

Clinical features and management of painless biliary type sphincter of Oddi dysfunction

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Abstract

Objective: The objective of this study was to clarify the characteristics and management of painless biliary type sphincter of Oddi dysfunction (SOD).

Methods: From June 2002 to July 2018, 12 patients who had recurrent liver dysfunction with a dilated bile duct or acute cholestasis of unknown cause without biliary pain (painless SOD) were included in this study. These patients' characteristics were compared with those of 36 patients with biliary type SOD based on the conventional definition (criteria-based SOD).

Results: Patients with painless SOD had significantly more prominent bile duct dilation than patients with criteria-based SOD (13.9 vs. 12.2 mm, respectively). Prophylactic biliary drainage was performed significantly more often in patients with painless SOD than criteria-based SOD (67% vs. 11%, respectively). The short-term effectiveness rate of endoscopic sphincterotomy, the symptom recurrence rate, and the incidence of adverse events were not significantly different between the two groups.

Conclusions: Painless SOD is a specific subtype of biliary SOD that causes recurring liver dysfunction or acute cholestasis without biliary pain. Endoscopic sphincterotomy was effective in the present study, but the relapse rate was as high as that in typical SOD.

Keywords

Sphincter of Oddi dysfunction, endoscopic sphincterotomy, cholangitis, post-ERCP pancreatitis, liver dysfunction, cholestasis

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Introduction

Biliary type pain is essential for the diagnosis of biliary type sphincter of Oddi dysfunction (SOD) based on the Rome IV criteria.¹ According to these criteria, biliary pain is defined as pain severe enough to interrupt daily activities or lead to an emergency department visit.¹ However, some patients with recurring liver dysfunction or acute cholestasis (AC) have no pain or only weak symptoms (i.e., abdominal discomfort, nausea, non-typical biliary type weak pain) that seem to be due to SOD. Additionally, some patients with gastroesophageal reflux disease have reflux esophagitis with erosions but without symptoms.² Esophagitis without heartburn can also cause complications such as esophageal stricture and bleeding. Similar concepts may apply to biliary type SOD. Some aspects of SOD are consistent with a functional disorder.³ The threshold of abdominal pain with transient increases in biliary pressure differs among individuals. The appearance of symptoms and complications of SOD vary according to differences in papillary stenosis, functional abnormalities, and pain thresholds. Psychosocial problems may play an important role in patients with functional biliary sphincter disorder (prior sphincter of Oddi dyskinesia).^{3,4} Therefore, antidepressants may be effective for pain in some patients with SOD.⁵

Recurring liver dysfunction with a dilated bile duct (LDDB) without obvious biliary pain is rare in clinical practice. Rare cases of painless AC without identifiable causes such as biliary calculi, malignant tumors, or strictures of the bile duct have been reported. If other causes are excluded, these cases of painless AC are considered to be caused by SOD. We have termed this disease entity "painless SOD." In such cases, we must exclude small pancreatobiliary malignant diseases⁶ such as duodenal papillary carcinoma or inferior bile duct

carcinoma, but this is sometimes very difficult. Invasive surgery such as pancreatoduodenectomy has reportedly been performed for SOD.⁶ However, few studies have investigated painless SOD and its features. The objective of this study was to clarify the characteristics and management of painless biliary type SOD.

Materials and methods

From June 2002 to July 2018, we identified patients with AC without typical biliary pain and patients with recurring LDDB who were suspected to have painless SOD. These patients were selected by questionnaire, liver function tests (LFTs), hepatobiliary scintigraphy, abdominal ultrasonography, upper gastrointestinal endoscopy, endoscopic ultrasonography, and magnetic resonance cholangiopancreatography (MRCP). The diagnostic criteria for AC without typical biliary pain (painless SOD) were as follows: (1) AC was present with abnormal aspartate aminotransferase, alanine aminotransferase, bilirubin, or alkaline phosphatase concentrations of >1.5 times the reference values; (2) no organic disease such as stones, stenosis, or malignant tumor in the biliary tract (including the gallbladder) was present as confirmed by imaging; and (3) the criterion for biliary pain was not met. The diagnostic criteria for LDDB (painless SOD) were as follows: (1) abnormal aspartate aminotransferase, alanine aminotransferase, bilirubin, or alkaline phosphatase concentrations of >1.5 times the reference values were documented on two or more occasions; (2) a dilated bile duct of >10 mm was confirmed by imaging, and no organic disease such as stones, stenosis, or malignant tumor in the biliary tract (including the gallbladder) was present; and (3) the criterion for biliary pain was not met.¹

The patients had no history of biliary stones or hepatopancreatobiliary surgery other than cholecystectomy. One patient with AC without typical biliary pain had a history of distal gastrectomy for duodenal ulceration 37 years before the onset of AC. None of the patients had viral hepatitis, alcoholic liver disease, or other diseases that can cause chronic liver disease in LDDB. None of the patients had taken narcotics, anticholinergics, or other drugs that could cause bile duct dilation. Endoscopic cholangiopancreatography (ERCP) was performed in all patients, and no stones, obvious bile sludge, gravel, biliary stenosis, or other organic diseases were present as confirmed by cholangiography and/or intraductal ultrasonography (IDUS). IDUS was performed in all patients except those in whom pancreatitis after ERCP in a small papilla was a concern. When IDUS could not be performed, abdominal ultrasonography confirmed the absence of stones, obvious bile sludge, or gravel that could be the cause of cholangitis. Bile crystal analysis was not performed. Hepatobiliary scintigraphy was performed in patients other than those who required immediate ERCP. Among patients with AC without typical biliary pain, a medium-length endoscopic sphincterotomy (EST) was performed in those with AC and abnormal findings of scintigraphy (hepatic hilum–duodenum transit time of >45 minutes). Among patients with LDDB, a small-length EST was performed for biopsy to differentiate the condition from an unexposed papillary tumor. According to the conventional diagnostic criteria, manometry is not considered essential for a diagnosis of type I SOD. Manometry was not performed in all patients with bile duct dilation equivalent to type I SOD. Among patients with AC without typical biliary pain, manometry was performed for relatively young patients (<70 years old) to determine whether EST should be performed. We considered the

addition of manometry in patients without bile duct dilation equivalent to type II SOD. However, manometry was not performed for patients with a small papilla to avoid post-ERCP pancreatitis. Acute cholangitis during the course was defined as a fever of >38°C with worsened LFT results. Sepsis and other infectious diseases were ruled out by imaging and blood tests.

From July 1998 to September 2018, patients with typical biliary type SOD as confirmed and diagnosed by ERCP (criteria-based SOD) were included in this study as controls. These patients were selected by questionnaire, LFTs, hepatobiliary scintigraphy, abdominal ultrasonography, upper gastrointestinal endoscopy, endoscopic ultrasonography, and MRCP. We excluded patients with suspected choledocholithiasis, cholecystolithiasis, chronic pancreatitis, obvious mental disorders, previous EST, previous endoscopic papillary balloon dilatation, and other medical treatments. The diagnostic criteria for criteria-based SOD were as follows: (1) biliary pain according to the Rome IV criteria and (2) elevated liver enzymes and/or a dilated bile duct (>8 mm as confirmed by imaging).¹ Based on their clinical, radiographic, and laboratory data, the patients were categorized according to the Rome IV criteria¹ as having prior type I (papillary stenosis) or prior type II (functional biliary sphincter disorder) SOD; type I is characterized by elevated liver enzymes and a dilated bile duct, and type II is characterized by elevated liver enzymes or a dilated bile duct. Patients with type III SOD as classified by the Rome III criteria⁷ were excluded according to the Rome IV criteria.¹

Among patients with criteria-based SOD, manometry was performed for those with type II SOD whenever possible. EST was performed for patients with type I SOD, and manometry confirmed the presence of type II SOD. An EST of adequate length was performed in all patients. When

patients were diagnosed with type I SOD with a low frequency of severe attacks (<2 times/year), EST was not performed at the time of initial ERCP. In these patients, medical treatment was indicated after other organic disorders including malignancy and choledocholithiasis were excluded by ERCP.

In patients with painless SOD, we defined EST as effective when the cholestasis disappeared and the LFT parameters were normalized. In patients with criteria-based SOD, we defined EST as effective when the previous pain disappeared. In patients with painless SOD, recurrence was defined as the development of AC, cholangitis, and liver dysfunction without other causes either after EST or after starting medical treatment. In patients with criteria-based SOD, recurrence was defined as the return of pain without other causes either after EST or after starting medical treatment. Catechol-O-methyltransferase inhibitors, anticholinergics, and other medications were used as indicated on an individual-patient basis.

Difficult cannulation was defined according to the time taken for biliary cannulation. An attempt at biliary cannulation lasting >15 minutes was defined as difficult cannulation. When selective bile duct cannulation was difficult, cannulation was attempted using the pancreatic duct guide-wire technique. In cases of further difficulties, precut sphincterotomy was performed.

Post-ERCP pancreatitis was defined as new or worsened abdominal pain, hyperamylasemia (≥ 3 times the upper limit of the reference range), and the requirement for treatment with prolonged hospitalization. The severity of post-ERCP pancreatitis was graded as mild, moderate, or severe according to a previous report.⁸ Post-ERCP cholangitis was defined as the development of a fever with new or worsened abdominal pain, new or worsened LFT

results, and the requirement for treatment with prolonged hospitalization.

The data of all patients in both groups (painless SOD and criteria-based SOD) were retrospectively reviewed. The characteristics of patients with painless SOD were compared with those of patients with criteria-based SOD.

This study was approved by the Institutional Ethics Committee of Jichi Medical University, Faculty of Medicine (Approval number: S16-030). The need for written informed consent was waived because of the retrospective nature of this study.

Outcomes and measures

The outcomes of this study were the short-term effectiveness rate of EST, symptom recurrence rate, and adverse events. Among patients who underwent EST, the short-term effectiveness rate was defined as the ratio of patients in whom no previous symptoms requiring endoscopic retreatment recurred within 30 days after treatment. Among patients who were observed for >1 year, symptom recurrence was defined as the re-emergence of previous symptoms and the need to add oral drugs or endoscopic treatment.

Statistical analysis

The chi-squared test was used to analyze categorical data. Quantitative data were compared using the Mann-Whitney U-test, median test, or Student's *t*-test. Values of $P < 0.05$ were considered significant. The statistical analysis was performed with StatMate V (ATMS Co., Ltd., Tokyo, Japan).

Results

Eight patients had AC without typical biliary pain and 4 patients had recurring LDDB (painless SOD group), and 36

Table 1. Demographics of patients with painless biliary type sphincter of Oddi dysfunction.

Age (years) / sex	History of cholecystectomy	Bile duct diameter (mm)	Post-ERCP pancreatitis/ cholangitis	IDUS/ manometry/ histology	Treatment	Rec
<i>AC without typical biliary pain</i>						
85 / M	–	17	– / –	– / – / –	Medical	–
65 / M	–	11	– / –	– / $\geq 40^*$ / –	Medical	+
83 / M	+	15	Mild / +	+ / – / –	Medical	+
80 / F	–	18	– / –	+ / – / +	EST	+
86 / F	–	13	– / –	+ / – / +	EST	+
77 / M	–	12	– / +	+ / – / +	EST	–
68 / M	–	12	– / –	+ / $< 40^*$ / –	EST	–
51 / F	–	7	Mild / –	– / – / –	Medical	–
<i>LDDB</i>						
56 / M	–	17	– / –	+ / $\geq 40^*$ / +	Medical	+
58 / F	–	15	Mild / +	+ / – / +	Medical	–
71 / F	–	17	Moderate / –	+ / – / +	Medical	–
62 / M	+	13	– / –	+ / – / –	Medical	+

M: male, F: female, AC: acute cholestasis, LDDB: liver dysfunction with dilated bile duct, ERCP: endoscopic retrograde cholangiopancreatography, IDUS: intraductal ultrasonography, Rec: recurrence, EST: endoscopic sphincterotomy.

*basal sphincter pressure (mmHg).

patients had typical biliary type SOD as confirmed and diagnosed by ERCP (criteria-based SOD group). The basic characteristics of patients in both groups are shown in Tables 1 and 2. Six of the 12 patients in the painless SOD group were suspected to have a malignant tumor and were referred for further examinations from other hospitals. In these six patients, forceps biopsy and/or brush cytology of the papilla or lower bile duct was performed, but no malignant findings were obtained. Ten of the 12 patients had no gallbladder stones as confirmed by abdominal ultrasonography and computed tomography. Two of the 12 patients had mild abdominal bloating. Three of the 12 patients had a peripapillary diverticulum. However, two of these three had small diverticula with no possibility of affecting the bile drainage. According to the MRCP and ERCP findings, the lower part of the common bile duct of these patients was not displaced by the peripapillary diverticulum. Five patients with AC

without typical biliary pain had acute cholangitis. Biliary drainage was performed in all patients with AC without typical biliary pain except for one patient who underwent unsuccessful ERCP, and EST was performed in combination in four patients. In the one patient with ERCP failure, cholangitis was cured by the administration of an antimicrobial agent.

More patients with painless SOD than criteria-based SOD had a bile duct diameter of >10 mm (92% vs. 53%, respectively), but the difference was not significant. The bile duct was significantly more dilated in patients with painless SOD than criteria-based SOD (13.9 vs. 12.2 mm, respectively; $P < 0.05$). Previous cholecystectomy was less common in patients with painless SOD than criteria-based SOD (17% vs. 47% respectively), but the difference was not significant.

Relevant factors at ERCP in this study are shown in Table 3. EST was performed in 5 patients with painless SOD (AC

Table 2. Basic characteristics of patients with painless and criteria-based biliary type sphincter of Oddi dysfunction.

	Painless type (n = 12)	Criteria-based (n = 36)	P-value
Age at diagnosis, years	70 ± 12	61 ± 15	0.065
Sex, (male/female)	7 / 5	11 / 25	0.168
Comorbidity, AC without typical biliary pain / LDDB	4 / 8		
Previous cholecystectomy	2 (17)	17 (47)	0.125
History of pancreatitis	0 (0)	8 (22)	0.180
CBD diameter of >10 mm	11 (92)	19 (53)	0.054
CBD diameter, mm	13.9 ± 3.2	12.2 ± 5.5	0.020
MPD diameter, mm	4.1 ± 1.7	3.2 ± 1.7	0.601

Data are presented as mean ± standard deviation, n, or n (%).

AC: acute cholestasis, LDDB: liver dysfunction with dilated bile duct, SOD: sphincter of Oddi dysfunction, CBD: common bile duct, MPD: main pancreatic duct.

Table 3. Relevant factors at ERCP between patients with painless and criteria-based biliary type sphincter of Oddi dysfunction.

	Painless type (n = 12)	Criteria-based (n = 36)	P-value
EST	5 (42)	22 (61)	0.401
Biliary drainage	8 (67)	4 (11)	0.0005
IDUS	9 (75)	24 (67)	0.857
Manometry	3 (25)	15 (42)	0.491
Pancreatic duct opacification	7 (58)	27 (75)	0.286
PGW technique	5 (42)	16 (36)	0.867
Precut sphincterotomy	0 (0)	6 (17)	0.314
Pancreatic stent placement	2 (17)	9 (25)	0.842
Difficult cannulation	10 (83)	21 (58)	0.223
Failed cannulation	1 (8)	1 (3)	1.000

Data are presented as n (%).

ERCP: endoscopic retrograde cholangiopancreatography, EST: endoscopic sphincterotomy, IDUS: intraductal ultrasonography, PGW: pancreatic duct guidewire.

without typical biliary pain, n = 4; LDDB, n = 1) and in 22 patients with criteria-based SOD. Prophylactic biliary drainage after ERCP was performed significantly more often in patients with painless SOD than criteria-based SOD (67% vs. 11%, respectively; $P < 0.001$). There were no differences in the rates of other ERCP-related procedures (IDUS, manometry, pancreatic duct opacification, pancreatic duct guidewire technique, precut sphincterotomy, and

pancreatic duct stent placement). There was also no difference in the rate of difficult cannulation and cannulation failure between the two groups.

The short-term effectiveness rate of EST, the final remission rate, and the recurrence rate were not significantly different between the two groups (Table 4). In patients with AC without typical biliary pain, the short-term effectiveness rate of EST was high (4/4 patients). However, two of the four patients

Table 4. Clinical outcomes after ERCP between patients with painless and criteria-based biliary type sphincter of Oddi dysfunction.

	Painless type (n = 12)	Criteria-based (n = 36)	P-value
EST performed for AC without typical biliary pain	(n = 4)	(n = 22)	
Short-term efficacy of EST	4/4 (100)	20/22 (91)	0.695
Follow-up of >1 year	(All cases, n = 10) (EST cases, n = 4)	(All cases, n = 31) (EST cases, n = 19)	
Recurrence All cases	6/10 (60)	11/31 (35)	0.318
EST cases	2/4 (50)	7/19 (37)	0.941
Time to recurrence, months	19.0 ± 18.8 (1–48)	15.0 ± 20.0 (1–67)	0.617
Mean observation period, months	63 ± 65 (16–197)	89 ± 66 (14–244)	0.479

Data are presented as n (%) or mean ± standard deviation (range).

ERCP: endoscopic retrograde cholangiopancreatography, EST: endoscopic sphincterotomy, AC: acute cholestasis

who underwent EST developed relapse. Additional EST was performed in one patient, and a plastic bile duct stent was placed the other patient. In one patient with LDDB, a small EST was performed for biopsy to differentiate the patient's condition from an unexposed papillary tumor. The incidence of adverse events after ERCP, post-ERCP pancreatitis, post-ERCP cholangitis, and new occurrence of choledocholithiasis were not significantly different between the two groups (Table 5).

No procedure-related deaths occurred. Additionally, no deaths from painless SOD or criteria-based SOD occurred.

Discussion

Papillary stenosis with biliary type pain is considered to be type I SOD of the Milwaukee classification^{9,10} and Rome IV criteria.¹ In many cases, papillary stenosis becomes a problem when the patient experiences repeated biliary pain.^{10–12} In clinical practice, however, clinicians may encounter patients with liver dysfunction, AC,¹³ and obstructive jaundice⁶ for which a sphincter of Oddi disorder is considered to be the main cause. In such cases, a duodenal papillary tumor or lower bile duct carcinoma may be suspected, and the diagnosis may

be difficult.⁶ If SOD is difficult to distinguish from a malignant disease, excessive invasive surgery such as pancreatoduodenectomy may be performed in some cases.⁶ Indeed, in 6 of 12 of the patients in the present study, histological examination was performed to rule out malignant disease. Follow-up studies, including repeated biopsy and bile juice cytology, were performed to confirm the absence of malignancy. The clinical condition in two of the six patients was difficult to distinguish from malignancy, requiring reexamination and long-term follow-up. Five of the eight patients with AC without typical biliary pain had acute cholangitis, but acute cholangitis was rare among patients with SOD. Indeed, no patients in the control group had acute cholangitis. We speculate that relatively long-term cholestasis can lead to cholangitis because of absent or minimal pain. This can also be understood from cholestasis due to a duodenal papillary tumor or lower bile duct carcinoma, which rarely cause cholangitis.

In the present study, all but one patient with painless SOD had a bile duct diameter of >10 mm. These cases were considered to be consistent with type I SOD when judged according to the modified Milwaukee classification and Rome IV criteria¹ excluding

Table 5. Adverse events after ERCP

	Painless type (<i>n</i> = 12)	Criteria-based (<i>n</i> = 36)	P-value
Post-ERCP pancreatitis (mild/moderate/severe)	4 (33) (3/1/0)	11 (31) (4/6/1)	0.857
Post-ERCP cholangitis	3 (25)	5 (14)	0.655
New occurrence of choledocholithiasis	3 (25)	4 (11)	0.479

Data are presented as n (%) or n.

ERCP: endoscopic retrograde cholangiopancreatography

biliary pain. The efficacy of EST varies according to the type of SOD. EST is most effective in patients with type I SOD (the rate of pain relief by EST is 90%–95%).¹⁴ Among our patients with painless SOD, the short-term effectiveness rate of EST was high (4/4 patients). However, half of the patients who underwent EST developed relapse (2/4 patients). Few reports have described the recurrence rate in long-term follow-up after EST in patients with biliary type SOD. One report stated that the recurrence rate was 20% with EST and medical treatment.¹⁵ In a long-term follow-up report, symptoms often remained after EST.¹⁶ Because of the lack of pain in painless SOD, papillary stenosis may progress and EST may be inadequate even when the first EST was endoscopically sufficient. However, once an adequate papilla opening was obtained, long-term remission could be expected. Because bile duct stones may occur, follow-up observation is necessary after remission. We found no studies that investigated the incidence of new bile duct stones after EST for SOD, but when cholestasis remains, it is likely to occur with aging.

The characteristic feature of painless SOD in the present study was the absence of cholecystectomy except in two patients. This seems to be related to the bile duct diameter being larger in patients with painless SOD. Originally, SOD was used to describe pain after cholecystectomy.^{17–19} In the presence of the gallbladder, the

pain is thought to rarely occur owing to buffering of the internal pressure within the bile duct even under sphincter of Oddi dyskinesia or papillary stenosis. The bile duct reportedly dilates after cholecystectomy.^{20,21} The bile duct is presumed to expand because of the chronic pressure load on the bile duct after cholecystectomy. Thus, the mechanism of bile duct dilatation in patients with painless SOD is considered to involve a pressure load exceeding the buffering effect of the gallbladder is caused by papillary stenosis. Although the compliance of the bile duct wall is initially high and the wall readily expands and contracts, as the elasticity of the wall is gradually lost, the bile duct may become dilated and resemble “extended rubber” because of the chronic pressure load. If the patient has a high pain threshold, he or she may not feel pain as the bile duct gradually expands with pressure loading.

Although patients with painless SOD tended to be slightly older than those with criteria-based SOD, there was no significant difference in the other characteristics between the two groups.

Except for the frequency of biliary drainage, there was also no difference in the related interventions performed at the time of ERCP. Post-ERCP cholangitis is empirically known to be more frequent in patients with prominent biliary dilation; thus, drainage may be performed more frequently among patients with painless SOD. In fact, one report states that post-ERCP

cholangitis is more common in patients with a dilated bile duct.²²

Adverse events after ERCP occurred frequently in both groups in the present study compared with general reports not limited to SOD.^{23–25} SOD is a well-known risk factor for post-ERCP pancreatitis.^{24–27} The rate of adverse events was highest when the indication for the procedure was suspected SOD (21.7%).²⁵ Because these adverse events can also occur frequently with ERCP for painless SOD, preventive measures such as the administration of non-steroidal anti-inflammatory drugs in addition to pancreatic stenting should be used, as for patients with criteria-based SOD.²⁸

Because ERCP is invasive to patients, it is important to consider the indications after adequate noninvasive testing has been performed for the diagnosis of painless SOD, especially LDDB.

In summary, painless SOD is pathophysiologically similar to criteria-based SOD and requires adequate attention for post-ERCP pancreatitis and post-ERCP cholangitis. Diagnosis of painless SOD can be difficult because other diseases such as small pancreatobiliary malignant tumors that cause bile duct dilation, liver injury, or cholestasis cannot be found on blood tests and images. Additionally, because typical pain is absent, the condition cannot be diagnosed as SOD. Therefore, we propose the disease concept of painless SOD as a special subtype of SOD. To definitively establish this disease concept, a detailed prospective study including analysis of bile crystals and manometry in many patients is necessary.

This study has two main limitations. First, it was a retrospective, single-center study. Second, the number of patients was small because painless SOD is rare. A large multicenter study is needed to confirm the characteristics and management of painless SOD.

Conclusions

Painless SOD is a specific subtype of biliary SOD that causes recurring liver dysfunction and cholestasis without biliary pain due to an abnormality of the papillary sphincter function. EST was effective in the present study, but the symptom relapse rate was high. Because adverse events can occur frequently, preventive measures such as those in place for patients with criteria-based SOD are needed.

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Declaration of conflicting interest

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