Donor-to-recipient transmission of factor XII deficiency by orthotopic liver transplantation

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ABSTRACT

Transmission of congenital clotting factor deficiencies following orthotopic liver transplantation is rare. There has been one reported case of donor-to-recipient transmission of factor XII deficiency in a transplant, and we report the second case.

KEYWORDS Coagulation; factor XII deficiency; liver transplantation; primary hyperoxaluria

rthotopic liver transplantation (OLT) may be associated with donor-transmitted deficiencies of coagulation factors due to lack of proteins synthesized by the liver. Some of these deficiencies do not have clinical significance, whereas others can lead to bleeding or thrombotic complications after OLT.

CASE REPORT

An 18-year-old man with type 1 primary hyperoxaluria received preemptive OLT in February 2017. Pre-OLT coagulation studies demonstrated a normal activated partial thromboplastin time (aPTT) of 29 seconds and international normalized ratio (INR) of 1. After successful OLT, the patient was maintained on mycophenolate mofetil and low-dose tacrolimus. After OLT, laboratory values revealed a persistently prolonged aPTT (>150 seconds), which was corrected on mixing study (indicating no inhibitors). He had not experienced any abnormal bleeding episodes or evidence of recurrent thrombosis. Results of factor analyses are shown in *Table 1*, demonstrating evidence of a severe factor XII deficiency. Because aPTT was normal before OLT, there was no indication to test for factor XII level. The liver donor was an 11-year-old healthy girl who had been shot in the head;

her aPTT was 132 seconds with a normal prothrombin time, platelet count, hemoglobin, and basic metabolic panel.

DISCUSSION

Factor XII deficiency is a rare autosomal recessive trait presenting with prolongation of the aPTT, without increased risk of bleeding.¹ Although thrombophilic tendency (venous thromboembolism and myocardial infarction) has been reported in patients with factor XII deficiency, this was not shown when studying families with factor XII deficiency.^{2–7} Therefore, the relation between factor XII deficiency and an increased risk of thrombosis is not well established.

This case represents the second reported case of donor-to-recipient transmission of factor XII deficiency after OLT. The first case was a 62-year-old man whose aPTT was normal prior to OLT and >240 seconds after OLT, without any abnormal bleeding episodes or evidence of recurrent thrombosis. Factor analysis confirmed severe factor XII deficiency with activity levels <2% (normal, 60%–160%); the liver donor's aPTT was 125 seconds on admission.⁸

Previous reports have documented donor-to-recipient transmission of protein C deficiency with dysfibrinogenemia, protein S, factor I (fibrinogen), factor VII, factor VIII, and

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Table 1. Coagulation evaluation for prolonged activated partial thromboplastin time after liver transplantation

Variable	Value	Reference range
Factor VIII activity (IU/mL)	2.00	0.60–1.50
Von Willebrand factor antigen (IU/mL)	>2.00	0.50–1.60
Von Willebrand factor assay (IU/mL)	>2.00	0.54–1.24
Factor IX activity (IU/mL)	1.73	0.60–1.50
Factor XI activity (IU/mL)	1.15	0.60–1.50
Factor XII activity (IU/mL)	<0.10	0.60–1.50
Prothrombin time (seconds)	13	12.3–14
International normalized ratio	0.9	0.9–1.1
aPTT (seconds)	>150	30.5–40.4
Thrombin time (seconds)	19	14–21
Anticardiolipin IgA	<9.4	0–12.0
Anticardiolipin IgG	<9.4	0–15.0
Anticardiolipin IgM	<9.4	0–12.5
Antiphosphatidylserine IgG (GPS U/mL)	4.69	0–10.9
Antiphosphatidylserine IgM (MPS U/mL)	8.68	0–24.9
Anti B2-glycoprotein I IgA (SAU)	<9.4	0–20.0
Anti B2-glycoprotein I IgG (SGU)	<9.4	0–20.0
Anti B2-glycoprotein I IgM (SMU)	<9.4	0–20.0
IgM (g/L)	0.82	0.4–2.3
IgG (g/L)	15.1	7.0–16.0

aPTT indicates activated partial thromboplastin time; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

factor XI deficiencies.^{9–16} Indeed, OLT may correct hepatic coagulation abnormalities, including protein C, protein S,¹⁰ hemophilia,^{17,18,19} and antithrombin III deficiencies. In contrast, transplantation of livers with a synthetic defect of a particular factor such as protein C, protein S, or antithrombin III deficiency may impose a coagulation abnormality upon these recipients that is not benign (*Table 2*).

The differential diagnosis of an isolated increase in aPTT (normal prothrombin time/INR and platelet count) and its clinical significance if acquired through transplantation is shown in *Table 3*. Etiological diagnosis of a prolonged aPTT requires a detailed interview for a personal and family history of bleeding, examination for evidence of recurrent or inappropriate bleeding, and additional testing. Failure of the aPTT to correct with a mixing study suggests a lupus anticoagulant or acquired factor VIII or factor IX deficiency due to antibodies. The specific defect can be diagnosed by testing of factor levels. The transmission of other coagulation factor deficiencies causing a prolonged aPTT does not result in clinically significant problems in the recipient (*Table 2*). Consultation with a hematologist will help ensure that a potentially serious condition is not transmitted through transplantation, even in the limited time available for donor evaluation.

This case highlights the ever-present risk of donor-to-recipient disease transmission during transplantation. To our knowledge, this is the second reported case of factor XII deficiency acquired through OLT. The extremely low prevalence of coagulation factor deficiency caused by OLT does not justify routine screening of donors in the absence of abnormal prothrombin time or aPTT. Although the presence of

Table 2. Reports of donor-to-recipient transmission of coagulation defect after liver transplantation

Defect	Donor	Complication	Manifestation	Year	Reference
Protein S	Not reported	Multiple thrombotic events	Isolated protein S after second transplant (normal in first and third liver transplant)	1999	Schuetze and Linenberger ¹⁰
Protein C	Thrombosis	Thrombosis	Low protein C	1995	Cransac et al ⁹
Factor I (fibrinogen)	Prolonged PT	Cellulitis	High PT/INR	2017	Milani et al ¹⁵
Factor VII	History of two CVAs	None	Prolonged PT, low factor VII	1999	Guy et al ¹¹
Factor XI		None, retransplant?	Prolonged aPTT, low factor XI	2015	Yankol et al ¹⁴
Factor XI	Prolonged aPTT	None	Prolonged aPTT, absolute deficiency of factor XI	1991	Clarkson et al ¹³
Factor VIII inhibitor (hemophilia A)	Known hemophilia A, died of intracranial bleeding	Bleeding	Factor VIII inhibitor not responding to therapy requiring retransplantation	2003	Hisatake et al ¹²
Factor VIII (hemophilia B)	Prolonged aPTT, two large thigh hematomas	Postoperative abdominal bleeding, hematoma after dental extraction	Factor VIII deficiency (11%), prolonged aPTT	2016	Brunetta et al ¹⁶
Factor XII	Prolonged aPTT	None	Prolonged aPTT, low factor XII	2006	Osborn et al ⁸
Factor XII	Prolonged aPTT	None	Prolonged aPTT, low factor XII	2017	This case

aPTT indicates activated partial thromboplastin time; CVA, cerebrovascular accident; INR, international normalized ratio; PT, prothrombin time.

Table 3. Differential diagnosis of prolonged activated partial thromboplastin time^a

Etiology	Significance if transmitted
Heparin use	Not applicable
Lupus anticoagulation	Clotting
Factor VIII deficiency	Bleeding
Factor IX deficiency	Bleeding
Von Willebrand's disease	No significance
Factor XI deficiency	Bleeding
Factor XII deficiency	No significance
Prekallikrein deficiency	No significance

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an abnormal aPTT could suggest a severe clotting factor deficiency, this test does not detect many other coagulation defects. However, a detailed evaluation of the donor and the family may not be possible in the short interval available before the donor liver is implanted. As in this case of factor XII deficiency transmission, the recipient's need for transplantation and the minimal effect of transmission of disease warrants use of the donor organ for transplantation.

Both cases reported were diagnosed following OLT despite having prolonged aPTT in both donors on initial presentation. Proper identification prior to donation may prevent the transmission of coagulation defects that can adversely affect outcomes.

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