

Blood, Sweat, and Fears: A Novel Mutation Associated With Anaphylaxis and Nonresponse in a Patient With Afibrinogenemia

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Summary: Congenital afibrinogenemia is a rare disorder characterized by a lack of detectable fibrinogen. The mainstay of treatment for acute bleeding episodes or perioperative management is replacement with fibrinogen concentrate or fibrinogen-containing blood products. The development of neutralizing antibodies and severe allergic reactions to fibrinogen replacement is rarely reported in afibrinogenemia patients. Here the treatment regimen is described for a 6-year-old girl with a severe allergic reaction to multiple fibrinogen-containing products who became refractory to treatment because of a presumed inhibitor to fibrinogen.

Key Words: afibrinogenemia, anaphylaxis, nonresponse, fibrinogen replacement therapy

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Congenital afibrinogenemia is a life-threatening disorder with an estimated prevalence of one per million.¹ Currently available treatments include fibrinogen concentrate or fibrinogen-containing blood products for acute bleeding. Options are limited for patients who do not respond to replacement therapy, leading to potentially fatal outcomes. The development of neutralizing antibodies is a recognized complication of replacement therapy for hemophilia but is rarely reported in afibrinogenemia.^{2,3} In addition, severe allergic reactions can be seen in patients with severe hemophilia B during their early exposures to factor IX replacement, but are rare in afibrinogenemia.^{2,4} We describe the strategy used to treat a 6-year-old girl with severe allergic reactions to fibrinogen products and diminished response to factor replacement.

CASE PRESENTATION

A 21-month-old, African-American female individual initially presented with a cheek hematoma and prolonged prothrombin time, activated partial thromboplastin time, thrombin time, and reptilase time with undetectable levels of functional and antigenic fibrinogen, consistent with afibrinogenemia. Upon further questioning, her medical history was significant for prolonged bleeding from her umbilical stump and easy bruising especially at sites of her

vaccinations. Her symptoms and coagulation studies improved after 1 infusion of 2 units of cryoprecipitate. Another infusion of 2 units of cryoprecipitate was given before discharge to ensure hemostasis was achieved. After this initial presentation, she had several episodes of prolonged epistaxis, trauma-related hematomas in her right cheek and lower extremity, and a spontaneous small left subdural hemorrhage. For the first few bleeding events, she received human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH, Marburg, Germany)⁵ 70 mg/kg with initial improvement in her symptoms. However, 6 months later during her third human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) infusion for a muscle hematoma, she developed rigors and fevers. Despite premedication with acetaminophen and diphenhydramine for subsequent infusions, she continued to have chills and fever with both human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) and cryoprecipitate. Hydrocortisone was then added to her premedication regimen and the infusion rate was decreased, which improved her symptoms, and her hematomas also resolved.

The patient was then lost to follow-up and presented again at 6 years old when she developed a mandibular hematoma after trauma. Given her previous reactions, she received human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) through slow infusion after premedication with hydrocortisone, diphenhydramine, ranitidine, ondansetron, and acetaminophen. However, even with this regimen, she developed an anaphylactic reaction during her human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) infusion manifesting as a rash, chills, lip and facial swelling, and emesis. Thus, Allergy and Immunology was consulted to devise a desensitization regimen to human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) (Table 1). Our patient tolerated desensitization well, leading to symptom improvement and an increase in her functional fibrinogen level. Two weeks later, she presented with a left tibial fracture and was again desensitized and tolerated human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH). However, her fibrinogen level drawn 1 hour after the infusion of her second dose of human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) at 70 mg/kg daily (weight 20 kg) remained undetectable (< 15 mg/dL). This raised concern for the development of an inhibitor; however, mixing studies could not confirm the presence of a neutralizing antibody as our patient's fibrinogen level and thrombin time was normalized after mixing with normal pooled plasma (Table 2). The presence of a non-neutralizing antibody was also considered, although there was no measurable increase in fibrinogen immediately after human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) administration. Further, with D-dimer within the normal reference range of quantification (0.23 µg/mL fibrinogen equivalent unit, reference range <0.44 µg/mL fibrinogen

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TABLE 1. Desensitization Protocol for Administration of Human Fibrinogen Concentrate (RiaSTAP)

Premedication	RiaSTAP Concentration (mg/mL)	Rate (mL/h)	Time (min)	Cumulative Dose Administered (mg)
Diphenhydramine 1 mg/kg IV	0.2	2	15	0.1
Ranitidine 150 mg po	0.2	5	15	0.35
Hydrocortisone 1-2 mg/kg IV	0.2	10	15	0.85
Acetaminophen 10 mg/kg po	0.2	20	15	1.85
Cetirizine 5 mg po	2	5	15	4.35
Montelukast 5 mg po	2	10	15	9.35
	2	20	15	19.35
	2	40	15	39.35
	20	10	15	89.35
	20	20	15	289.35
	20	40	15	389.35
	20	60	30.5	1000 (70 mg/kg)

Premedication was given 30 to 60 minutes before human fibrinogen concentrate (RiaSTAP) infusion. Desensitization utilized 3 different solutions with increasing concentrations, which were used in a stepwise manner. If infusion was well tolerated, rate and/or concentration were increased at 15-minutes intervals.

equivalent unit) and lack of acute blood loss, increased exogenous fibrinogen consumption of the transfused human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) was also unlikely. Because our patient was clinically improving with decreased knee pain and swelling, she was discharged home with close follow-up.

However, 3 weeks later, radiograph imaging of her left knee revealed increasing bone lucency and soft tissue swelling concerning for tibial osteomyelitis. Orthopedic surgery recommended bone biopsy and debridement; however, because of her poor response to fibrinogen replacement, surgery was deferred until a plan for fibrinogen replacement could be made. She initially received human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) at 50 mg/kg through the prior desensitization plan followed by dose escalation to 100 mg/kg but continued to have undetectable functional fibrinogen level and no clot formation identified on rotational thromboelastometry (ROTEM). As mixing studies (Table 2) showed correction of coagulation defects with the addition of fresh frozen plasma (FFP), replacement of fibrinogen with FFP and cryoprecipitate transfusions was also attempted, with no measurable response. The patient continued empiric treatment with a fibrinogen-containing product daily, for example, 5 units of cryoprecipitate or 10 mL/kg of FFP, to maintain allergic desensitization despite the lack of improvement in laboratory values.

After 1 week of empiric replacement with no detectable response, the patient developed severe headache and hypertension with magnetic resonance imaging findings of posterior

reversible encephalopathy syndrome. She was transferred to the intensive care unit for continuous blood pressure control and subsequently suffered a seizure, after which a head computerized tomography scan revealed an acute subarachnoid hemorrhage. Given the urgent need for hemostasis, she was treated with continuous cryoprecipitate transfusion of 5 units every 4 hours in addition to tranexamic acid 10 mg/kg every 6 hours. Seven hours after initiation of this regimen, fibrinogen levels became detectable at 70 mg/dL and continued to rise to normal range (> 150 mg/dL). ROTEMs also showed improved clot formation. She received tranexamic acid with continuous cryoprecipitate transfusion for 36 hours, then intermittent cryoprecipitate transfusions, and eventually an alternative human fibrinogen concentrate (Fibryga, OctaPharma, Vienna, Austria)⁶ at 50 to 100 mg/kg intermittently to maintain a fibrinogen level above 150 mg/dL (Fig. 1). Her subarachnoid hemorrhage stabilized, and she was able to successfully undergo incision and drainage of the tibial abscess.

DISCUSSION

Congenital afibrinogenemia is an autosomal-recessive disease characterized by undetectable fibrinogen activity and antigen with thrombotic and bleeding risk. Bleeding can be treated with

TABLE 2. Mixing Study

	Fibrinogen (mg/dL)		Thrombin Time (s)	
	Initial	Post 2-hour Incubation	Initial	Post 2-hour Incubation
NPP	319	323	16.6	17.4
Our patient	<15	<15	>120	>120
Our patient mixed 1:1 with NPP	148	138	19.8	20.5

Fibrinogen level and thrombin time of NPP, our patient's plasma, and our patient's plasma mixed with NPP 1:1, at initial time of assay and after a 2-hour incubation period. Our patient's fibrinogen level and thrombin time normalized after mixture with NPP, making the development of a neutralizing inhibitor to fibrinogen unlikely.

NPP indicates normal pooled plasma.

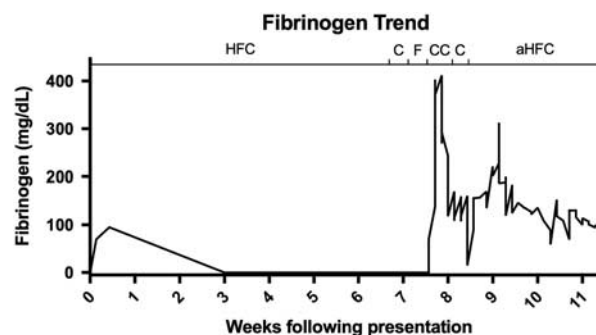


FIGURE 1. Fibrinogen levels during replacement therapy with different fibrinogen-containing products beginning from the presentation for mandibular hematoma. aHFC indicates alternative human fibrinogen concentrate (Fibryga) at various dosing (range, 50 to 100 mg/kg); C, intermittent cryoprecipitate; CC, continuous cryoprecipitate given 5 units every 4 hours with tranexamic acid 50 mg/kg every 6 hours; F, fresh frozen plasma; HFC, human fibrinogen concentrate (RiaSTAP) at various dosing (range 50 mg/kg to 100 mg/kg).

transfusions (eg, FFP, cryoprecipitate), fibrinogen concentrate, or antifibrinolytic agents with concurrent fibrinogen supplementation. Fibrinogen concentrates are considered the treatments of choice because of their improved safety, smaller infusion volume, rapid onset of action, and consistent fibrinogen content.⁷

Our patient's course was complicated by both allergic reactions after her third dose of human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) and 2 treatment days with cryoprecipitate and a lack of laboratory response to all fibrinogen products. A 2015 systematic review of 27 years of pharmacovigilance data on human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) showed 20 of 106 reported adverse events (18.9%) were possible hypersensitivity reactions.⁸ The most common reported adverse reaction was hypersensitivity (8 cases), followed by anaphylaxis (5 cases) and shock (5 cases). No desensitization regimen was reported in these cases as most symptoms resolved without intervention. Our patient developed an allergic reaction after her third dose of human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH) with temporary improvement after the addition of premedications and a decreased infusion rate. Her symptoms progressed with subsequent fibrinogen exposure requiring the development of a desensitization regimen (Table 1). This regimen allowed her to tolerate fibrinogen replacement without further reactions.

Another complication in this patient was her lack of measurable response to different fibrinogen products that occurred after her 20th infusion of human fibrinogen concentrate (RiaSTAP, CSL Behring GmbH), possibly consistent with the development of a neutralizing antibody, which is not commonly seen in patients with fibrinogen disorders. A systematic review describing the clinical course of 22 prior patients with various fibrinogen disorders described only 2 patients with suspected antibodies, only one of which was confirmed.⁹ The first case report was published in 1961 by de Vries et al,² who described a 16-year-old female individual with congenital afibrinogenemia who was found to have circulating antifibrinogen antibodies after receiving 9 human plasma fraction I infusions (containing fibrinogen). She ultimately died from anaphylactic shock during a blood transfusion. The authors conclude that this antibody was specific to fibrinogen because of its precipitation reaction with purified human fibrinogen, its negative reaction with supernatant of human fibrinogen clotted with thrombin, and its reaction with purified bovine fibrinogen concentrate. Although she had a history of rheumatic valvular heart disease and bacterial endocarditis, the autopsy indicated that the mitral valvular lesions were made up of agglutinated platelets, and the vegetations that were seen were not rheumatic in nature but more consistent with degenerative verrucal endocarditis, which is considered a hypersensitivity reaction. The second case report was published in 1999 by Henselmans et al,³ detailing the course of a 22-year-old woman with congenital afibrinogenemia who developed recurrent hemiparesis secondary to intracranial hemorrhage. Fibrinogen replacement therapy was initiated with cryoprecipitate; however, she developed worsening hemiparesis and severe headache with undetectable fibrinogen levels while receiving regular cryoprecipitate infusions. Furthermore, these infusions were complicated by recurrent pulmonary emboli requiring treatment with low molecular-weight heparin. She was then switched to a higher dosing scheme with a different fibrinogen concentrate (Hemocomplettan P) with an increase in her fibrinogen levels and no further bleeding or thromboembolic events. In this case, fibrinogen antibodies were tested for but not detected.

Our patient eventually achieved detectable fibrinogen levels after repeated daily exposure and continuous

fibrinogen infusion. One possible explanation is that repeated exposure to fibrinogen induced immune tolerance and suppression of antibody formation, similar to immune tolerance induction utilized in hemophilia management.¹⁰ In addition, the concurrent use of tranexamic acid with continuous cryoprecipitate may have contributed to her rise in fibrinogen levels by inhibiting the antifibrinolytic pathway, although this is unlikely to account for the entire increase. After detectable levels were achieved, her fibrinogen replacement needs remained high. Typical dosing in patients with fibrinogen disorders utilizes replacement dosing every 2 to 5 days to maintain fibrinogen levels >100 mg/dL,⁹ whereas our patient required replacement every 6 to 12 hours to achieve the same effect. Dose recommendations for alternative human fibrinogen concentrate (Fibryga, OctaPharma), the primary replacement product used in our patient, anticipate that 50 mg/kg would raise the plasma fibrinogen level by 90 mg/dL, however, our patient's plasma level only rose by 50 mg/dL. This may reflect a partial response to immune tolerization, or variation in the pharmacokinetics of alternative human fibrinogen concentrate (Fibryga, OctaPharma) in the pediatric population, as fibrinogen concentrates are known to have increased clearance and decreased half-life in children. A recent population pharmacokinetic study of fibrinogen concentrate confirmed these findings and also showed that in patients <40 kg, 1 g/kg of fibrinogen concentrate only raises plasma fibrinogen by 19 versus the 23 g/L increase seen with the same dosing in patients >40 kg.¹¹ Furthermore, multiple studies have also shown variability in prophylactic dosing of fibrinogen replacement in pediatric patients less than 12 years of age, reflecting the likelihood of pharmacokinetic variability across age subgroups.^{12,13}

Fibrinogen is a hexameric glycoprotein encoded by 3 genes clustered on chromosome 4—*FGA*, *FGB*, and *FGG*. Mutations causing afibrinogenemia have been detected in all 3 genes, with the majority being found in *FGA*.¹⁴ Genetic testing on our patient revealed heterozygosity for 2 novel mutations within *FGG* (6.04 kb deletion of exons 1 to 4 and sequence variant c.852-1G>A). Although large deletions in hemophilias A and B have been associated with inhibitor development and/or anaphylaxis, this association is not often seen in large deletions (>1 kb) causing afibrinogenemia.^{15–17} Our patient is heterozygous for both a large deletion and a sequence variant in *FGG*, and even though these mutations have not been previously described, they are likely pathogenic and may contribute to her diminished response to fibrinogen replacement and/or anaphylaxis. Therefore, genetic testing may be a useful diagnostic and prognostic tool that could help predict clinical response to fibrinogen replacement in congenital afibrinogenemia.

In conclusion, the management of bleeding in congenital afibrinogenemia may be complicated by severe allergic reactions and a lack of response to fibrinogen replacement. Our patient successfully underwent surgical intervention and stabilization of an intracranial hemorrhage using an extensive desensitization protocol followed by frequent or continuous exposure to fibrinogen replacement products. Two novel *FGG* mutations found in our patient have not previously been reported in the literature. These mutations are likely to be pathogenic and could contribute to the management challenges in this case.

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