Early Recognition of Alpha-1 Antitrypsin Deficiency and Considerations for Liver Transplantation

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G&H What is the role of alpha-1 antitrypsin?

AT Alpha-1 antitrypsin, which is synthesized by the liver, keeps neutrophil elastase in check through inhibitory processes to prevent overexpression that will cause degradation of connective tissue in the lungs and, in turn, result in the development of emphysema.

G&H What is the underlying cause of alpha-1 antitrypsin deficiency?

AT Alpha-1 antitrypsin deficiency is the most common inherited metabolic disease of the liver and primarily affects individuals of white, Northern European descent. The incidence of this deficiency has been reported to be 1 in 2,000 individuals in the general population. Alpha-1 antitrypsin deficiency is an autosomal recessive disorder that results from a single point mutation in the \( \alpha_1 \)-antitrypsin gene. The mutation causes polymer formation in the endoplasmic reticulum of hepatocytes.

G&H Which organs are most often affected by alpha-1 antitrypsin deficiency? What clinical symptoms are associated with involvement of these organs?

AT Alpha-1 antitrypsin deficiency affects 2 vital organs, the liver and the lungs. It causes cirrhosis of the liver and emphysema of the lungs. The clinical symptoms differ from 1 patient to another and most commonly affect 1 of these 2 vital organs. Obstructive lung disease progresses to respiratory insufficiency. Cirrhosis is usually complicated by portal hypertension, ascites, gastrointestinal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatocellular carcinoma.

Unfortunately, patients with alpha-1 antitrypsin deficiency first present with portal hypertension; the other manifestations emerge later. Thus, these patients usually have low Model for End-Stage Liver Disease (MELD) scores until very late in the disease process. These patients usually have liver disease that is more advanced than their MELD scores indicate. In the future, it may be possible to include alpha-1 antitrypsin deficiency among the other metabolic diseases for which more MELD points are automatically authorized.

G&H How can clinicians ensure that this condition is promptly diagnosed? What signs and symptoms or patient-reported (or caregiver-reported) complaints should prompt a clinician to test for alpha-1 antitrypsin deficiency?

AT Clinical suspicion should arise when a patient who is younger than age 45 years presents with emphysema, when emphysema develops in a nonsmoker, or when no other cause can be identified for liver disease or hepatitis. This patient then can be tested for alpha-1 antitrypsin deficiency.

G&H Why is early recognition of alpha-1 antitrypsin deficiency important in relation to treatment?

AT Early recognition is important for 2 reasons. The first reason is to prevent, recognize, and treat early the
complications of the disease, which can include portal hypertension, encephalopathy, and tumors. In the future, early recognition may be important in order to provide alpha-1 antitrypsin enzyme replacement. The second reason is to advise the patient to avoid injurious habits, such as cigarette smoking and alcohol consumption, which can accelerate the disease process. Interestingly, patients who undergo liver transplantation for other causes have a higher incidence of being heterozygous for alpha-1 antitrypsin deficiency than the general population.

**G&H What are the pros and cons of liver transplantation as a treatment for patients with alpha-1 antitrypsin deficiency?**

**AT** The pros are that the function of the liver is restored to normal and the complications of the liver disease are reversed. A phenotypically healthy liver produces antitrypsin. Consequently, liver disease will not recur, and damage to the lungs is brought to an end. The con of this treatment strategy is that surgery carries a risk. At this time, the average 1-year survival rate is nearly 90%.

The risk of rejection is highest immediately after transplantation. Risk subsides with time, but there is a lifelong need for immunosuppressive medications. Research by several groups, including ours, has shown that it is possible to completely withdraw immunosuppressive medications 3 years or more following liver transplantation in 15–20% of patients. Unfortunately, it is not possible to predict who these patients are. Until now, they have been identified by trial and error.

Reduction of, and possibly withdrawal from, immunosuppressive medications is highly desirable because their presence predisposes the patient to infections and an increased incidence of cancers. Calcineurin inhibitors, which are the most commonly used medications, can cause kidney damage as well as neurotoxicity and diabetes. There has been a good deal of progress in the way that patients are treated after liver transplantation. Although the incidence of adverse events has been drastically reduced, they always remain a possible threat.

**G&H Given the pros and cons of surgical intervention, when should liver transplantation be considered for a patient with alpha-1 antitrypsin deficiency?**

**AT** Liver transplantation should be considered when there are complications of liver disease, such as bleeding, uncontrolled ascites or encephalopathy, muscle wasting, weakness, and the patient’s inability to live normally.

**G&H If patients need to be reviewed on a case-by-case basis for liver transplantation, how can the process be streamlined?**

**AT** There is a shortage of life-saving livers. As a result, they are distributed to the sickest patients first according to their MELD scores, which take into consideration the patients’ bilirubin levels, renal function, and coagulation. Patients who have end-stage disease need to be followed by their hepatologists in communication with a transplant center in order to determine the best time for them to be prepared for liver transplantation. Ideally, patients need to receive liver transplants just before they start to rapidly deteriorate. This may be difficult in patients with alpha-1 antitrypsin deficiency because they usually do not mount a high MELD score until very late in the course of their disease.

**G&H What is the prognosis for patients who undergo liver transplantation before significant complications develop?**

**AT** The prognosis is excellent and has been reported to be better than average. The 1-year survival rate is almost 90%. The 5-year survival rate is between 70% and 75% in most programs. One beneficial aspect about the use of liver transplantation for treatment of alpha-1 antitrypsin deficiency is that, as mentioned, it corrects the underlying problem, and the disease does not recur.

**G&H Have there been any large studies on liver transplantation in patients with alpha-1 antitrypsin deficiency?**

**AT** There has been a review of 567 adults and children in the United Network for Organ Sharing database who have undergone liver transplantation. In this review, 1% of all adult liver transplants and 4% of pediatric liver transplants were for treatment of alpha-1 antitrypsin deficiency. The 1-, 3-, and 5-year survival rates for these subsets of patients were 89%, 85%, and 83%, respectively, for adults and 92%, 90%, and 90%, respectively, for children. The rate of graft survival was 83%, 79%, and 77% for adults and 84%, 81%, and 78% for children. These results are better than average.

**G&H What further research is needed regarding liver transplantation specifically for treatment of alpha-1 antitrypsin deficiency?**

**AT** The incidence of liver transplants for treatment of alpha-1 antitrypsin deficiency is not that high; this indication perhaps makes up 1–2% of all liver transplantations that are performed. Further research would likely
focus on the development of gene therapies that can show that both the liver and lungs are protected from alpha-1 antitrypsin deficiency, such that patients will not need an organ transplant.

A proof-of-concept study in murine models suggested that correction of alpha-1 antitrypsin deficiency in the liver might be possible. The research team showed that technology using zinc finger nucleases and a moth-derived DNA transposon in human-induced pluripotent stem cells can correct a point mutation. Corrected hepatocytes were derived through this technology and were transplanted into the livers of live mice. After 14 days, the livers were harvested and examined. The researchers found that the transplanted human hepatocytes were distributed throughout the livers and were being integrated into the parenchyma; in addition, there was no evidence of tumorigenesis.

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