□ Case Report □

# A case of hepatopulmonary syndrome in a child with fatty liver disease secondary to hypopituitarism after craniopharyngioma resection

Sun Ju Im, M.D., Hyoung Doo Lee, M.D.
Jae Hong Park, M.D. and Hee Ju Park, M.D.

Departments of Pediatrics, College of Medicine, Pusan National University, Busan, Korea

Hepatopulmonary syndrome is a triad that includes: hepatic dysfunction, intrapulmonary vascular dilatation and abnormal arterial oxygenation. The incidence of intrapulmonary vascular dilatations, in adults with end-stage liver disease, has been reported to be 13% to 47%, however the incidence in children is unclear and the cases in Korean children have never been reported. The hepatopulmonary syndrome may occur as a result of chronic liver disease following nonalcoholic steatohepatitis in children with hypothalamic or pituitary dysfunction. We report a case of hepatopulmonary syndrome in a 13-year-old child who had rapidly progressive liver dysfunction secondary to panhypopituitarism after craniopharyngioma resection. Careful monitoring and treatment of endocrine abnormalities and metabolic status, as well as liver function, are required in all children undergoing pituitary tumor resection. (Korean J Pediatr 2007;50:794-798)

**Key Words :** Hepatopulmonary syndrome, Fatty liver disease, Hypopituitarism, Craniopharyngioma

## Introduction

Chronic liver dysfunction is associated with abnormal pulmonary manifestations due to alteration of the production or clearance of circulating cytokines and other mediators[1]. Hepatopulmonary syndrome is a triad that includes: hepatic dysfunction, intrapulmonary vascular dilatation and abnormal arterial oxygenation; results in hypoxemia due to pulmonary vasodilatation with significant arteriovenous shunting and ventilation-perfusion mismatch[1-3].

Advanced liver cirrhosis is rarely reported in patients with nonalcoholic fatty liver disease (NAFLD), however children with pituitary dysfunction can develop progressive liver disease and may present with the hepatopulmonary syndrome. Reports of NAFLD and cirrhosis following hypothalamus and pituitary surgeries for suprasellar tumors are now increasingly recognized[4-8].

We report a case of hepatopulmonary syndrome in a 13-year-old child who had rapidly progressive liver dysfunction secondary to panhypopituitarism after craniopharyngioma resection.

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책임저자 : 박희주, 부산대학교 의과대학 소아과학교실
Correspondence : Hee Ju Park, M.D.
Tel : 051)240-7294 Fax : 051)248-6205
E-mail : phj7294@hanmail.net

## Case Report

An 11-year-old boy presented with seizures; diagnostic workup revealed a craniopharyngioma. Preoperative blood testing showed elevated liver enzyme (AST 27 IU/L, ALT 109 IU/L); abdominal ultrasonography and a liver biopsy revealed fatty liver (Fig. 1). The patient subsequently underwent surgery to remove craniopharyngioma. Postoperatively panhypopituitarism developed and was treated with thyroxine, hydrocortisone and desmopressin. Hyperphagia resulting in gradual weight gain was also present; the body mass index increased from 20.2 kg/m$^2$ (75 to 85 percentile) to 28.6 kg/m$^2$ (above 95 percentile) over 2.5 years. In addition, the patient developed insulin resistance with an elevated insulin level (38.6 $\mu$IU/mL, where normal upper limit is 30 $\mu$IU/mL); however, the fasting glucose remained normal.

Two and half years after resection of craniopharyngioma the patient presented with cyanosis and dyspnea at minimal exertion. Starting a few months earlier, he reported a pro-

gressive increasing exertional dyspnea; three days before admission he became febrile and developed a cough. On presentation his body temperature were 38℃ with pulse rate 95 beats/min, respiratory rate 25 breaths/min, blood pressure 130/80 mmHg, and transcutaneous oxygen saturation from 70 to 75 percent on room air. The oxygen saturation worsened at upright position, but improved at supine with symptomatic relief. Physical examination revealed mild finger clubbing and multiple spider nevi on his face, neck and chest. The breath sounds were clear with no murmur heard on auscultation. The liver and spleen were markedly enlarged.

The hematological laboratory tests showed reduced white cell count 2,830/$mm^3$, hemoglobin 11.2 g/dL and platelets 116,000/$mm^3$, which were consistent with hypersplenism.

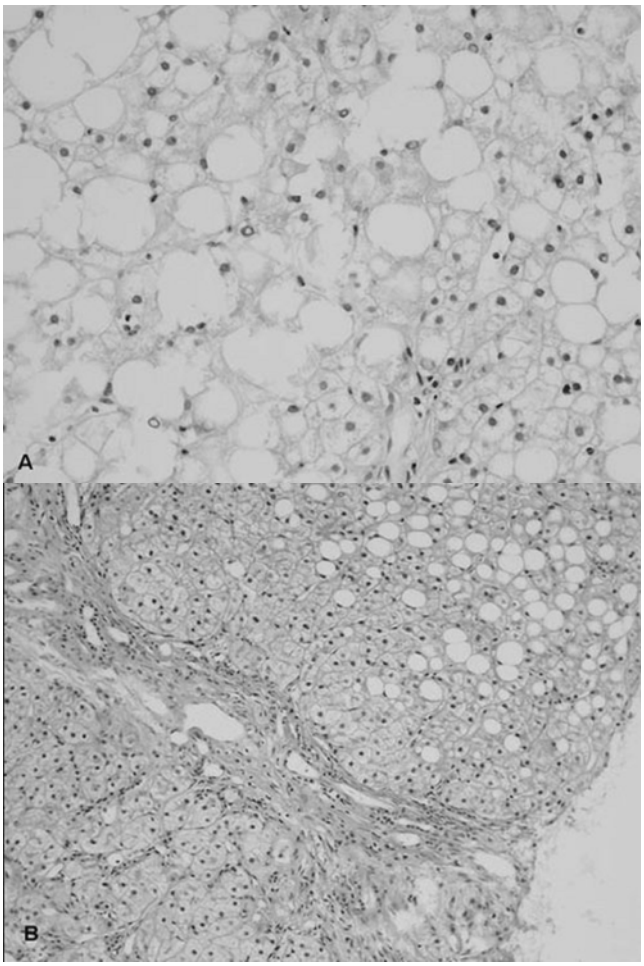


**Fig. 1.** (A) A liver biopsy before craniopharyngioma resection showed moderate to marked microvesicular and macrovesicular steatosis of hepatocytes and no evidence of cirrhotic change (H&E stain, ×400). (B) But two and half years after resection of craniopharyngioma, a liver biopsy showd a well-eatablished nodular cirrhosis with mild portal and septal chronic inflammation, and hepatocellular steatosis (H&E stain, ×100).

Blood chemistry was unremarkable except for a total bilirubin 2.82 mg/dL. Coagulation studies were abnormal with prothrombin time 20.6 seconds, international normalized ratio (INR) 1.80 and activated partial thrombin time 64 seconds. This signified decreased hepatic synthetic function. Arterial blood gases on room air revealed a pH 7.375, $PaCO_2$ 36.6 mmHg, and $PaO_2$ 48.1 mmHg, whereas $PaO_2$ on 100% inspired oxygen was 78.2 mmHg. Growth hormone, thyroid stimulating hormone and adrenal corticotropin hormone were not detectable, and $T_3$, free $T_4$ and cortisol levels were very low.

The chest X-ray showed mild cardiomegaly with some pneumonic consolidation, however there was no structural abnormality on echocardiography.

The patient was treated with intravenous ceftizoxime and amoxicillin with clavulanate, and oral azithromycin. Fever and other systemic symptoms subsided in eight days. Transcutaneous oxygen saturation on room air ranged between 70 to 75 percent, but increased to 94 percent with 3 L/min of oxygen through a rebreather mask. This moderate response to 100% oxygen by increased alveolar-arterial oxygen gradient (about 60 mmHg) with normal partial pressure of $CO_2$ suggested that the hypoxemia was secondary to a shunt or ventilation-perfusion mismatch.

A scintigrafic study with technetium-99m-macroaggregated albumin demonstrated normal pulmonary perfusion but an abnormal uptake in the brain and kidney (Fig. 2), suggesting the presence of pronounced right-to-left shunt. A CT scan of the chest showed dilated peripheral pulmonary vessels at the subpleural portion of the lung with significantly increased ratio of the segmental arterial diameter to the adjacent bronchial diameter (Fig. 2). Contrast enhanced echocardiography with agitated saline also confirmed the presence of an intrapulmonary shunt (Fig. 3). A follow up liver biopsy now showed hepatic cirrhosis, whereas steatohepatitis was seen two years previously (Fig. 1). Therefore, the hepatopulmonary syndrome was diagnosed, a recognized complication of cirrhosis.

## Discussion

Hepatopulmonary syndrome was first reported by Kennedy and Knudson in 1977. It is characterized by severe hypoxemia with intrapulmonary vasodilatations in the setting of hepatic dysfunction[3]. The incidence of intrapulmonary vascular dilatations, in adults with end-stage liver disease, has

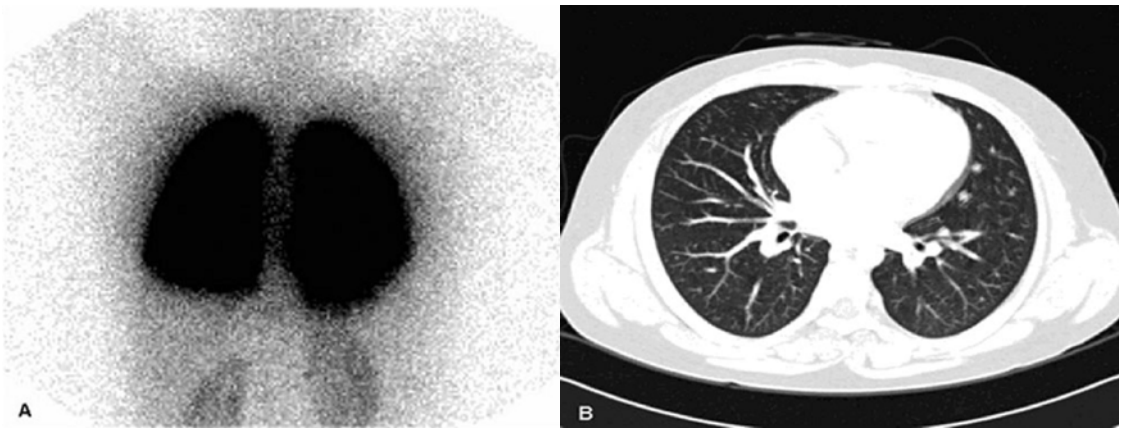


**Fig. 2.** (A) Perfusion lung scan with 99mTc-MAA shows no definite perfusion defect in both lungs. Kidnes are visualized, which suggests right to left shunting of the injected 99mTc-MAA. (B) CT scan shows tortuous dilated peripheral vessels 2 cm from the pleura. The size of the arteries is increased relative to that of the adjacent bronchi.

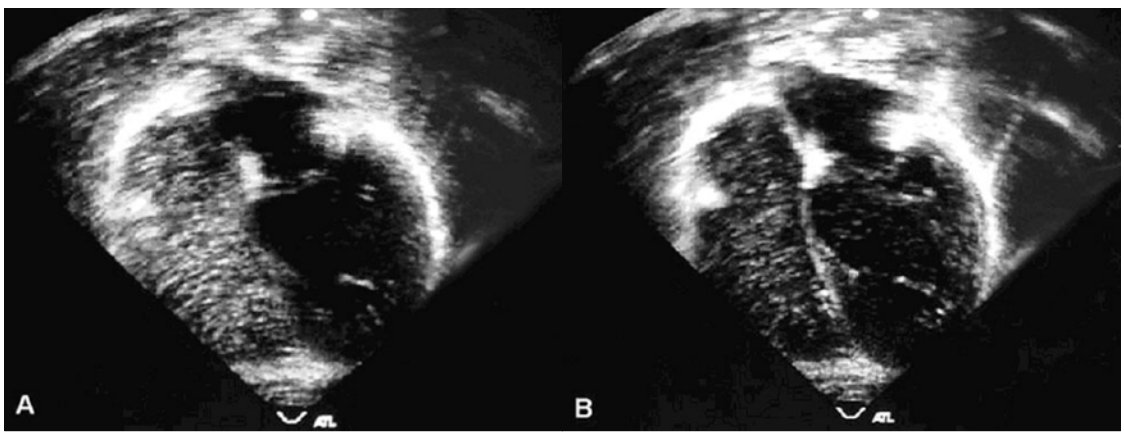


**Fig. 3.** (A) Contrast echocardiography with agitated saline shows a stream microbubbles opacifying only the right chamber. (B) After three heart beats, microbubbles opacify the left heart chamber demonstrating intrapulmonary shunt.

been reported to be 13% to 47%, half of which were associated with hypoxemia[9]. However the incidence in children is unclear and only a few cases have been reported in the medical literature[8, 10, 11].

The clinical findings of hepatopulmonary syndrome include a various of signs and symptoms of liver disease such as; finger clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia[2]. Platypnea and orthodeoxia are more prevalent in patients with severe hypoxemia, and are characteristic of hepatopulmonary syndrome[12]. It has been hypothesized that orthodeoxia is caused by preferential perfusion of intrapulmonary vascular dilations in the lung bases so that shuntng is increased when the patients is upright. In the case here presented, the main pulmonary symptom was dyspnea, accompanied by platypnea and orthodeoxia. Spider nevi, another common clinical feature of hepatopulmonary syndrome were also present; these nevi has been proposed as cutaneous markers of intrapulmonary vascular dilatations[13].

The Intrapulmonary vasodilatation correlates with increased levels of pulmonary vasodilators, such as endothelial nitric oxide and endothelin-1, with certain forms of hepatic injury [14]. The mechanisms underlying shunting with hepatopulmonary syndrome is different from that of the more tranditional shunt in which blood bypasses the alveoli. In the normal lung, the capillary diameter is 8 to 15 $\mu$m and oxygen diffuses rapidly into the capillary, whereas in the presence of the hepatopulmonary syndrome the capillaries are dilated to 15 to 100 $\mu$m in diameter and oxygen fails to diffuse into the center of the dilated capillary[11].

Pathological studies have demonstrated two distinct vas-

cular abnormalities: precapillary and/or capillary vascular dilatations (type I), and discrete direct arteriovenous communications (type II)[15]. Type I lesions are generally related with excellent response to 100% inspired oxygen and liver transplantation, while type II lesions show little response to 100 % oxygen but anatomical repair is possible[15]. Our patient had type I lesions. He did not show full response to 100% inspired oxygen, but rather moderate response. It is likely that he had advanced diffuse intrapulmonary dilatations, limiting response to 100% oxygen.

In our case, because of the low oxygen saturation and concern about the possible presence of an infiltrate, the patient was admitted to the hospital with a presumptive diagnosis of pneumonia, howevere he continued to require oxygen to maintain adequate oxygen saturation levels after the fever resolved. Therefore the diagnosis of hepatopulmonary syndrome was considered associated with liver dysfunction leading to the symptom of severe dyspnea and cyanosis. Clinical suspicion of hepatopulmonary syndrome was supported by a technetium 99m-labeled macroaggregated albumin scan and by contrast-enhanced echocardiography, which confirmed intrapulmonary vascular shunting. Howevere, pulmonary angiography was not performed due to invasive nature.

To date, experimental medical therapy for this syndrome has been ineffective[2]. Inhibitors of vasodilatation, including somatostatin analogues, nitric oxide synthase inhibitors, and indomethacin, have resulted in poor responses and significant side effects[2]. Liver transplantation has been attempted in some cases[16]. For those who survive, liver transplantation is an effective therapy, with intrapulmonary shunting improving over six weeks period[13, 17].

In our patient, after brain surgery he developed hyperphagia, weight gain and insulin resistance; NAFLD progressed rapidly to liver cirrhosis. The development of advanced liver disease was found to be associated with hypopituitarism after the craniopharyngioma resection. The metabolic syndrome with hyperphagia, obesity and insulin resistance has been recognized with increasing frequency in children with hypothalamic and pituitary dysfunction secondary to brain tumors[4-6, 18]. Patients with NAFLD are generally obese and insulin resistant. It has been shown in recent studies that obesity, resulting from hypothalamic and pituitary injury is accompanied by liver damage, which occasionally progress to cirrhosis[4-8].

The etiological mechanisms, causing fatty liver diseases in children with pituitary dysfunction have been proposed in several reports[4, 5]. The hypothalamus is involved in appetite and weight regulation via the actions of leptin and insulin. Leptin is produced almost exclusively in adipose tissue and acts centrally in the hypothalamus to decrease food intake and increase energy expenditure. Damage to the pituitary and hypothalamus during cranial tumor surgery is therefore likely to result in raised leptin and insulin, hyperphagia and lower metabolic rate. Leptin, insulin resistance and obesity further increase fat deposition and fibrosis within the liver.

Although liver transplantation is thought to be the last therapeutic choice for the treatment of hepatopulmonary syndrome, nonalcoholic fatty liver disease with hypothalamic and pituitary dysfunction is likely to recur very quickly after successful liver transplantation. Jankowska et al.[7] reported that teenager, who had steatohepatitis following resection of pituitary tumor, was found to develop nonalchoholic fatty liver disease in six months after liver transplant, and Jonas et al.[8] observed the same phenomena at two months post transplantation surgery. These cases, similar to our case, illustrate the concern for recurrence of nonalcoholic steatohepatitis after liver transplantation.

In conclusion, hepatopulmonary syndrome may occur in significant chronic liver disease following nonalcoholic steatohepatitis in pediatric patients with hypothalamic or pituitary dysfunction. Careful monitoring and treatment of endocrine abnormalities and metabolic status, as well as possible progression of liver disease, are required in children undergoing pituitary tumor resection.

## 한 글 요 약

### 지방간을 가진 소아에서 두개인두종 절제술 후의 뇌하수체기능저하증으로 인해 급격하게 진행된 간-폐 증후군 1예

*부산대학교 의과대학 소아과학교실*

**임선주 · 박현석 · 이형두 · 박재홍 · 박희주**

간-폐 증후군이란 진행된 간경변을 가진 환자에서 폐혈관의 확장으로 인해 동맥혈 산소 포화도가 감소하는 것을 특징으로 한다. 간경화 환자에서 동맥 산소 포화도의 감소가 보고된 이후로 간-폐 증후군은 말기 간질환을 가진 성인의 13-47% 정도에서 발생한다고 보고하고 있으나, 소아에서 발생한 국내 보고는 없다. 또한 시상하부 및 뇌하수체 기능 저하를 보이는 환자에서

비알코올성 지방간이 급격하게 간부전으로 진행되는 증례가 최근에 보고되고 있다. 저자들은 지방간을 가진 소아에서 두 개인 두종 절제술 후에 발생한 뇌하수체기능저하증으로 인해 간질환이 급격하게 진행하여 간-폐 증후군으로 발현된 증례를 경험하였기에 보고하는 바이다. 두부 수술 후에 시상하부 및 뇌하수체 기능 저하를 보이는 환아에서는 내분비 질환이나 대사 장애 뿐 아니라, 간질환에 대한 추적 관찰이 필요할 것이다.

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