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Hereditary Angioedema Post-liver Transplant

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Abstract: Liver transplantation is the standard of care in managing different types of liver disorders as well as a variety of inborn errors of metabolism. In the latter scenario, the liver-based enzyme abnormality is corrected by transplantation. Although rare, liver transplantation may result in the transmission of an inborn error of metabolism to the recipient. The present report describes the development of acquired hereditary angioedema likely following liver transplantation, with notable improvement with the initiation of C1 esterase inhibitor replacement therapy. This case report describes another example of a hepatic synthesis defect that, although rare, but can be acquired from donor's livers.

Key Words: cholestatic liver disease, Hereditary angioedema, inborn errors of metabolism

INTRODUCTION

Liver transplantation is the standard of care for treating a variety of liver disorders, from end-stage chronic liver disease to acute hepatic failure. It is also increasingly utilized for several inborn errors of metabolism (IEM), where the liver-based enzyme abnormality is corrected by transplantation. Conversely, several cases report liver transplantation surreptitiously resulting in the transmission of an IEM to the recipient (1). The incidence of such acquired defects is unknown, and the outcome of such complications depends on the newly acquired condition. Here, we report an adolescent girl who was diagnosed with hereditary angioedema (HAE) following liver transplantation as an infant, thought to be acquired from the donor's liver.

CASE REPORT

A 16-year-old Caucasian girl received a whole graft liver transplant at 12 months of age for end-stage liver disease due to Progressive Familial Intrahepatic Cholestasis type 3. The donor was a neonate with anencephaly who died from global cerebral hypoxia.

She developed intermittent colicky abdominal pain at 7 years of age (6 years post-transplant). These episodes initially occurred at least weekly, would last for an hour, and then spontaneously settle. The pain was unrelated to meal times or exercise, and was not associated with nausea, vomiting, or diarrhea, but became increasingly frequent and disruptive in adolescence. She had no peripheral swelling or rashes. Investigations including full blood count, inflammatory markers, pancreatic enzymes, abdominal Doppler ultrasound, upper gastrointestinal endoscopy, and barium meal plus follow-through, were all normal. Her graft function remained stable throughout (aspartate aminotransferase 61 U/L (10–50), alanine aminotransferase of 41 U/L (0–45), and gamma-glutamyltransferase of 15 U/L (0–45), although serum albumin was slightly low at 32 g/L (35–51).

A complement C4 level was performed as a screen for C1 esterase inhibitor (C1-INH) deficiency. The C4 was low at 0.06 g/L (0.13–0.52); C3 level of 0.75 g/L (0.75–1.75) was normal. Subsequent C1-INH level was low at 0.12 g/L (0.19–0.40), with abnormal C1-INH function. These results confirmed a diagnosis of HAE. Treatment with C1-INH replacement therapy intravenously twice weekly (Berinert, 1000 unit) was commenced at age 14, resulting in complete resolution of her abdominal pain. The replacement therapy was weaned to weekly injections after 8 months and was ceased 4 months later. Recurrence of symptoms 4 months after cessation of therapy responded to the reinstitution of treatment. Currently, she has C1-INH therapy as needed. Intriguingly, the transaminases increased when C1-INH therapy was stopped, which then improved after restarting therapy (Fig. 1). Liver biopsy at the time did not show any significant evidence of acute cellular rejection.

Complement C4 level was performed as a screening test for C1-INH deficiency in our patient's parents; both had normal levels (0.17g/L for father and 0.29g/L for mother).

DISCUSSION

HAE is a rare autosomal dominant inherited disorder affecting 1:70,000 in the general population (2). It is classically due to mutations in SERPING1 which results in C1-esterase inhibitor (C1-INH) deficiency (3), although other genetic defects have been described. The disease is heterogeneous in presentation, ranging from abdominal pain to fatal upper airway obstruction (2). The severity and site of HAE attacks vary between patients and within the same patient, and often the diagnosis is delayed for 8–22 years from the first episode. Most children are reported to have mild disease, often escalating in adolescence (2) as what happened to our patient. HAE is characterized by episodic intense nonpruritic, nonpitting edema of the skin. Submucosal edema of the upper airways may cause airway obstruction, while submucosal edema of the bowel is associated with abdominal pain, nausea, vomiting, diarrhea, or even bowel obstruction (3). Screening for low complement 4 (C4) levels is readily available and a good marker for HAE, even between episodes. HAE can then be confirmed by C1-INH level and function testing (4).

C1-INH is mainly produced in the liver, with some suggestions that HAE be considered as a metabolic liver disease that could be cured by liver transplant (2). Conversely, liver involvement from HAE has been reported to present with elevated transaminase levels

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The patient and the family have consented to the publication of the case report.

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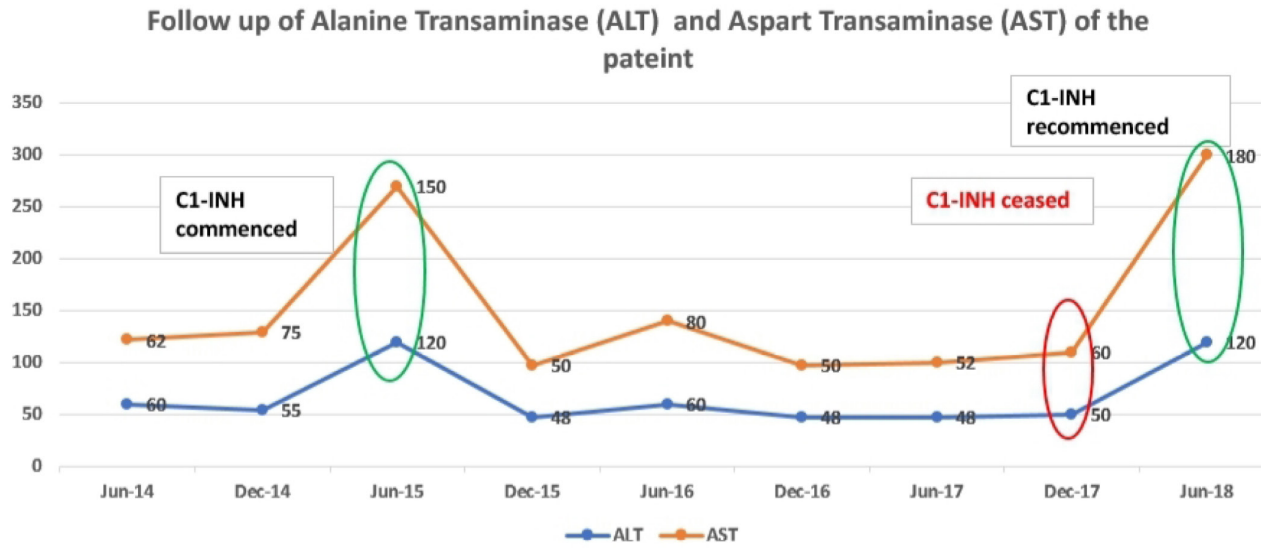

FIGURE 1. Improvement of liver transaminases with initiation of C1-INH therapy and the worsening after ceasing the C1-INH therapy. C1-INH, C1 esterase inhibitor.

and reversible parenchymal changes on ultrasound (5), which might possibly explain our patient's rise in transaminases with cessation of C1-INH therapy.

Although it has not been proven that the neonatal anencephalic donor had HAE, the strong suspicion is that our patient acquired it via liver transplantation since her parents do not have HAE. Two our knowledge, 2 other publications report cases of HAE acquired via liver transplant (6,7). One of them was published in an abstract form, reporting a series of 18 patients with acquired HAE, one of whom was via liver transplant (6). The second report was an adult who developed C1-INH deficiency after a liver transplant (7).

Our patient suffered debilitating symptoms with frequent and severe abdominal pain, translating into poor school attendance and emotional and behavioral disruption. The use of C1-INH replacement therapy significantly improved her symptoms. After a period of stability, she was able to wean down to "on demand" therapy.

This case report illustrates a potential rare complication of liver transplant which is hepatic synthesis defects or IEM that can be acquired via transplantation. Other cases are reported where liver transplantation has resulted in transmission of IEM to the recipient including one recent report from our unit (1). This complication is encountered if the donor has subtle or no symptoms. Other examples of such complications are hemophilia and alpha-1 antitrypsin deficiency (7). Our report highlights 2 main points: (1) the potential for transferring rare hepatic-derived synthetic proteins and enzymes through liver transplantation especially if the donor has subtle or no symptoms, and (2) recurrent severe abdominal pain in children can be a manifestation of HAE.

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