



**LIVER TRANSPLANTATION FOR ADVANCED LIVER DISEASE WITH ALPHA-1-ANTITRYPSIN DEFICIENCY**

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ALPHA-1-antitrypsin deficiency associated with chronic obstructive airway disease was recognized in 1963 by Laurell and Ericksson.<sup>1</sup> In 1969, Sharp<sup>2</sup> described the first cases of alpha-1-antitrypsin-deficiency disease in children with cirrhosis. Since then, this inborn error has been recognized as one of the more common factors in cirrhosis of infancy and childhood,<sup>3</sup> including "neonatal hepatitis."<sup>4</sup> Alpha-1-antitrypsin is a glycoprotein that accounts for a major portion of the alpha-1 globulin fraction of the serum.<sup>5</sup> It is responsible for approximately 90 per cent of the antitrypsin activity<sup>6</sup> of the serum, and it also inhibits several other plasma enzymes, including plasmin,<sup>7</sup> elastase,<sup>8</sup> collagenase,<sup>9</sup> and chymotrypsin.<sup>10</sup>

Cirrhosis develops in about 15 per cent of patients with homozygous phenotype PiZZ (Pi = protease inhibitor),<sup>11</sup> and there have been a few recent reports of cirrhosis in heterozygous patients.<sup>12,13</sup> There has been no effective, specific medical treatment for such patients. This report will examine the place of orthotopic liver transplantation in the treatment of seven white patients who had end-stage liver disease due to alpha-1-antitrypsin deficiency. After transplantation, the phenotypes of the recipients became those of the donors, and alpha-1-antitrypsin levels were restored to normal. Thus, the metabolic basis of the

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disease was corrected for as long as the patients survived the transplantation procedure. Three of the patients are still alive after 13, 21, and 36 months. The others died between 12 days and 28 months after transplantation.

**METHODS**

Liver replacements were performed in seven patients who had alpha-1-antitrypsin deficiency disease. One of these cases has been reported previously.<sup>14</sup> Phenotypes for alpha-1-antitrypsin (Pi) were determined by means of acid-starch electrophoresis followed by crossed immunoelectrophoresis, as described elsewhere.<sup>15,16</sup> The nomenclature recommended by the International Alpha-1-antitrypsin Pi Committee was used.<sup>16</sup> The normal alpha-1-antitrypsin values were established by means of analysis of serum from 2213 Red Cross donors in Los Angeles, all with the phenotype MM. The range of 140 to 470 mg per 100 ml encompassed approximately two standard deviations from the mean.

**CASE REPORTS**

**Case 1**

This case has been reported in detail previously.<sup>14</sup> A 16-year-old girl with alpha-1-antitrypsin-deficiency liver disease had an orthotopic liver transplant in November, 1973. After transplantation her phenotype became MM, identical to the donor's. The graft functioned well for 1½ years but then deteriorated from chronic rejection during the next nine months. Retransplantation was carried out in February, 1976, and again there was change to the donor phenotype, in this case MZ. She died of infection five weeks after the operation.

**Case 2**

A 15-year-old boy who had had a "neonatal hepatitis" was found to have a deficiency of alpha-1-antitrypsin and cirrhosis with progressive liver failure. Liver transplantation was performed in November, 1976. After the operation pneumatosis cystoides intestinalis and rectal bleeding developed, necessitating a subtotal colectomy. He was discharged in April, 1977, and remains well with normal liver function three years later.

**Case 3**

A 25-year-old man had been well until his 17th year, when he had right-sided abdominal pain. At laparotomy, splenomegaly and cirrhosis (Laennec's) were diagnosed. In 1976, at 25 years of age, he had a second liver biopsy; the diagnosis of alpha-1-antitrypsin deficiency was established. Because of progressive hepatic failure, liver transplantation was carried out in December, 1976. Portal-vein thrombosis was found, requiring phlebotomy before an end-to-end portal-vein anastomosis could be attempted. After the operation he had progressive liver failure, and a second transplantation was performed 10 days later. The recipient portal vein was clotted, and the second graft was inserted without a portal inflow. The liver failure was not relieved, and he died two days after retransplantation.

**Case 4**

A five-year-old girl had been found to have alpha-1-antitrypsin deficiency shortly after birth. Hepatic transplantation was performed in February, 1978, because of cirrhosis and liver failure. An unsuspected tumor consisting of primitive hepatocytes without neoplastic stromal elements but with some features of hepatoblastoma was found. She has done well for 21 months and has normal liver function.

### Case 5

An eight-year-old boy had been found to have alpha-1-antitrypsin-deficiency disease in infancy. He had cirrhosis, portal hypertension, and recurrent bleeding from esophageal varices. Orthotopic liver transplantation was carried out in September, 1978. Initially, the liver functioned well, but he developed peritonitis and required three exploratory laparotomies. At first, only infected ascitic fluid was found, but later a left subphrenic abscess and multiple liver abscesses developed. He died in November, 1978, of sepsis.

### Case 6

An 11-year-old boy had been found to have "neonatal hepatitis" and was subsequently shown to have alpha-1-antitrypsin-deficiency disease. Because of progressive cirrhosis and ascites, he had an orthotopic liver transplant in October, 1978. He remains well with normal liver function 13 months after transplantation.

### Case 7

A 9½-year-old girl had been jaundiced shortly after birth and had progressive liver disease. She was thought to have cryptogenic cirrhosis but was later shown to be heterozygous for alpha-1-antitrypsin deficiency. Transplantation was performed in January, 1979. She did well for seven weeks after the operation and then died suddenly from a pulmonary embolus.

## RESULTS

The cases are summarized in Table 1. None of the patients had clinical or laboratory evidence of obstructive lung disease. Liver failure was the reason for transplantation. After transplantation, good initial graft function was obtained in all but Case 3. The final liver function obtained in each recipient is shown in Table 1. Several serum alpha-1-antitrypsin deter-

minations were available for each patient; representative individual values at specific times are shown in Table 1. After transplantation, the Pi types of the recipients matched those of the donors (Table 1).

## DISCUSSION

It is thought that the Pi alleles are inherited as co-dominant alleles, with each allele responsible for the production of its own type of alpha-1-antitrypsin. Chromosome 2 probably carries the Pi allele.<sup>17</sup> PiM is the most common allele, with a frequency that varies geographically. In the United States its frequency seems to be 0.938 to 0.950.<sup>18</sup> In people of European ancestry the Z allele has an incidence of 0.010 to 0.016.<sup>18</sup>

Although alpha-1-antitrypsin deficiency is typically associated with either obstructive lung disease or childhood cirrhosis, it has been reported in association with such diverse conditions as chronic pancreatitis,<sup>19</sup> glomerulonephritis,<sup>20</sup> rheumatoid arthritis,<sup>21</sup> subcutaneous and systemic panniculitis,<sup>22</sup> a connective-tissue disorder similar to the Ehlers-Danlos syndrome,<sup>23</sup> and a multisystemic fibrosis.<sup>24</sup>

The liver disease associated with alpha-1-antitrypsin deficiency usually presents as cholestatic jaundice within the first three or four months of life,<sup>25</sup> and accounts for approximately 40 per cent of all jaundice in the first two months of life.<sup>26</sup> The condition then usually abates until late childhood or early adolescence, when cirrhosis and liver failure appear. The severity of the later disease does not appear related to the degree of jaundice in the early months.<sup>27</sup> In a small

Table 1. Characteristics of Seven Patients Who Underwent Liver Transplantation for Treatment of Liver Disease with Alpha-1-Antitrypsin Deficiency.

CASE NO.	PHENOTYPE OF RECIPIENT BEFORE TRANSPLANTATION	PHENOTYPE OF DONOR	ALPHA-1-ANTITRYPSIN LEVEL*			BILIRUBIN†		PROTHROMBIN TIME‡		OUTCOME
			BEFORE TRANSPLANTATION	AFTER TRANSPLANTATION	(days)	BEFORE TRANSPLANTATION	AFTER TRANSPLANTATION	BEFORE TRANSPLANTATION	AFTER TRANSPLANTATION	
			mg per 100 ml			mg per 100 ml		sec		
1	ZZ	MM (1st) MZ (2d)	55	264	(540)§	27.0	0.6	21	12	Retransplantation after 27 mo. Died 5 wk later.
2	ZZ	MM	120	420	(180)	30.0	0.5	21	11	Alive & well 3 yr after transplantation.
3	ZZ	MM	55	140	(8)	41.0	25.0	19	20	Retransplantation after 10 days. Died 2 days later.
4	ZZ	MM	20	240	(70)	6.0	0.7	18	11	Alive & well 21 mo after transplantation.
5	ZZ	MM	55	390	(18)	10.0	11.0	14	23	Died of sepsis 54 days after transplantation.
6	ZZ	MM	30	360	(10 & 365)	4.5	0.3	12	11	Alive & well 13 mo after transplantation.
7	MZ	MM	40	190	(33)	60.0	1.0	30	10.5	Died from pulmonary emboli 53 days after transplantation.

\*The normal range is 140 to 470 mg per 100 ml.

†The normal value is 1.5 mg per 100 ml. Values after transplantation were the last analyses in the patients who died; the values are current for patients still alive.

‡In controls, the time varies from 10.5 to 12 seconds.

§Figures in parentheses denote number of days after first transplantation that analysis was performed.

number of patients resolution of the disease occurs.<sup>28</sup> Patients who do not develop the cholestatic pattern of disease are usually identified either when they present with hepatosplenomegaly or when a sibling is found to have the disease; without liver transplantation, they usually die in childhood or early adulthood from gastrointestinal bleeding or progressive liver failure.

Fagerhol and Laurell<sup>29</sup> were the first to determine the phenotypes of patients on the basis of antigen-antibody crossed electrophoresis. With this test many polymorphic variants have been identified. The important variant from the clinical standpoint is the homozygote PiZZ, in whom the level of alpha-1-antitrypsin is 1 to 15 per cent of normal. With the PiNull phenotype that was discovered by Talamo et al.<sup>30</sup> there is virtually no measurable alpha-1-antitrypsin, and there is an association with liver disease. The serum level of alpha-1-antitrypsin is less reduced with the PiMZ phenotype, and the clinical implications are less ominous.

The pathophysiology of alpha-1-antitrypsin disease is not understood, but much evidence points to the role of the liver in influencing serum levels of the alpha protein. The characteristic histologic feature of the liver of patients with the Z allele is a rounded cytoplasmic inclusion body, which is diastase resistant and positive for the periodic acid-Schiff stain. The inclusion body is found near the rough endoplasmic reticulum and can be shown to be alpha-1-antitrypsin by means of immunochemical methods.<sup>3</sup> What causes retention of this material in the liver is not known, but the explanation is almost certainly related to an abnormal glycoprotein portion of the alpha-1-antitrypsin molecule.<sup>31</sup> Early reports suggested that this abnormality in the glycoprotein was simply a deficiency of sialic acid,<sup>32</sup> but more recently it has been recognized that there is also an absence of galactose, an appreciable decrease in N-acetylglycosamine, and an almost twofold increase in mannose residues.<sup>33</sup>

It has been suggested that such biochemical abnormalities interfere with the transport of alpha-1-antitrypsin into the bloodstream from the interior of the hepatocyte where it is synthesized. Some of this abnormal alpha-1-antitrypsin could diffuse passively into the bloodstream, accounting for the fact that even in the deficient state alpha-1-antitrypsin is not totally absent from serum.

If the disease is primarily a failure in the transport of an abnormal protein, the nature of the enzymes responsible for the defective synthesis is unknown. Furthermore, the variability of clinical manifestations is perplexing. All persons with the Z allele accumulate alpha-1-antitrypsin in their hepatocytes, but apparently not all develop liver disease even with the PiZZ state, and hepatic complications are less common in persons with the single-Z-allele states PiMZ<sup>33</sup> and PiSZ.<sup>34</sup> Our heterozygous patient (Case 7) had very low levels of alpha-1-antitrypsin before transplantation (Table 1); her clinical course and liver histopathology were entirely consistent with the disease.

Although the precise pathophysiology of the disease has not been elucidated, the crucial role of the liver is well demonstrated by the data presented here. It has been shown previously in single-case reports both by us<sup>14</sup> and by Sharp<sup>35</sup> that the phenotype of the recipient becomes that of the donor; this more extensive series confirms that such a change occurs. Furthermore, data from prolonged follow-up are available on three patients who are still alive, and after periods of up to three years there has been no evidence of reversion to the original phenotype or of a diminution in the serum levels of alpha-1-antitrypsin. It seems, therefore, that although the manifestations of the disease are many and variable, the fundamental defect lies within the liver and can be corrected by means of liver transplantation. It remains to be shown that patients who have successful liver transplants are immune to the development of other complications of the disease, such as lung disease, but to date no other complications have been seen.

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