinguishing features of each type of chronic pancreatitis and avoid any overlap between the groups, Layer *et al*. [1] included patients in the idiopathic group only if they absolutely abstained from alcohol and had no recognized causes of chronic pancreatitis and included patients in the alcoholic group only if they abused alcohol. Consequently, they excluded from the study all patients with an uncertain etiology of chronic pancreatitis, including patients who consumed a moderate or unknown amount of alcohol. Using these strict criteria, they obtained very homogeneous and selected groups of patients within the idiopathic groups which permitted the identification of early and late onset idiopathic pancreatitis. The clinical findings in the early onset group (slow destruction of the parenchyma and late development of pancreatic insufficiency and calcification) are very important because it may be difficult to make an early diagnosis due to the lack of diagnostic criteria such as structural abnormalities on ERCP or calcification. This has been confirmed in a recent paper [5] in which the time lapse between the onset of the symptoms and the diagnosis averaged 5 years. The recent introduction of magnetic resonance cholangiopancreatography (MRCP) allows a non-invasive visualization of the pancreatic ducts [6]. In the initial phases of early onset ICP, the main pancreatic duct (MPD) has a normal size; one limitation of MRCP is the difficulty of visualizing the side branches of the pancreas, whose alterations are indicative of early chronic pancreatitis. Improved visualization of the side branches at MRCP with secretin stimulation (s-MRCP) allows an earlier diagnosis of chronic pancreatitis and reduces the false negative rate of MRCP to make it a valid non-invasive alternative to diagnostic ERCP in patients suspected of having pancreatic disease [7, 8].

Furthermore, functional studies can be performed to quantitate duodenal filling before and after secretin stimulation [9].

In the experience of Layer *et al*. [1], significantly more patients having early onset ICP undergo surgery as compared to those having late onset ICP (60% vs. 32%), intractable pain being the indication for operation in all cases. The origin of pancreatic pain in patients with chronic pancreatitis is not completely understood and is probably multifactorial, including inflammation, duct obstruction with increased pressure within the duct [10], high pancreatic tissue pressure (compartment syndrome) [11], fibrotic encasement of sensory nerves, and neuropathy characterized by both increased numbers and the size of intrapancreatic sensory nerves, and by inflammatory injury to the nerve sheaths allowing exposure of the neural elements to toxic substances [12, 13]. Surgical options for the treatment of pain include drainage procedures and pancreatic resection. Drainage procedures are based upon the presence of a widely dilated main pancreatic duct (greater than 6-7 mm) and resection procedures should be considered in patients whose ducts are not dilated. It has been suggested that resectional surgery should be avoided to preserve, as far as possible, the remaining function especially in young patients. In the derivative series, short pain relief is achieved in about 80% of patients with very low morbidity and mortality (0-5%). The series with a long term follow-up show that pain not uncommonly recurs; pain relief persists for more than 2 years in only 60% of patients [14]. Therapeutic endoscopy offers several modalities for pancreatic duct drainage: endoscopic pancreatic sphincterotomy (EPS), stone removal, extracorporeal shock-wave lithotripsy (ESWL) in case of pancreatic duct stones unextractable by endoscopic techniques alone and the insertion of a pancreatic stent for strictures of the distal main pancreatic duct [15]. The effectiveness of endotherapy must be correlated with the ability to achieve decompression and complete clearance of stones from the main pancreatic duct. Endoscopic treatment should be reserved for patients with a dilated MPD. MRCP allows the selection of patients who might benefit from endoscopic treatment. No data are available on surgical treatment in patients with early onset ICP. Recently, a paper on endoscopic treatment in this highly selected subgroup of patients has been published [5]. This is the only paper which has been published on endoscopic treatment in patients with early onset ICP. Results of the study indicate that endoscopic treatment is highly effective in short, medium and long term follow up. Unfortunately, it is a retrospective, non randomized *versus* surgery study. As noted by Cotton [16], it is extremely difficult to randomize patients to two treatments that have such different levels of invasiveness. Furthermore, Cotton [16] believes that most of our knowledge of effectiveness does and will come from non-randomized studies, in which precise definitions for each element are used, as suggested by the American Gastro-enterological Association (AGA), for the treatment of patients with pain caused by chronic pancreatitis [14]. In the Italian study [5], the efficacy of endoscopic treatment was confirmed by the statistically significant difference between rates of hospitalization during the year before and at 1, 3 and 6 years after endoscopic treatment. The number of hospitalizations appears to be an objective method of analyzing the effectiveness of endotherapy for the relief of pain. A mean follow up of 6 years must be considered necessary to confirm treatment efficacy even in patients with relapsing pain. Moreover recurrences of pain were successfully managed endoscopically in all cases. This is very important for two main reasons: the possibility of repeated treatment is an advantage compared with surgery in patients with a chronic disease like chronic pancreatitis and furthermore, endotherapy does not preclude subsequent surgery if it should become necessary. Unfortunately, in the study, there are no data about the exocrine function of the pancreas. More long term studies are needed to assess the effect of endoscopic treatment on endocrine and

exocrine functions (with the aid of s-MRCP) especially in young patients. Another very important point that should be stressed is that endoscopists interested in chronic pancreatitis treatment must be familiar with all the procedures needed to obtain clearance and detension of MPD such as ESWL. Also in patients with early onset ICP, ESWL was required in 5 of 6 patients with pancreatic stones. As previously outlined [17], ESWL should be considered complementary and not alternative to the endoscopic drainage of the MPD and increase the success rate of non-surgical treatment of patients with chronic pancreatitis. All patients treated in the Italian study [5] had a dilated MPD as demonstrated by pancreatography. With the advent of non-invasive imaging modality for the pancreas (s-MRCP), it will be very interesting to analyze the efficacy of endotherapy in modifying the natural history in patients in the initial stages of chronic pancreatitis. We are waiting for the preliminary results of endotherapy in patients with clinical symptoms (pain and elevation of amylase and lipase) and small alterations of side branches with a normal MPD or only the alteration of the pancreatic juice outflow as demonstrated by prolonged modification of the main pancreatic duct diameter after secretin stimulation. Endotherapy is characterized by low morbidity and no mortality. This is true for patients with severe chronic pancreatitis having a fibrotic pancreas but what will the results be of the endoscopic treatment - in term of morbidity and mortality - in a "normal pancreas" at the initial stage of the disease? Moreover, will the recent discovery of genetic mutations in patients with chronic pancreatitis [18, 19] help us to recognize patients with “different patterns" of chronic pancreatitis?

In conclusion, endoscopic treatment of patients with early onset chronic pancreatitis could be considered an effective treatment and could be regarded as the initial management of choice in this very selective group of patients.

Keywords Cholangiopancreatography, Endoscopic Retrograde; Lithotripsy; Magnetic Resonance Imaging; Pancreatic Disease; Pancreatitis; Pancreatitis, Alcoholic; Sphincterotomy, Endoscopic

Abbreviations AGA: American Gastroenterological Association; AP: alcoholic pancreatitis; EPS: endoscopic pancreatic sphincterotomy; ESWL: extracorporeal shock-wave lithotripsy; ICP: idiopathic chronic pancreatitis; MPD: main pancreatic duct; MRCP: magnetic resonance cholangiopancreatography; s-MRCP: MRCP with secretin stimulation

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