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CASE REPORT

Liver transplantation as a novel strategy for resolution of congenital afibrinogenemia in a pediatric patient

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Abstract

Fibrinogen replacement therapy is a treatment mainstay for patients with afibrinogenemia and significant bleeding. A male infant with congenital afibrinogenemia and several spontaneous hemarthroses commenced cryoprecipitate prophylaxis but developed severe urticarial reactions. He transitioned to a human fibrinogen concentrate (HFC) (RiaSTAP®, CSL Behring; 70 mg/kg biweekly) but continued experiencing hemarthroses (estimated annualized bleeding rate [ABR]: 5-6) and severe anaphylactic reactions, despite pre- and postinfusion medications. Following switching to a new HFC (Fibryga®, Octapharma; 50 mg/kg biweekly), ABR was 0-1 with no further infusion reactions. Aged 9 years, because of limited quality of life, development of obesity and fatty liver disease, he underwent orthotopic liver transplant (OLT) under HFC coverage. Pharmacokinetic analysis guided presurgical fibrinogen levels > 150 mg/dL. No intraoperative HFC infusions were required. Coagulation profile and fibrinogen levels remained within normal limits during and posttransplant. To our knowledge, this is the first pediatric report of afibrinogenemia successfully treated with OLT.

KEYWORDS
afibrinogenemia, child, fibrinogen, liver transplantation, pediatrics

1 | INTRODUCTION

Fibrinogen plays a central role in hemostasis, specifically in clot formation and stabilization.[1] Congenital fibrinogen disorders are rare, affecting ~1 to 2 in every million people worldwide.[2] Although healthy individuals have a plasma fibrinogen level ranging from 150 to 450 mg/dL, those with afibrinogenemia have undetectable levels of circulating fibrinogen.[3,4] Symptoms, including frequent and/or severe bleeding episodes, typically present in the neonatal period.[5,6] A study of 100 patients with congenital fibrinogen deficiency found that among patients with severe deficiency, hemarthroses were the most common type of bleed, and came with a risk of progressive musculoskeletal damage.[2]

In patients with congenital afibrinogenemia, fibrinogen replacement therapy is recommended in case of acute hemorrhagic episodes and/or when undergoing surgical procedures.[7,8] Although not routinely used, long-term prophylaxis is recommended for those presenting with recurrent and severe bleeding episodes, and for female patients during pregnancy.[9]

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Fibrinogen replacement therapy has traditionally been provided with cryoprecipitate.[10,11] Cryoprecipitate has a variable fibrinogen concentration and, because it is pooled from multiple donors, is associated with safety concerns, including risk of pathogen transmission and transfusion-related reactions.[10] Human fibrinogen concentrates (HFC) have therefore become the preferred option, with advantages including greater purity, faster preparation and administration, improved safety because of viral inactivation, and a less variable fibrinogen concentration.

A growing body of evidence shows HFCs to be safe and effective[11-15]; however, allergic or hypersensitivity reactions, seen with other coagulation factor replacement therapies, constitute a potential risk for patients on HFCs or cryoprecipitate. These can range from mild episodes characterized by the appearance of transient skin rashes or urticaria to more severe, and even life-threatening anaphylactic events. These complications impact the physician's ability to provide adequate treatment for these patients.

In this report, we describe the resolution of afibrinogenemia and restoration of normal hemostasis after orthotopic liver transplantation (OLT) in a pediatric patient with congenital afibrinogenemia including a history of severe allergic reactions to different fibrinogen replacement therapies.

Essentials

- Fibrinogen replacement is used in patients with afibrinogenemia and a severe bleeding phenotype.
- A child with afibrinogenemia had anaphylactic reactions to fibrinogen replacement therapies.
- A new human fibrinogen concentrate improved tolerability and reduced the frequency of bleeds.
- Orthotopic liver transplant was successful in reversing the patient's fibrinogen disorder.

2 | CASE PRESENTATION

A Hispanic male presented at 2 days of life with mild oozing on one foot after a routine heel stick. Bleeding spontaneously resolved and the patient was ultimately discharged. Five days later, his right thigh became progressively swollen and discolored at the intramuscular vitamin K injection site, for which he was taken to the hospital for evaluation. Initial laboratory analyses revealed elevated prothrombin time (PT; 120 seconds) and activated partial thromboplastin time (APTT; 245 seconds), indicating an abnormal coagulation profile. Factor V and X activity levels were within normal limits (97 and 105 IU/mL, respectively); however, serum fibrinogen activity level was below the detectable laboratory cutoff of 50 mg/dL. Genetic testing revealed a compound heterozygosity for NM_000508.4:c.532C>T (p.Arg178Ter) and NM_000508.4:c.1103del (p.Gly368GlufsTer53) mutation variants in the FGA gene within chromosome 4, with the former mutation not described previously in patients with congenital fibrinogen disorders. The patient was subsequently diagnosed with congenital afibrinogenemia. He was admitted to the pediatric intensive care unit for management of an acute, severe intramuscular hematoma and treated with cryoprecipitate infusions.

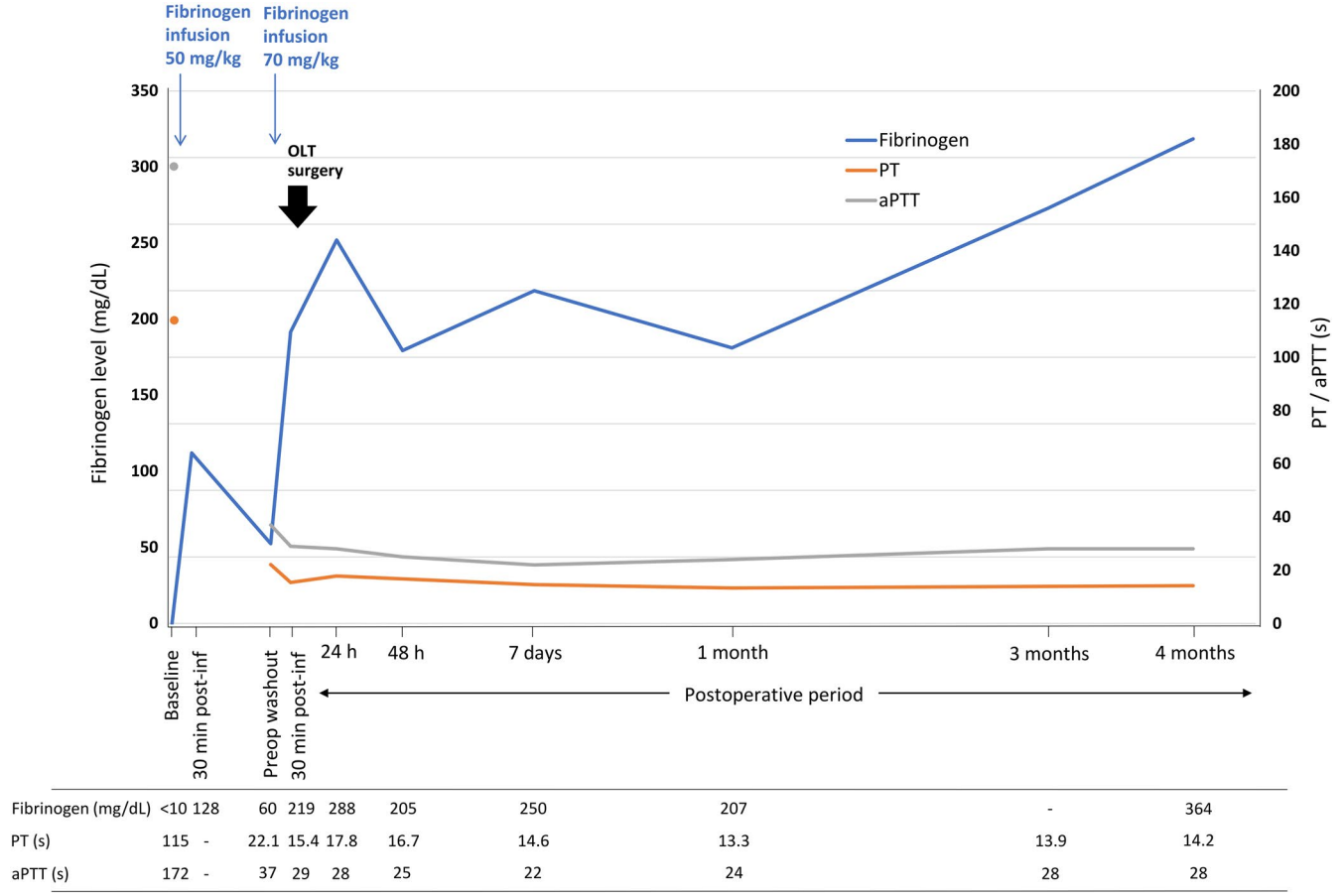
Following hospital discharge, the patient presented with two episodes of spontaneous hemarthroses affecting his right ankle and knee, requiring further cryoprecipitate infusions. Because of this bleeding phenotype, a prophylactic regimen was initiated with cryoprecipitate administered once every 2 weeks. At 2 years of age, the patient started developing severe urticarial skin reactions related to cryoprecipitate infusion for which he was transitioned to prophylactic treatment with HFC (RiaSTAP®, CSL Behring LLC) at a dose of 70 mg/kg every 4 weeks. The regimen was eventually adjusted to 50 mg/kg every 2 weeks because of recurrent spontaneous hemarthroses.

Despite prophylactic treatment with HFC, the patient experienced an average annualized bleeding rate (ABR) of five to six bleeds over a period of 3 years. He also started to experience severe anaphylactic reactions similar to those experienced while on cryoprecipitate, characterized by the sudden onset of generalized hives and angioedema a few hours after the end of HFC infusions. Episodes persisted despite the use of premedication regimens with acetaminophen and diphenhydramine and postinfusion corticosteroids and antihistamines. At 7 years old, to avoid infusion-related reactions, the patient switched to a new HFC (Fibryga) at a dose of 50 mg/kg every 2 weeks. On this regimen, better bleeding control was achieved, with an ABR of 0 to 1. The patient continued to receive premedication with acetaminophen and diphenhydramine, with no further reported infusion-related adverse reactions.

When the patient was 9 years old, he was referred for OLT evaluation because of severe limitations to his quality of life, including the need for intravenous infusions. He was also found to have steatosis secondary to obesity (body mass index 29.5) because of his sedentary lifestyle. After careful review of his medical history, he was considered to be an adequate candidate because of his underlying coagulation disorder and potential for achieving a “cure” for his condition.

Before OLT, pharmacokinetics of his current HFC were evaluated to determine the hemostatic regimen for use during the transplant. The patient's baseline fibrinogen level was <10 mg/dL, with a 30-minute peak level of 128 mg/dL after receiving his usual 50 mg/kg dose of HFC. Based on these results, a higher dose (4000 mg equal to 70 mg/kg) was recommended to achieve an optimal presurgical level of at least 150 mg/dL.

On the day of surgery, after a 6-day washout period, the patient's preoperative fibrinogen level was 60 mg/dL and both PT and APTT were prolonged. Eight hours before transplant, he received 4000 mg HFC as calculated previously. Thirty-minutes postinfusion, fibrinogen level, PT, and APTT were corrected. No bleeding complications were reported during the surgery and no further HFC infusions were required. Upon completion of surgery, Doppler ultrasound confirmed normal blood flow in the hepatic artery, portal vein, and hepatic veins.



Fibrinogen (mg/dL)	<10	128	60	219	288	205	250	207	-	364
PT (s)	115	-	22.1	15.4	17.8	16.7	14.6	13.3	13.9	14.2
aPTT (s)	172	-	37	29	28	25	22	24	28	28

FIGURE 1 Fibrinogen levels and coagulation parameters pre-operatively and up to 4 mo after liver transplant. APTT, activated partial thromboplastin time; inf, infusion; OLT, orthotopic liver transplant; PT, prothrombin time

Liver explant showed fatty infiltration with bridging fibrosis (stage 3). Twenty-four hours posttransplant, the patient's coagulation profile and fibrinogen level remained within normal limits (Figure 1). After an uneventful posttransplant course, the patient was discharged in stable condition 8 days after OLT. Four months after transplant, the patient's fibrinogen level was 364 mg/dL with a normal coagulation profile and graft function. He has not required further hospitalizations, remains on a full diet, is attending school, and has increased his physical activity with subsequent body mass index improvement to 27.5.

3 | DISCUSSION

Fibrinogen replacement therapy is the mainstay treatment for patients with afibrinogenemia and a significant bleeding phenotype. Allergic or hypersensitivity reactions, although rare, are one of the most frequently reported adverse events related to these therapies.[13] Results from a phase 3 clinical study investigating the efficacy and safety of an HFC reported a single mild allergic skin reaction in one of 25 enrolled patients who received a total of 131 infusions.[11] A postmarketing study examined HFC safety over 27 years and found 20 possible cases of hypersensitivity reactions, equating to one in every 32 600 doses.[13] The tolerability of fibrinogen concentrates is most likely patient-dependent and, as seen in this case, may be attributed to differences in purification processes between fibrinogen products; for example, the new HFC used in this case is the only HFC to include solvent/detergent treatment and nanofiltration with a 20-nm filter as purification steps in its manufacturing process.[16] In our case, the patient was able to continue receiving HFC infusions with the new HFC with a premedication regimen, after experiencing adverse events with cryoprecipitate and another HFC.

To our knowledge, this case represents the only reported pediatric patient with congenital afibrinogenemia successfully treated with OLT, with only four reported cases to date in adult patients.[17-20] These patients also suffered from other liver-related comorbidities including Budd-Chiari syndrome, liver cirrhosis, and hepatocellular carcinoma. Liver transplantation has been very successful in treating children with end-stage liver disease, offering the opportunity for a long, healthy life. In our case, the decision to undergo liver transplantation was based primarily on the potential for improving the patient's quality of life, considering his relatively young age and the presence of nonalcoholic fatty liver disease secondary to his sedentary lifestyle.

Surgical care of patients with afibrinogenemia is extremely complex, with no current consensus on the optimal approach to balance

the risks of bleeding, poor wound healing, and provoked thrombosis. A prospective, multinational phase 3 study recently provided evidence of the efficacy of a new HFC for surgical prophylaxis in patients with congenital fibrinogen deficiency.[11] Nine patients received surgical prophylaxis for a total of 12 surgeries. Intraoperative and postoperative hemostatic prophylaxis was rated as success in 100% of cases, and no intraoperative or postoperative transfusions were necessary, demonstrating that HFC is effective as surgical prophylaxis in this patient population. Our study provides further evidence for the effectiveness and tolerability of this HFC for surgical prophylaxis.

4 | CONCLUSION

To our knowledge, this report represents the first case of a pediatric patient with congenital afibrinogenemia successfully treated with OLT, performed under the cover of HFC. Before OLT, switching to the new HFC for long-term prophylaxis resulted in reduction of the frequency of bleeds and improved tolerability vs other fibrinogen-containing products, which had previously caused severe anaphylactic reactions.

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CONFLICT OF INTEREST

Dr. Corrales-Medina receives research support from Bayer, Takeda, and the American Thrombosis and Hemostasis Network (ATHN); he is an advisory board member for Octapharma, Bayer, and Takeda. Dr. De Angulo receives research support from Gradalis and Biomarck and speaker honorarium from Octapharma, Sanofi, and Amgen. The remaining authors have no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

Fernando F. Corrales-Medina conceived the study. Fernando F. Corrales-Medina and Guillermo De Angulo contributed to data interpretation, data collection, and writing. Tamir Miloh, Candelaria O'Farrell, David M. Andrews, and Akin Tekin contributed to data collection and analysis. All authors reviewed the manuscript for intellectual content and approved the final submitted version.

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