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BRIEF ARTICLE

Sphincter of Oddi laxity: An important factor in hepatolithiasis

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Abstract

AIM: To evaluate the importance of sphincter of Oddi laxity (SOL) in hepatolithiasis (HL).

METHODS: Subjects included 98 patients diagnosed with HL between 2002 and 2007. Detailed histories were taken and the subjects were monitored until July 2008. HL patients were divided into two groups: Group Ⅰ included 45 patients with SOL, and Group Ⅱ included 53 patients without. Recurrence and reoperation indices of both groups were calculated and compared.

RESULTS: The recurrence index was 0.135 in Group Ⅰ and 0.018 in Group Ⅱ ($P < 0.001$). The reoperation index was 0.070 in Group Ⅰ and 0.010 in Group Ⅱ ($P < 0.001$). The mean frequency of biliary operation was 2.07 in Group Ⅰ and 1.21 in Group Ⅱ ($P = 0.001$). Differences between the two groups are significant.

CONCLUSION: HL patients with SOL tend to have a higher risk of recurrence and a larger demand for reoperation than those without this condition.

Key words: Sphincter of Oddi laxity; Hepatolithiasis; Recurrence index; Reoperation index; Choledochojejunostomy

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INTRODUCTION

Hepatolithiasis (HL) is prevalent in East Asia, especially in China[1-3]. While this condition results from multiple etiological factors, obstructive cholangitis is usually the main cause[2]. In our clinical practice, we have found few cases with obstruction of the common bile duct or sphincter of Oddi (SO); to the contrary, almost half of our clinical cases showed sphincter of Oddi laxity (SOL). We have also found that patients with SOL had a tendency for recurrence and always needed reoperation. The goal of this study was to determine the effect of SOL on recurrence and reoperation frequencies among patients with HL in order to recommend the most suitable therapy for this condition.

The SO is made up of the bile duct, pancreatic duct and ampulla sphincters. Regular contraction and relaxation maintain the normal pressure differences between the bile duct, pancreatic duct and the SO. The diameter of the duodenum papilla orifice is very small, no more than 2-3 mm even when the SO is completely relaxed with drugs. Normally, the SO can regulate the discharge of bile and pancreatic juice, and also prevent duodenum juice reflux. In patients with SOL, a larger diameter (≥ 10 mm) of the biliary tract orifice facilitates the entry of bile juice into the duodenum without resistance, appearing as SO absence.

MATERIALS AND METHODS

Case selection

We considered 121 patients with HL who were admitted to the First Affiliated Hospital of the Medical College of Zhejiang University between April 2002 and March 2007. Seven cases were excluded due to histories of choledochojejunostomy discovered during surgery, and ten cases were eliminated due to extensive complexity, resulting in a total of 104 selected cases. During the follow-up period of almost 6 years (until July 2008), six patients were lost. Thus, the study included 98 patients: 29 with simple intra-hepatolithiasis (IHL) and 69 with both IHL and choledocholithiasis.

Detailed histories were obtained from the patients, including age of first onset, frequency of recurrence, and previous biliary tract operation. The mean age of the patients was 52.8 ± 12.2 years (range: 17-80 years), and mean age of the first onset was 45.1 ± 16.1 years (range: 8-78 years) (Table 1). All patients were diagnosed by preoperative magnetic resonance cholangiopancreatography (MRCP) and B-ultrasonography (BUS), and diagnoses were confirmed in operation. The absence of residual stones was confirmed by routine choledochoscope (OLYMPUS CHF P20, external diameter 4.9 mm) examination during operation. The following parameters were set for biliary tract operation: (1) simple cholecystectomy was removed from consideration; and (2) operation was defined as all procedures for clearing stones from the intrahepatic and extrahepatic bile ducts, including hepatectomy, endoscopic stone extraction, calculus removal from the T tube, and choledochojejunostomy. Simple choledocholithotomy and T-tube drainage were performed on 35 patients, simple hepatectomy on 20 patients, choledocholithotomy and T-tube drainage with hepatectomy on 35 patients, simple choledochojejunostomy on 5 patients, and choledochojejunostomy with hepatectomy on 3 patients. BUS was routinely performed every 2 mo after operation, and abnormalities were confirmed with MRCP. Patients showing the symptoms related to HL were immediately examined with BUS and MRCP.

Table 1 Patient characteristics (n = 98)

Characteristics	
Male/female	35/63
Mean age (yr)	52.8
Mean age of first onset (yr)	45.1
Mean follow-up period (mo)	42.1
Follow-up prevalence	100%
Simple IHL/IHL with choledocholith	38/60
Recurrence rate of this operation	16.3%
Mean number of operations	1.60
Number of patients with 1 operation	67
Number of patients with 2 operations	19
Number of patients with 3 operations	7
Number of patients with 4 operations	1
Number of patients with 5 operations	1
Number of patients with 6 operations	2
Number of patients with 11 operations	1
Number of patients with simple choledocholithotomy and T-tube drainage	35
Number of patients with simple hepatectomy	20
Number of patients with choledocholithotomy, T-tube drainage and hepatectomy	35
Number of patients with simple choledochojejunostomy	5
Number of patients with choledochojejunostomy and hepatectomy	3
Recurrence index	0.072
Reoperation index	0.037

IHL: Intra-hepatolithiasis.

SOL and patient groups

SOL, related to HL formation, may be primary or secondary. Patients without a history of choledochojejunostomy or choledochoduodenostomy may be diagnosed with SOL according to either of the following criteria: (1) contrast media may be found in the common bile duct during duodenography; or (2) a Bake's dilator with a diameter of 10 mm is able to reach the duodenum *via* the SO without pre-dilation during surgery. Patients without a history of any sphincterotomy, including endoscopic sphincterotomy, can be defined as having primary SOL, while those with a history of sphincterotomy can be diagnosed with secondary SOL.

The patients were divided into two groups: HL patients with SOL (Group Ⅰ) and those without (Group Ⅱ). Group Ⅰ included 45 patients (39 with primary SOL, 6 with secondary SOL) and Group Ⅱ included 53 patients. The mean age of the patients, the mean age of the first onset, and operative procedures are presented in Table 2. Group Ⅰ was divided into 2 subgroups according to the operative procedures: 6 patients who underwent choledochojejunostomy (end-to-side anastomosis with common bile duct and jejunum) were placed in Group Ⅰ A and 39 patients who did not undergo choledochojejunostomy were placed in Group Ⅰ B. The patients in Group Ⅰ A had no operative histories before this hospitalization. Biliary visualization was undertaken with duodenography (hypaque meglumine 60%) in 19 (42.2%) patients of Group Ⅰ and none in the patients of (0%) Group Ⅱ.

Recurrence and reoperation indices

Recurrence rate is a frequently used index in the study of lithiasis. As a traditional index, recurrence rate is al-

Table 2 Characteristics of patients in Groups Ⅰ and Ⅱ

	Group Ⅰ	Group Ⅱ
Number of patients	45	53
Male/female	18/27	17/36
Mean age (yr)	52.8	52.8
Mean age of first onset (yr)	41.9	47.8
Biliary visualization rate during duodenography	42.2%	0%
Mean follow-up period (mo)	38.4	41.9
Simple IHL/IHL with choledocholithiasis	15/30	14/39
Recurrence rate	22.2%	11.3%
Mean number of operations	2.07	1.21
Number of patients with 1 operation	22	45
Number of patients with 2 operations	12	7
Number of patients with 3 operations	7	0
Number of patients with 4 operations	1	0
Number of patients with 5 operations	0	1
Number of patients with 6 operations	2	0
Number of patients with 11 operations	1	0
Number of patients with simple choledocholithotomy and T-tube drainage	14	21
Number of patients with simple hepatectomy	7	13
Number of patients with choledocholithotomy, T-tube drainage and hepatectomy	18	17
Number of patients with simple choledochojejunostomy	4	1
Number of patients with choledochojejunostomy and hepatectomy	2	1

ways confined to consideration of a certain operation. Due to the frequent recurrence of HL, however, it is inappropriate to use only a single operation to evaluate the prognosis of this disease. To accurately describe and compare the whole history (from first onset to July 2008) of HL in each patient, we thus used the recurrence and reoperation indices concurrently. This allowed consideration of every recurrence or operation, and the intervals between two recurrences or two operations.

To determine the recurrence index, we recorded intervals (months) between each recurrence for a patient, calculated the reciprocal of each interval, and used the mean reciprocal as the recurrence index for that patient. If no recurrence occurred in the final operation, the corresponding reciprocal was designated as 0. A larger reciprocal value suggested a higher risk of recurrence. For example, the record of one patient showed that: 10 mo after the first operation, a recurrence occurred; the second recurrence occurred 5 mo after the second operation; and no recurrence occurred in the third operation. For this patient, the recurrence index is: $(1/10 + 1/5 + 0)/3 = 0.1$.

Like the recurrence index, there is a positive correlation between the reoperation index and the necessity of reoperation. To calculate the reoperation index, we recorded intervals (months) between every two closely succeeding operations for each patient, calculated the reciprocal of each interval, and used the mean reciprocal as the reoperation index for that patient. The reciprocal corresponding to the interval from the last operation to July 2008 was designated as 0. Thus, if the patient underwent only 1 operation, the reoperation index value was 0. For example, one patient's record shows: the second operation was performed 10 mo after the first operation; the third and final operations were performed 5 mo after the second one. For this patient, the reoperation index is: $(1/10 + 1/5 + 0)/3 = 0.1$.

Table 3 Comparison of Groups Ⅰ and Ⅱ

	Group Ⅰ	Group Ⅱ	*P*
Number of patients	45	53	-
Male/female	18/27	17/36	0.126
Mean age (yr)	52.8	52.8	0.771
Mean age of first onset (yr)	41.9	47.8	0.463
Mean follow-up period (mo)	39.9	43.9	0.145
Mean number of operations	2.07	1.21	< 0.001
Recurrence index	0.135	0.018	< 0.001
Reoperation index	0.07	0.01	< 0.001

Statistical analysis

All data are expressed as mean ± SD. The *t* test was used to compare the differences of parameter mean values between groups. All *P* values were two-sided. A *P* value of < 0.05 indicated a statistically significant difference. All calculations were done using SPSS (version 11.5) software.

RESULTS

Patient data

The patients were monitored for a period ranging between 14 and 75 mo (median 42.1 ± 17.1 mo). During this follow-up period, stones reappeared in the bile ducts of 16 of 98 patients (with a recurrence rate of 16.3%), including 2 cases of stones in the common bile duct, 4 cases in the intrahepatic bile duct, and 10 cases in both ducts. Seven of these patients received a reoperation, and the disease recurred again in 4 of them. The number of operations performed from the first onset to July 2008 are shown in Table 1; the mean number of operations was 1.60 ± 1.38 (range: 1-11). The mean recurrence index was 0.0717 ± 0.193 and the mean reoperation index was 0.0373 ± 0.127 (Table 1).

Comparison of Groups Ⅰ and Ⅱ

The patients were followed up for 16-73 mo (mean 39.9 ± 15.6 mo) in Group Ⅰ and for 14-75 mo (mean 43.9 ± 18.1 mo) in Group Ⅱ ($P = 0.145$). Recurrence was observed in 10 Group Ⅰ patients (a recurrence rate of 22.2%) and 6 Group Ⅱ patients (a recurrence rate of11.3%). The mean number of operations from first onset to July 2008 was 2.07 ± 1.83 (range: 1-11) in Group Ⅰ, being significantly higher than that of Group Ⅱ (1.21 ± 0.63; range: 1-5). The mean recurrence index was 0.135 ± 0.256 for Group Ⅰ, which was significantly higher than that of Group Ⅱ (0.018 ± 0.086) ($P < 0.001$). The mean reoperation index was 0.070 ± 0.171 for Group Ⅰ, being also significantly higher than that of Group Ⅱ (0.010 ± 0.060) ($P < 0.001$) (Tables 2 and 3).

Comparison of Groups Ⅰ A and Ⅰ B

To evaluate the effect of choledochojejunostomy on the

Table 4 Comparison of Groups I A and I B

	Group I A	Group I B	*P*
Number of patients	6	39	-
Male/female	2/4	16/23	0.385
Mean age (yr)	58	52	0.845
Mean age of first onset (yr)	30.5	43.6	0.666
Mean follow-up period (mo)	42.5	39.5	0.905
Recurrence index	0	0.156	0.006
Reoperation index	0	0.081	0.034

SOL patients, we compared the recurrence and reoperation indices of Groups I A and I B. The follow-up period was between 18 and 61 mo (mean 42.5 ± 16.9 mo) in Group I A, and between 18 and 73 mo (mean 39.5 ± 15.6 mo) in Group I B ($P = 0.905$). We found no recurrence among patients in Group I A (a recurrence rate of 0%), whereas recurrence occurred in 10 of 39 patients in Group I B (a recurrence rate of 25.6%). The mean recurrence indices were thus 0 for Group I A and 0.156 ± 0.270 for Group IB. The mean reoperation indices were 0 for Group I A and 0.081 ± 0.182 for Group I B. The differences in both the recurrence index and reoperation index values were statistically significant between groups (Table 4).

DISCUSSION

HL is prevalent in the Asian countries of Japan, Korea and China[1-3], and also occasionally occurs in Europe and America[4,5]. The disease is characterized by its intractable nature and frequent recurrence. Because of complications, potential carcinogenesis and even fatality[6-11], most HL patients receive multiple operations. This study examined the role of SOL in the course of HL, and found that the frequencies of recurrence and reoperation were significantly higher in patients with SOL.

The obviously larger diameter of the papilla orifice in SOL patients indicates the injury to the SO muscle fibre and the absence of regular SO contraction. These conditions lead to duodenum juice reflux, similar to that seen in choledochoduodenostomy. During surgery on SOL patients, a Bake CBD dilator (CE-125-10-G, diameter = 10 mm) and choledochoscope (OLYMPUS CHF P20, external diameter = 4.9 mm) passed smoothly through the SO; even in some patients, a forefinger could enter the duodenum *via* the SO without any resistance, and food debris could be seen in the CBD. It results in *Escherichia coli* (*E. coli*) infection and decrease in biliary pH. *E. coli* can generate β-glucuronidase, which hydrolyzes direct bilirubin (water-soluble) into indirect bilirubin (water-insoluble) and may lead to the formation of stones in the biliary tract. Thus, HL tends to recur in SOL patients.

The specific causes of SOL, however, remain unknown. Congenital abnormality, mechanical injury by stones, chemical injury by bacteria, or iatrogenic injury are all possible etiological factors. Congenital maldevelopment of the smooth muscle and deficiency of some neurotransmitter receptors can also contribute to SOL. Under inflammatory conditions where large amounts of inflammation mediators are generated over time[12], the SO response to nitrergic neurotransmission is impaired, which may induce adnormal SO relaxation. Dilation of the common bile duct due to obstruction by stones may result in excessive dilation of the common bile duct sphincter and SOL development. In this study, absence of congenital abnormality in family histories and similarity among the mean age of the first onset ($P > 0.05$) did not support congenital abnormality as a primary etiological factor of SOL.

It is not difficult to diagnose SOL. Duodenography is still considered to be a good method for describing the modality, despite its relatively low sensitivity (42.2%, Table 2). SO manometry is the best method of evaluating patients for sphincter dysfunction[13], and it may be a feasible diagnostic method. The confidence of SO manometry, however, is suspected due to multiple factors (abdominal pressure, dynamic changes caused by the manometry, drug reactions). The invasive nature of manometry, the complexity of the operation, and the potential complication of pancreatitis restrict the use of SO manometry as a routine diagnostic method[14,15]. Due to the existence of intestinal juice reflux, simple calculus removal or hepatectomy are not sufficient for SOL patients, while choledochojejunostomy with an anti-reflux ansa intestinalis may be suitable for these patients[16]. The outcomes of six patients in Group I A showed the advantage of choledochojejunostomy, although the sample size is small. Further research on the effectiveness of this method should be conducted with a larger number of patients.

Endoscopic sphincterotomy may destroy the muscle fibres of the SO and cause iatrogenesis. The risks of cholangitis and cholangiocarcinom have also been shown to markedly increase if the postoperative follow-up period is long enough[17]. This method should therefore be restricted to patients without SOL. Endoscopic balloon dilation is an effective alternative to endoscopic sphincterotomy[18-20], which has been shown to result in complete recovery of sphincter function 21 d after operation[21]. An appropriate balloon size can preserve the SO and avoid undesirable effects due to an incompetent sphincter[22-26].

SOL commonly arises in HL. HL patients with SOL tend to have a higher risk of recurrence and a larger demand for reoperation compared to those without SOL. Choledochojejunostomy with an anti-reflux ansa intestinalis may be the most promising therapy.

COMMENTS

Background

Hepatolithiasis (HL) is prevalent in East Asia, especially in China and obstructive cholangitis is usually considered the main cause. The authors found that almost half of the cases showed sphincter of Oddi laxity (SOL) in their clinical experience and the patients with SOL had a tendency for recurrence and always needed reoperation.

Research frontiers

The obstructive cholangitis is usually considered as the main cause of HL. No report has put forward the conception of SOL up to date. The phenomenon and significance of SOL is still rarely known.

Innovations and breakthroughs

The study has proposed the conception of SOL for the first time and considered SOL as a significant cause of occurrence or recurrence of HL. The authors of the study also put forward the recurrence and reoperation indices for the first time instead of recurrence rate, and suggested the choledochojejunostomy should be used as the surgical approach to the patients with SOL.

Applications

By understanding SOL, this study may represent a new strategy in the treatment of HL patients with SOL.

Terminology

SOL: an obviously large diameter of the papilla orifice makes the choledochoscope (OLYMPUS CHF P20, external diameter = 4.9 mm) pass smoothly through the SO. The recurrence and reoperation indices are used to accurately describe and compare the complete history of HL from the first onset to July 2008 in each patient, which allows consideration of each recurrence or operation, and the intervals between two recurrences or two operations.

Peer review

The study revealed that SOL is an important factor associated with a higher risk of HL recurrence and reoperation frequency in the HL patients.

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