Clinical Significance of Hepatopulmonary Syndrome in Biliary Atresia

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Clinical Significance of Hepatopulmonary Syndrome in Biliary Atresia

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It was a great accomplishment of mine that I could broaden my academic knowledge and upgrade my experimental skill while completing this thesis. Based on it, I would like to contribute to the advance of the treatment of biliary atresia.

Lastly, I appreciate to my family and friends. I could be here because of your undoubtable believes to me. I always love you.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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(Objectives) The clinical characteristics of intrapulmonary shunt (IPS) that can lead to development of hepatopulmonary syndrome (HPS) in biliary atresia (BA) have not been well described. Therefore, we investigated the incidence and clinical significance of IPS and HPS in BA. **(Methods)**We evaluated 72 patients with BA between March 2010 and May 2013 for diagnosis of IPS by contrast-enhanced echocardiography (CEE) and HPS by arterial blood-gas analysis (ABGA). ABGA was performed only in patients who had IPS by CEE. Clinical data were reviewed retrospectively by grouping patients; normal group in which patients had no evidence of IPS by CEE, IPS group in which patients had IPS but did not have any evidence of HPS by ABGA, and HPS group in which patients had evidences of both of IPS and HPS. **(Results)**IPS was identified in 41 patients (56.9%) and normal group was identified in 31 patients (43.1%). Six patients with IPS were excluded from data analysis because ABGA were not examined in these patients. IPS group included 20 patients, and HPS group included 15 patients. Compared to the normal group, the bilirubin level at the time of CEE and the hepatic

fibrosis score were significantly increased in the IPS group and HPS group, and liver transplantation was performed significantly more frequent in the HPS group. **(Conclusion)**The incidence of IPS in BA was considerably high. Patients with IPS have worse clinical outcomes than patients without IPS. The identification and close-monitoring of IPS in BA lead to favorable outcomes by preventing the late liver transplantation.

Key words: biliary atresia, intrapulmonary shunt, hepatopulmonary syndrome

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I. INTRODUCTION

An intrapulmonary shunt (IPS) is one of the long-term serious complications in chronic liver disease (1). The pathophysiology of IPS remains unclear. However, enhanced pulmonary production of nitric oxide and increased hepatic production of the vasodilator endothelin-1 in cirrhotic patients are associated with the development of IPS (2). If a patient with IPS and chronic liver disease is identified as having an arterial oxygen defect, hepatopulmonary syndrome (HPS) may be diagnosed (3). The presence of HPS is an important factor for predicting the survival of patients with chronic liver disease. In severe cases, patients should be evaluated for liver transplantation and closely monitored for liver failure (4). According to several retrospective studies about HPS in pediatric chronic liver disease patients, the prevalence of HPS is 8–20%, and early liver transplantation allows regression of pulmonary arteriovenous shunt (5-8).

However, few clinical studies about IPS and HPS in biliary atresia (BA) have been

published. Moreover, the characteristics of patients with IPS in BA that can lead to development of HPS have not been well characterized. Therefore, we investigated the incidence of IPS and HPS in BA and evaluated their clinical significance.

II. MATERIALS AND METHODS

Between March 2010 and May 2013, children with BA who received a regular follow-up after the Kasai operation in the Department of Pediatric Surgery in Severance Children's Hospital were prospectively recruited for evaluation of IPS. We considered that IPS would not be developed in young children before 6 months. Therefore, we tried to select the patients with ages from 12 months to six years. However, in some younger or older patients were also selected when they are needed the examination about IPS because their laboratory finding appeared the uncompensated status of liver. Patients with congenital heart disease with a right-to-left shunt and patients who underwent the liver transplantation were excluded in the study. And patients were excluded also when the patient's guardians did not agree with CEE.

Patients were evaluated for the presence of IPS and HPS using contrast-enhanced echocardiography (CEE) (9) and arterial blood–gas analysis (ABGA) including the alveolar-arterial oxygen gradient ($AaDO_2$). IPS was identified as an arteriovenous shunt in CEE. HPS was diagnosed according to the criteria in the study by Rodriguez-Rosin et al (2) (Table 1). In all patients who were diagnosed with IPS or HPS, the chest x-rays

were performed. As a result, patients were identified without the intrinsic pulmonary abnormalities. Other additive chest examinations such as chest computed tomography or lung perfusion scan was not performed because we considered that these studies are invasive, expensive and unnecessary in young patients.

TABLE 1. *Diagnostic criteria for hepatopulmonary syndrome*

Variable	Criterion
Oxygen defect	PaO_2* <80 mmHg or $AaDO_2$† ≥15 mmHg
Intrapulmonary shunt	Positive findings on CEE** within six heart-beats
Liver disease	All biliary atresia patients
Degree of severity	
Mild	$AaDO_2$ ≥15 mmHg, PaO_2 ≥80 mmHg
Moderate	$AaDO_2$ ≥15 mmHg, PaO_2 ≥60 mmHg to <80 mmHg
Severe	$AaDO_2$ ≥15 mmHg, PaO_2 ≥50 mmHg to <60 mmHg
Very severe	$AaDO_2$ ≥15 mmHg, PaO_2 <50 mmHg

*Partial pressure of oxygen, †alveolar-arterial oxygen gradient, **contrast-enhanced echocardiography

1. CEE

CEE was randomly performed by three pediatric cardiologists using an echocardiography device with 3- and 5-MHz probes with patients lying in a supine position. The four-chamber view was used to assess the right-to-left shunt. Ten milliliters of agitated saline was injected into the peripheral vein via a three-way stopcock. CEE was considered positive when micro-bubbles appeared in the left heart within six heart–beats after the right-atrial opacification (10, 11).

2. ABGA

For ABGA, the patient's radial artery was punctured in a sitting position while breathing room air after resting for 5 minutes. Arterial hypoxemia was defined as partial pressure of arterial oxygen (PaO_2) <80 mmHg (2). $AaDO_2$ was calculated using the alveolar gas equation:

$$AaDO_2 = PAO_2 – PaO_2 = (FiO_2 [Patm – PH_2O] – [PaCO_2/0.8]) – PaO_2,$$

where PAO_2 denotes the partial pressure of alveolar oxygen, PaO_2 is the partial pressure of arterial oxygen, FiO_2 is the fraction of inspired oxygen, Patm is atmospheric pressure, PH_2O is the partial pressure of water vapor at body temperature, and $PaCO_2$ is the partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas-exchange respiratory ratio at rest); the normal range is 4–8 mmHg (2). If children were identified as not having IPS with CEE, ABGA was not performed due to the invasiveness of ABGA.

To evaluate the severity of liver cirrhosis, several clinical parameters were obtained by performing biochemical laboratory examinations, liver elastography (FibroScan®, Echosense, SA, Paris, France), gastroduodenoscopy, and abdomen ultrasonography during the same period as CEE.

The clinical data were reviewed retrospectively and analyzed by grouping patients without IPS (normal group), patients with IPS without HPS (IPS group), and patients with IPS and HPS (HPS group).

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Continusous data were expressed as median value with range and categorical data were presented as number with percentage. The chi-square test or Fisher's exact test were used to compare categorical variables and the Kruskal-Wallis test was used for comparisons of continuous variables between groups. A *p* value less than 0.05 was considered statistically significant. This study was approved by our institutional review board.

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III. RESULTS

Two hundred nineteen patients with BA have been receiving regular check-ups in our institution. According to scheduled follow-ups, 72 patients were examined with CEE for evaluation of IPS. Among these, 41 patients (56.9%) were identified as having IPS. Patients with IPS were examined with ABGA to diagnose HPS. Six patients with IPS were not examined with ABGA and were excluded from the grouping. Twenty patients

with IPS were identified as having IPS without HPS (IPS group). Fifteen patients with IPS were identified as having HPS (HPS group) (Fig. 1). The grades of HPS were identified as mild in 10 patients (13.9%), moderate in 4 patients (5.5%), and severe in 1 patient (1.4%)(Table 2).

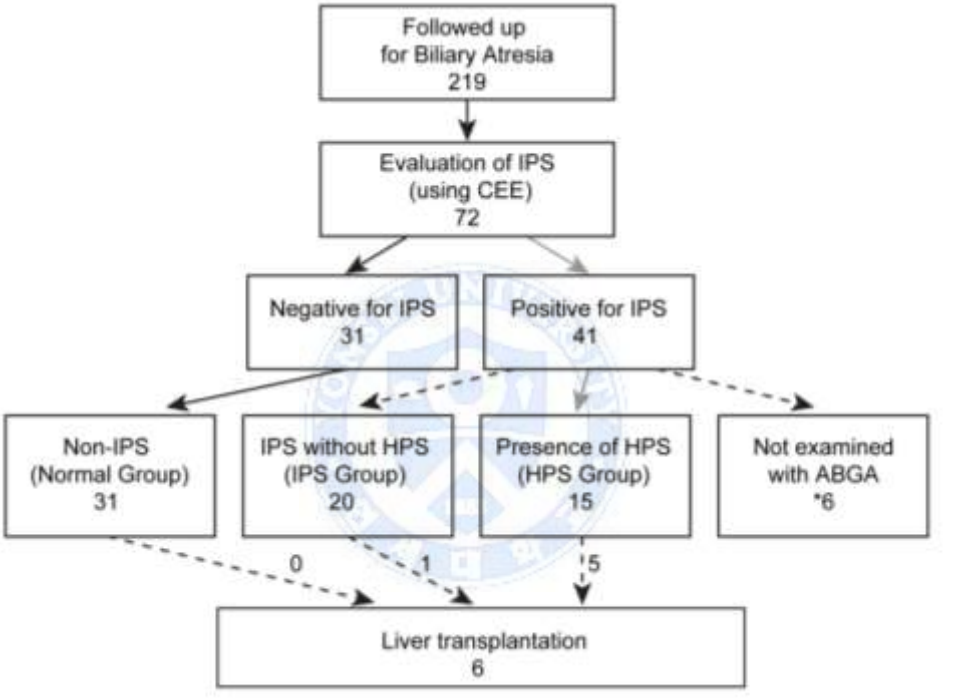

FIG. 1. Patient classification

(IPS: Intrapulmonary syndrome, CEE: contrast-enhanced echocardiography, HPS: hepatopulmonary syndrome, ABGA: arterial blood gas analysis)

TABLE 2. *Incidence of hepatopulmonary syndrome*

Grade of hepatopulmonary syndrome	N (%)
Mild	10 (13.9)
Moderated	4 (5.5)
Severe	1 (1.4)
Very severe	0 (0.0)
Total	15 (100.0)

The clinical characteristics of patients according to the groups are summarized in Table 3. Ages at the Kasai operation and at the time of CEE were similar among the groups. Sex distribution was also not different among the groups. The jaundice-free rate within 6 months after the Kasai operation was lower in the IPS group compared to the normal group (75.0% vs. 87.1%, respectively) and was also lower in the HPS group compared to the IPS group (60.0% vs. 75.0%, respectively). However, the difference was not statistically significant (p=0.108). However, total bilirubin levels at the time of CEE were significantly higher in the HPS group compared to the normal group (total: 1.9 mg/dL vs. 0.6 mg/dL, p = 0.005). And direct bilirubin levels at the time of CEE were significantly higher in the HPS group compared to the normal group (total: 1.2 mg/dL vs. 0.2 mg/dL, p = 0.001). The liver stiffness score was also significantly higher in the IPS group compared to the normal group (15.5 kPa vs. 8.7 kPa, p<0.001) and also was higher in the HPS group compared to the IPS group (29.3 kPa vs. 15.5 kPa, p<0.001).

The numbers of cholangitis events were not different among the groups. However, the numbers of patients who underwent liver transplantation were significantly higher in the HPS group compared to the normal group (33.3% vs. 0.0%, p=0.001). Except for one patient in the IPS group who died due to hematochezia, all patients in all groups survived with or without liver transplantation.

TABLE 3. *Clinical details of patients according to the groups*

Characteristics	**Normal group (n=31)**	**IPS group (n=20)**	**HPS group (n=15)**	**P-value**
Age at Kasai operation (days)	56 (10–178)	66 (36–132)	60 (17–87)	0.072
Age at the time of CEE (years)	5.6 (0.3–13.1)	6.1 (0.4–15.4)	3.7 (0.5–12.4)	0.504
Sex (male/female, n)	14/17	9/11	4/11	0.429
Surgery (n)				
Redo Kasai operation	0	2	2	
LT** after Kasai operation	0	1	5	
Jaundice free within 6 months after Kasai operation (n)	27 (87.1%)	15 (75.0%)	9 (60.0%)	0.108
Total bilirubin at the time of CEE (mg/dL)	0.6 (0.2–5.9)	1.5 (0.4–4.0)	1.9 (0.6–21.2)	0.005‡
Direct bilirubin at the time of CEE (mg/dL)	0.2 (0.1–5.1)	0.8 (0.1–3.5)	1.2 (0.3–17.1)	0.001‡
Liver stiffness score (kPa)	8.7 (3.1–75.0)	15.5 (6.1–41.3)	29.3 (12.0–75.0)	<0.001§
Cholangitis events (n)				0.434
None	9	4	1	
≤ 3 times	12	11	5	
>3 times	9	5	7	
Unknown	1	0	2	
LT after diagnosis of HPS (n)	0 (0.0%)	1 (5.0%)	5 (33.3%)	0.001‡

*IPS: Intrapulmonary shunt, †HPS: Hepatopulmonary syndrome, ** LT: liver transplantation
All continuous variables are reported as the median value with range.
‡Comparison between the normal group and the HPS group was significant in post-hoc tests.
§Comparisons between all three groups were significant in post-hoc tests.

IV. DISCUSSION

In chronic liver disease including BA, IPS is sometimes identified as a long-term complication, and when accompanied by hypoxia, HPS may be diagnosed. HPS is defined as hypoxemia induced by intrapulmonary vascular dilatation associated with cirrhotic or non-cirrhotic liver disease and portal hypertension (3). Many reports have been published regarding the treatment and prognosis of HPS. However, few studies have been reported about IPS, including the incidence, pathophysiology, and clinical significance. Considering that HPS in uncompensated liver disease subsequently requires liver transplantation as a last treatment, the clinical significance of IPS should be more highly emphasized because IPS precedes the development of HPS (12).

A few studies have reported the incidence of HPS in BA (1, 5, 6, 8, 13). In the literature, the incidences of HPS in children have been reported to be 8–28% in those with chronic liver disease and 17–19% in liver transplant recipients (5, 6, 8, 14-16). However, these incidences vary due to the heterogeneity of the disease and did not focus on the incidence of IPS in particular. Through our preliminary institutional study, we noticed that when considering BA only, the incidence of IPS was quite high. Therefore, we proceeded with this study and found that the incidence of IPS in BA was 56.9%, and the incidence of HPS was 20.8%. These high incidences of IPS and HPS have not been previously reported. Thus, we believe that this is the first and largest study about IPS and HPS that is restricted to BA.

However, the clinical meaning of this high incidence of IPS is not well understood.

According to our results, indicators of a poor clinical condition such as high bilirubin levels and high liver stiffness scores were significantly higher in the IPS group than in the normal group, and were also higher in the HPS group compared to the IPS group. Liver transplantation rate was also higher in the HPS group compared to the IPS group and in the IPS group compared to the normal group. These results indicate that patients with IPS are more likely to worsen clinically or to develop HPS than patients without IPS in BA. In other words, the presence of IPS in BA may lead to potential morbidities.

One significant finding leading to diagnosis of HPS is an arterial oxygenation defect. However, few patients with HPS complain of hypoxic symptoms, and monitoring of hypoxia is considerably difficult in pediatric patients during the follow-up period. Therefore, to detect the presence of IPS, even absence of clinical symptoms, examination for IPS and close monitoring for the development of HPS are crucial.

Once a diagnosis of HPS is made, the process of undergoing liver transplantation should proceed. In the past, severe hypoxemia due to HPS was considered a contraindication for liver transplantation. However, current medical therapies for HPS are not effective, and liver transplantation is the only successful treatment (12). At present, the prognosis of BA after liver transplantation is favorable, with 5-year-survival rate 85–98% (17). Although HPS is a rare cause of liver transplantation in BA, it is the only treatment that can reverse HPS. Therefore, early diagnosis of IPS and early liver transplantation to treat HPS are important.

The pathophysiology of IPS in BA is unclear. However, according to several studies, nitric oxide may be the cause of IPS. In dilated capillaries, less gas exchange occurs with oxygen-rich alveoli, resulting in a ventilation-perfusion mismatch (11). In animal models of IPS, elevated nitric oxide levels are detected in the lung of rats, and are

believed to be the most probable cause of IPS (18-20). In a recent study, angiogenesis, which is mediated by vascular endothelial growth factor A produced by activated intravascular monocytes, was shown to be a key contributor to the pathogenesis of IPS (21). However, this discovery is confined to animal models. Therefore, to define the clinical significance of IPS more accurately, further studies on the pathophysiology of IPS and HPS are needed in chronic liver diseases including BA.

This study has some limitations. First, when children cry during ABGA, the reliability of the procedure is unclear in terms of how the reading reflects the exact degree of hypoxemia. Second, this study did not include all our patients with BA because the follow-up schedule was different among patients. Lastly, all patients who underwent liver transplantation underwent surgery after diagnosis of HPS. However, the definitive cause of liver transplantation in patients with IPS and HPS is ambiguous. The indications of liver transplantation in our institution are: impending liver failure with signs of hepatic synthetic dysfunction such as growth failure, hypoalbuminemia, and coagulopathy, intractable portal hypertension such as uncontrolled variceal bleeding and intractable ascites, and hepatopulmonary syndrome (HPS). However, we did not have any patients who received liver transplantation just to resolve HPS. All patients with HPS in this study did not have any symptoms of HPS like dyspnea when they had been diagnosed HPS because they were carefully followed for the detection of IPS. Therefore, all patients with HPS who received liver transplantation in our study had another surgical indication of liver transplantation, but the fact of evidence of HPS influenced the decision of liver transplantation.

V. CONCLUSION

Our study is the one of the largest studies to investigate IPS and HPS confined in BA only. The incidences of IPS and HPS were considerably high in BA. Patients with IPS have worse clinical outcomes than patients without IPS. Therefore, the presence of IPS should be considered a “hidden morbidity”. Check-ups to look up for the presence of IPS and close monitoring of patients with IPS should be done so that early diagnosis of HPS and appropriate treatment, such as timely liver transplantation, can be performed, leading to a favorable outcome.

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ABSTRACT (IN KOREAN)

담도 폐쇄증에서 간폐증후군의 임상적 의의

<지도교수 한석주>

연세대학교 대학원 의학과

장 은 영

(배경) 만성 간질환 환자에서 폐내단락이 있는 경우에 저산소증까지 발생할 경우 간폐증후군으로 진행할 수 있는데 담도폐쇄증에서는 아직까지 잘 알려지지 않고 있다. 이에 담도폐쇄증에서의 폐내단락과 간폐증후군의 유병율과 임상적 의의에 대해 알아보고자 하였다. (방법) 2010년 3월부터 2013년 3월까지 72명의 담도폐쇄증 환자에서 조영증강 심초음파를 이용하여 폐내단락을 검사하였고, 이 중 폐내단락이 진단된 경우에는 추가로 동맥혈가스분석을 통하여 간폐증후군 유무를 확인하였다. 결과에 따라 정상군, 폐내단락만 있는 군, 간폐증후군까지 있는 군으로 분류하여 결과를 분석하였다. (결과) 전체환자 중 정상군은 31명 (43.1%) 이었고, 41명 (56.9%) 에서 폐내단락이 진단되었다. 이 중에서 동맥혈가스검사를 시행하지 않은 6명을 제외하고 폐내단락만 있는 경우는 20명이였으며, 간폐증후군까지 있는 경우는 15명이었다. 정상군에 비해 폐내단락군과 간폐증후군군에서 혈청 빌리루빈 수치와 간섬유화점수가 유의하게 증가되어 있었고, 간폐증후군 환자에서 간이식이 더 유의하게 시행되었다. (결론) 담도폐쇄증에서 폐내단락의 유병율은 상당히 높았으며, 폐내단락이 있는 환자는 그렇지 않은 환자에 비해 임상적으로 더 나쁜 예후를 보였다. 따라서 담도폐쇄증 환자에서 폐내단락의 발생을 유심히 살핀다면 적절한 시기에 간이식을

시행하게 함으로써 좀 더 나은 예후를 보일 수 있을 것으로 판단된다.

핵심되는 말: 담도폐쇄증, 폐내 단락, 간폐증후군