

Comparison of Functional Dyspepsia and Early Chronic Pancreatitis

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Functional dyspepsia (FD) is a common disease that can markedly impair quality of life. In the 2016 Rome IV criteria, a diagnosis of FD requires the presence of bothersome FD symptoms. In 2009, a new diagnosis, early chronic pancreatitis (ECP), was proposed as a means to facilitate early treatment of chronic pancreatitis and prevent progression to chronic pancreatitis. Although chronic pancreatitis was reported to be a cause of dyspepsia, data on the relation between ECP and FD patients are limited. We therefore investigated differences between ECP patients and FD patients in the percentages of those with severe epigastric pain, early satiety, and postprandial abdominal fullness. Several studies reported an association between the cause of chronic pancreatitis and endosonographic features. In addition, endosonography was useful for distinguishing ECP patients from FD patients with pancreatic enzyme abnormalities. Thus, we compared endosonographic characteristics in these patient groups. Future studies should attempt to determine why selected FD patients with pancreatic enzyme abnormalities develop ECP. (J Nippon Med Sch 2020; 87: 2–6)

Key words: functional dyspepsia, early chronic pancreatitis, endosonography, GLP-1

Introduction

Functional dyspepsia (FD) is a common disorder that can markedly impair quality of life. According to the Rome III classification criteria, the main symptoms of FD are bothersome postprandial fullness, early satiety, epigastralgia, and epigastric burning¹. In 2014, a guideline for FD was published in Japan². In 2016, the Rome IV criteria specified that a diagnosis of FD requires the presence of bothersome clinical symptoms, and the brain-gut axis was acknowledged as an important causative factor in functional gastrointestinal disorders^{3,4}.

In 2009, criteria for early chronic pancreatitis (ECP) were jointly published by the Research Committee of Inter-Active Pancreatic Diseases in Japan, Japan Pancreas Society, and Japanese Society of Gastroenterology⁵. According to these criteria, a diagnosis of ECP is based on four clinical findings: (1) recurrent upper abdominal pain, (2) abnormal pancreatic enzyme levels in serum or urine, (3) abnormal pancreatic exocrine function, and (4) continuous heavy consumption of alcohol (equivalent to ≥ 80 g/

day of ethanol) and imaging findings of ECP on endoscopic ultrasonography (EUS) or endoscopic retrograde cholangiopancreatography (ERCP) (Table 1)^{5,6}. ECP can be diagnosed if patients did not qualify for a definite or probable diagnosis of chronic pancreatitis but satisfied at least two of the above clinical findings and had imaging findings showing ECP on EUS or ERCP (Table 1).

Chronic Pancreatitis and ECP

Chronic pancreatitis is a syndrome characterized by chronic progressive pancreatic inflammation, fibrosis, and scarring that result in damage to and loss of exocrine, endocrine, and ductal cells. It is commonly associated with clinical features of abdominal pain, exocrine and endocrine insufficiency, secondary pancreatic cancer, and other complications. Chronic pancreatitis can be caused by alcohol misuse, hereditary factors, obstruction, autoimmune conditions, hyperlipidemia, and severe acute pancreatitis; some cases are idiopathic. The concept of ECP was first advanced in Japan in 2009 to encourage medical

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Table 1 Clinical diagnostic criteria for early chronic pancreatitis: More than two clinical criteria and imaging findings

Clinical signs	
1)	Repeated upper abdominal pain
2)	Abnormal pancreatic enzyme levels in serum or urine
3)	Abnormal pancreatic exocrine function
4)	Continuous consumption of alcohol equivalent to ≥ 80 g/day of pure ethanol
Imaging findings (either a or b)	
a. More than two of the following seven features, including any of (1) - (4)	
(1)	Lobularity with honeycombing
(2)	Lobularity without honeycombing
(3)	Hyperechoic foci without shadowing
(4)	Stranding
(5)	Cysts
(6)	Dilated side branches
(7)	Hyperechoic main pancreatic duct (MPD) margin
b. Irregular dilatation of more than 3 duct branches on ERP	

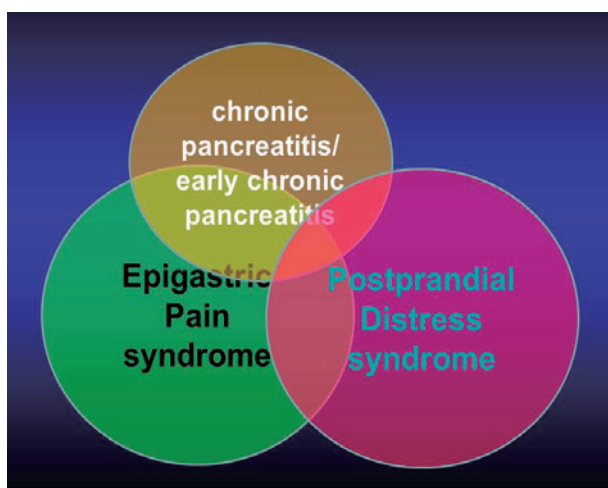


Fig. 1 Functional dyspepsia overlaps with early chronic pancreatitis.

treatment of chronic pancreatitis at an early stage (Table 1)⁷. New strategies for addressing chronic pancreatitis at its onset were proposed in order to stop progression to chronic pancreatitis.

Differences between ECP and FD

Chronic pancreatitis was reported to be a cause of dyspepsia (Fig. 1)⁸. Andersen et al reported that 35% of patients with dyspepsia had pancreatic dysfunction⁹. In addition, 27% of study participants with FD had pancreatic juice abnormalities consistent with chronic pancreatitis¹⁰. In addition, in a study using EUS, Sahai et al reported that dyspepsia may be an atypical presentation of pancreatic disease⁸.

In a recent study, we measured five kinds of pancreatic enzymes in 102 FD patients and found that nearly half of

patients with proton pump inhibitor-resistant FD had abnormalities in pancreatic enzymes (Fig. 2)¹¹. Interestingly, 50% of FD patients had pancreatic enzyme abnormalities compatible with a diagnosis of ECP (Fig. 2). Our previous study showed no significant difference between ECP and FD patients in age (60.8 ± 3.60 vs 58.3 ± 2.76 years), total GRS (2.19 \pm 0.109 vs 2.64 \pm 0.143), or SRQ-D score (9.47 \pm 1.11 vs 11.3 \pm 0.862) (Table 2). In addition, the proportion of women was significantly higher among ECP patients than among FD patients¹². Masamune et al reported that the most common cause of FD in male is alcohol misuse, followed by idiopathic pancreatitis. In women, idiopathic pancreatitis was the most common cause, followed by alcoholic pancreatitis¹³. We previously found no significant difference in alcohol consumption or smoking status between patients with ECP and those with FD-P¹¹. These previous findings suggest that proton pump inhibitor-resistant FD cannot be differentiated from ECP on the basis of clinical symptoms alone; endosonography must be used to identify the unique EUS characteristics of these diseases. Of note, Yamawaki et al reported that EUS scores tend to be low in RFD patients¹².

FD Symptoms in Patients with ECP, FD-P, and FD

Fujikawa et al reported a relation between FD and pancreatic exocrine dysfunction¹⁴. The percentage of patients with pancreatic exocrine dysfunction was 71.4% in an FD subgroup with postprandial distress syndrome and 69.6% in an FD subgroup with epigastric pain syndrome.

To identify differences in the clinical symptoms of patients with ECP, FD-P, and FD, we compared clinical symptoms by using GRS scores for the three groups.

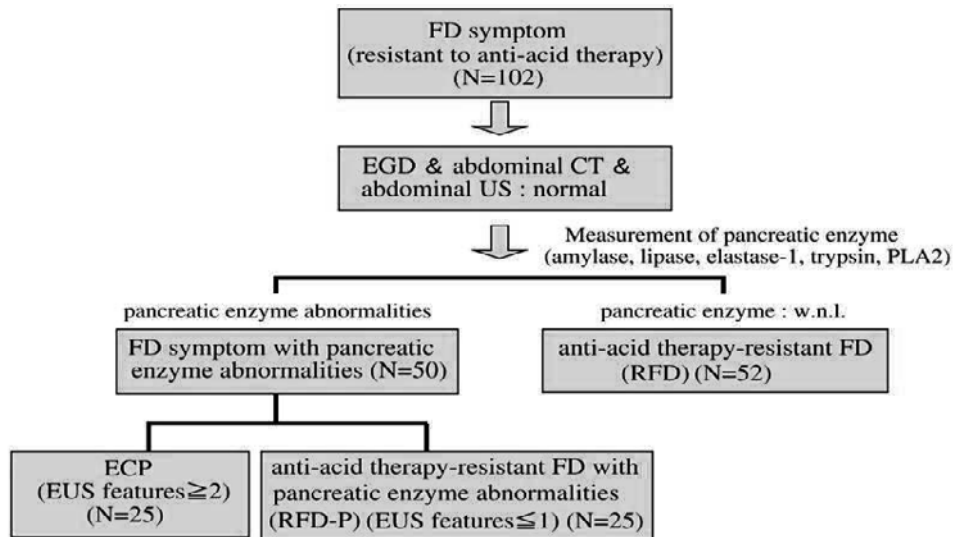


Fig. 2 Flow chart of enrollment of study participants.

Table 2 Characteristics of patient groups

	ECP (n=15)	FD-P (n=27)	FD (n=42)
Age	60.8±3.60	64.8±3.20	58.3±2.76
Sex (F · M)	12 · 3*	21 · 6**	20 · 22
GSRs	2.19±0.109	2.65±0.237	2.64±0.143
SRQ-D	9.47±1.11	10.8±1.27	11.3±0.862
STAI-state	48.0±8.10	53.3±5.26	51.0±3.93
STAI-trait	40.6±7.56	48.0±5.90	46.5±4.42

STAI: State-Trait Anxiety Inventory, SRQ-D: Self-Rating Questionnaire for Depression, ECP: Early chronic pancreatitis, FD-P: Functional dyspepsia with pancreatic enzyme abnormalities

*: $p=0.0302$ vs FD

** : $p=0.0123$ vs FD

The percentages of severe epigastric pain, early satiety, and postprandial abdominal fullness did not significantly differ between ECP patients and FD patients.

Endosonography Findings for ECP and FD

Recent advances in EUS have enabled detection of slight changes in the pancreas, which aids in the assessment of ECP. These endosonography features may reflect the varying causes of pancreatitis. Several studies reported associations of endosonography features with selected causes of chronic pancreatitis.

Heterogeneous echo patterns and echogenic duct walls are common findings in patients with alcoholic and non-alcoholic disease (Table 3)¹⁵. Sahai et al reported that the most common features for patients with a history of alcohol misuse were hyperechoic foci and hyperechoic ducts; those without such a history had more hyperechoic foci

Table 3 Association of chronic pancreatitis and endosonography features

Factors	Endosonography features	References
Alcohol	Heterogeneous echo pattern	Catalano, et al.
Alcohol	Hyperechoic foci Hyperechoic duct	Sahai, et al.
Alcohol	Hyperechoic parenchymal foci MPD dilatation	Petrone, et al.
Smoking	Hyperechoic parenchymal foci	Petrone, et al.
Smoking	Severe EUS features Pancreatic abnormalities	Yusoff, et al.

and hyperechoic strands¹⁶. Petrone et al reported that, even at low doses, alcohol consumption significantly increased the risk of hyperechoic parenchymal foci, main pancreatic duct dilatation, and wall hyperechogenicity (Table 3)¹⁷. In a multicenter study, Yadav et al found that smoking was an important reason for the increased incidence of chronic pancreatitis¹⁸. In addition, Yusoff et al reported that heavy smoking was one of the strongest independent predictors of severe EUS pancreatic abnormalities¹⁹. In our study, 64% of ECP patients had a score of 2, 28% of ECP patients had a score of 3, and 8% of ECP patients had a score of 4. In contrast, 52% of patients with refractory FD with pancreatic enzyme abnormalities (RFD-P) had a score of 0 and 48% of RFD-P patients had a score of 1¹¹.

The criteria for ECP, shown in Table 1, are different from those for FD without organic disease. During 2 years of follow-up, EUS features improved in a population of ECP patients¹². In contrast, EUS scores for two FD-P patients worsened (from 0 to 1), and FD-P progressed to ECP in one patient¹². In our data, most EUS

scores in FD-P patients did not change.

Duodenal Inflammatory Cell Infiltration in FD and ECP

Several recent studies reported a correlation between duodenal inflammation and FD²⁰⁻²². Impairment of the tight junction, eosinophil infiltration, and migration of CD68/CCR2-positive cells were observed in the duodenum of patients with FD²⁰⁻²⁴. In addition, because influx into the duodenum regulates gastric emptying, the pathophysiological characteristics of the duodenum might be important in the development of FD. Gut hormones, including ghrelin and GLP-1, regulate gastric emptying, and several studies of the association between ghrelin levels and FD found that ghrelin and GLP-1 production had effects during early gastric emptying²⁵⁻²⁷. Our study investigated infiltration of GLP-1-positive cells in the duodenum of patients with FD with pancreatic enzyme abnormalities (FD-P) and in patients with ECP and found no difference in the extent of GLP-1-positive cell infiltration in the duodenum of FD-P patients and ECP patients.

Future studies should investigate why certain FD patients with pancreatic enzyme abnormalities develop ECP.

Conflict of Interest: none.

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