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Reversal of intrapulmonary arteriovenous shunts associated with end stage liver disease after liver transplantation.

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Pulmonary arteriovenous shunting is a serious complication of endstage liver disease(ESLD) and presents with a chronic hypoxic syndrome. Severe hypoxia has been considered a contraindicaton to orthotopic liver transplantation(OLTx). Four pediatric patients with ESLD and severe pulmonary arteriovenous shunting underwent OLTx. Immunosuppression was with Cyclosporin A in one patient and with FK506 in three patients. Hypoxia was reversed by successful OLTx in all patients.

Case report (See patient profile in Table 1)

[Patient 1] This 16 year old boy with Biliary Atresia received a Kasai procedure at the age 2 months and mesocaval shunt at age 15 years. He presented to us with worsening liver function and hypoxia. He was extremely fatigued, had deteriorating performance status, and was unable to attend school regularly. physical examination revealed remarkable central cyanosis and digital clubbing. He was apathetic and demonstrated a low level of reactivity to external stimuli. He also presented with polycytemia(hemoglobin of 16.6 g/dl and hematocrit of 47%). His liver function tests are shown in Table2. Arterial blood gas measurement demonstrated severe hypoxia with a PaO_2 of 56 mmHg. His pulmonary function test (Table 3) showed mild dysfunction which did not correlate with the severity of his hypoxia.

He underwent OLTx on May 14, 1989 at age 16 years. Intraoperatively the mesocaval shunt was found to be functional. The patient's native portal vein was hypoplastic down to the confluence of the splenic and superior mesenteric veins. A cadaveric vein graft was interposed, and the mesocaval shunt was ligated. The OLTx was otherwise unremarkable. Postoperative immunosuppression was with Cyclosporin A 150 mg twice a day, azathioprine 100 mg/day, and 20 mg of methylprednisolone started at 200 mg/day and then rapidly tapered to 20 mg/day over a ** period. He was

extubated on the first postoperative day (POD#1). The patient's postoperative course was uneventful with the exception of one episode of acute cellular rejection which was treated with OKT3. He required supplemental oxygen for 10 days to keep SaO_2 greater than 90%. His oxygenation improved gradually showing a PaO_2 of 88 mmHg on room air and improved school performance 4 months after OLTx.

[Patient 2] This 7 year old girl with biliary atresia received a Kasai procedure at the age of 2 months. She was referred to our center because of worsening hypoxia which presented 6 months prior to admission. She had several episodes of viral upper respiratory tract infections, and progressively worsening oxygenation. The PaO_2 on room air was 38 mmHg, she exhibited cyanosis, mild polycytemia (hematocrit of 40.4% and hemoglobin of 14.1 g/dl), but no digital clubbing. Pulmonary function test was not performed. Her liver function tests are shown in Table2.

She underwent uneventful OLTx on May 30, 1990. She was extubated on POD #1, however, she required reintubation for atelectases and hypoxia on POD #2. Immunosuppression was with FK506(0.15mg/kg/day intravenous for the first 5 days, then 0.3 mg/kg/day orally), and low dose steroids (methylprednisolone 10 mg/day). She was extubated again on POD#4, and supplemental oxygen was required for 25 days to keep

SaO_2 greater than 90%. She had one episode of rejection, which was treated by increasing the baseline FK506 dose and a steroid volus of Hydrocortisone 300 mg intravenously. She was discharged without any oxgen therapy 30 days post OLTx. Her oxygenation improved showing PaO_2 of 94 mm Hg on room air 3 months post OLTx.

[Patient3] This nine year old girl was diagnosed with alpha-1-antitrypsin deficiency at birth. She had a positive history of asthma which was treated with Ventolin and home nebulization. Physical examination revealed remarkable central cyanosis and digital clubbing with PaO_2 of 43 mm Hg. She was mildly polycythemic(hematocrit 39.4%). Pulmonary function testing was not performed. Her liver function tests are shown in Table2.

She underwent an uneventful OLTx on May 31, 1991. She was extubated on POD #1, and started on FK506(0.15mg/kg/day intravenous for the first 5 days, then 0.3 mg/kg/day orally), and low dose steroids(methylprednisolone 10 mg per day). The post operative course was uneventful except for one episode of mild rejection, which was treated with inreasing the baseline FK506 dose and a steroid bolus of Hydrocortisone 1 g intravenously. She required oxygen supplementation for 14 days. Her oxygenation improved showing PaO_2 of 102 mmHg on room air 5 months post

OLTx and enjoying such physical activity as cheerleading.

[Patient 4] This 6 year old Arabian boy was diagnosed with cryptogenic cirrhosis at the age of 6 months. He was referred to our center for possible OLTx. Physical examination revealed clubbing but no central cyanosis. He complained of mild dyspnea on exertion. Echocardiogram demonstrated no evidence of cardiac shunting. His arterial blood gas showed mildly decreased PaO_2 of 74 mmHg. Pulmonary function testing was attempted, however adequate cooperation was not obtained. His liver function tests are shown in Table2. He was not polycythemic with hematocrit of 33.3%.

He underwent an OLTx on Nov 19,1991. Operation and postoperative course were quite uneventful. He was put on FK506(0.15 mg/kg /day intravenous for the first 5 days, then 0.3 mg/kg/day) and daily steroids(methylprednisolone 10 mg/day). He was extubated on POD#1 and oxygen supplement was continued for 7 days. However, two months after surgery he still has clubbing of the finger nails, but oxygenation is improved showing PaO_2 of 89 mmHg on room air.

Discussion

Hypoxia is a well known complication in patients with ESLD(1-3). It has been recognized that there are

two categories. One is due to the mechanical disturbances of the respiratory system caused by ascites and hepatosplenomegaly. In these cases, the hypoxia is usually mild. Another group of patients demonstrates severe hypoxia with central cyanosis. In 1968, Starzl et al described reversal of mild intrapulmonary arterio-venous shunt in 3 pediatric patients after OLTx(4). However, severe hypoxia with PaO_2<50 mmHg has been considered a contraindication to OLTx(5,6) because hypoxia is most likely secondary to intrapulmonary arterio-venous shunting, which is presumably a fixed pulmonary vascular abnormality. In fact, a few published reports described failed shunt closure post OLTx(5,7-8). On the other hand, there is one reported reversal of hypoxia following OLTx which is that presented by Stoller and associates(9). They described an adult female with primary biliary cirrhsis whose preoperation PaO_2 was 60 mmHg and improved to 89 mmHg post OLTx.

Several physiological mechanisms of pulmonary shunting have been proposed including: (A) ventilation perfusion mismatch, (B) intrapulmonary or subpleural arterio-venous shunting, (C) porto-pulmonary arterio-venous anastomosis, (D) systemic vein to pulmonary vein anastomosis, (E) shift ot the right of oxyhemoglobin dissociation curve, and (F) alveolar capillary diffusion abnormality(1). Based on accumulating evidence, Davis and associates proposed intrapulmonary shunting due to abnormal microvascular dilatation of the pulmonary circulation as the

predominant cause of severe hypoxia(10). Their hypothesis "Alveolar-Capillary Disequilibrium" implies that dilated lung capillaries present long diffusion paths for oxygen. As a result, red blood cells moving through the center of such vessels cannot receive adequate oxygen. They also proposed that vasoactive substances similar to those that induce vascular spidering in the skin result in pulmonary vasodilatation. OLTx presumably eliminates these vasoactive substances, thereby reducing the dilated capillaries to normal size and improving oxygenation.

Biliary atresia was the primary disease in two of the cases srudied and each had successful palliative procedure (Kasai procedure in both cases and mesocaval shunt in case 1), which allowed them to survive without severe jaundice. Their hypoxic presentation appeared later in their course of liver disease.

All patients were extubated POD#1. One required re-intubation for atelectasis and bronchoscopy. Particular attention was required to keep SaO_2 greater than 90% for at least 2 weeks post OLTx in order to prevent hypoxic damage to the liver. For this reason, supplemental oxygen was required for up to 25 days. Their oxygenation began to improve 2-3 weeks post OLTx, but recovery from hypoxia was not complete until nearly 3 months post OLTx. They were all discharged from the hospital without any oxygen therapy, representing dramatically improved oxygenation.

We reported four pediatric patients with pulmonary arterio-venous shunting secondary to ESLD which was reversed by successful OLTx. Our experience demonstrates OLTx as a valuable therapeutic option in normalizing oxygenation in these patients.

References

1. Rydell R, Hoffbauer FW. Multiple pulmonary arteriovenous fistula in juvenile cirrhosis. Am J Med 21: 450, 1956.

2. Silverman AC, Moller JH, Good RA. Syndrome of cyanosis, digital clubbing, and hepatic disease in siblings. J Pediatric 72: 70, 1968.

3. Senior ROM, Lefrak SS. The lungs and abdominal disease. In Murry JF, Nadel JA ed. Textbook of respiratory medicine. Philadelphia, W.B. Saunders Company. 1984, 1988.

4. Starzl TE, Groth CG, Brettschneider L, Moon JB, Fulginiti VA, Cotten FK, Porter KA. Extended survival in 3 cases of orthotopic homotransplantation of the human liver. Surgery 63: 549, 1968.

5. Van Thiel DH, Schade RR, Gavaler JS, Shaw BW, Iwatsuki S, Starzl TE. Medical aspects of liver transplantation. Hepatology 4: 79S, 1984.

6. Busuttil RW, Goldstein LI, Danovitch GM, Ament ME, Memsic LDF. Liver transplantation today. Ann Inter Med 104: 377, 1986.

7. Krwoka MJ, Cortese DA. Pulmonary aspect of chronic liver disease and transplantation. Mayo Clin Proc 60: 407, 1985

8. Krwoka MJ, Cortese DA. Severe hypoxia associated with liver disease. Mayo clinic experience and the experimental use of almitrine bismesylate. Mayo Clin Proc 62: 164, 1987.

9. Stoller JK, Moodie D, Schiavone WA, Vogt D, Broughan T, Winkelman E, Rem PK, Carey WD. Reduction of intrapulmonary shunt and resolution of digital clubbing associated with primary biliary cirrhosis afer liver transplantation. Hematology 11: 54, 1990.

10. Davis HH, Schwarts DJ, Lefrak SS, Susman N, Schainker BA. Alveolar-capillary oxygen disequilibrim in hepatic cirrhosis. Chest 73: 507, 1978.

Table 1 **Patient profile**

Case	I	II	III	IV
Age at OLTx (years)	16	7	9	6
Sex	M	F	F	M
Primary disease	Biliary atresia(BA)	BA	A1A*	Cryptogenic cirrhosis
Previous surgery	Kasai Mesocaval shunt	Kasai	None	None
Cyanosis	++	++	++	--
Clubbing	++	--	++	+
PaO2(mmHg) on room air				
Pre OLTx	56	38	43	74
Post OLTx (months)	88(4)	94(3)	102(5)	89(2)

* Alpha-1-antitrypsin deficincy

Liver fuction pre-OLTx

Case	I	II	III	IV
T-bilirubin	1.8	1.4	2.1	1.8
SGOT	87	145	109	96
SGPT	49	95	24	59
Alkaline phosphatase	408	717	331	467
G-GTP	109	351	256	139
PT	12.5	13.2	14.5	13.9
PTT	35.7	32.8	32.5	37.5
albumin	3.4	3.3	3.1	3.5
NH3	128	100	-	102

Table 3 Pulmonary function tests (Case 1)

	Pre bronchodilator		Post bronchodilator	
FVC	2.55 L	72 %	2.77 L	76 %
FEV	2.33 L	75 %	2.6 L	84 %
FEV/FVC		91 %		95 %
PEFR	4.25 L/S	75 %	5.25 L	93 %