Chronic Subdural Hematoma in a Patient With Congenital Afibrinogenemia Successfully Treated With Fibrinogen Replacement

—Case Report—

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Abstract

A 37-year-old woman with congenital afibrinogenemia presented with chronic subdural hematoma (CSDH) manifesting as severe headache, nausea, and somnolence after a minor head trauma. Brain computed tomography scans showed a right subdural hematoma associated with midline shift. Laboratory studies showed prolongation of prothrombin time, activated partial thromboplastin time, and undetectably low level of fibrinogen. Until the present episode, she had received plasma-derived fibrinogen concentrate around menstruation and pregnancy. She had also suffered from spinal cord infarction due to vertebral artery occlusion. Burr-hole evacuation and drainage of CSDH was successfully performed using fibrinogen concentrate. The development of CSDH with afibrinogenemia is very rare. Although the past repeated administrations of fibrinogen concentrate were suspected to generate CSDH, paradoxical thrombotic complications caused by upregulation of prothrombin activation, thrombin generation, and growth factors released from platelets might be related to the development of CSDH with congenital afibrinogenemia.

Key words: afibrinogenemia, intracerebral hemorrhage, chronic subdural hematoma, fibrinogen, coagulation disorder
Introduction

Congenital afibrinogenemia is a rare condition, most often associated with autosomal recessive disorder characterized by the complete absence of detectable fibrinogen. The estimated incidence is one per million in the general population. The majority of patients have truncating mutations in the fibrinogen alpha-chain (FGA) gene which causes defective fibrinogen synthesis. Hemorrhagic manifestations vary from minimal to catastrophic, including fatal umbilical cord hemorrhage at birth, and spontaneous mucosal or intracranial hemorrhage in the neonatal period. In later life, the disorder may be associated with bleeding from the mucosal surfaces, hemorrhage into the muscle and joints, spontaneous abortions, and spontaneous splenic rupture. A small number of cases of spontaneous intracerebral bleeding in adults have been reported, but none of chronic subdural hematoma (CSDH) with congenital afibrinogenemia. Here we report a case of CSDH in a 37-year-old woman that was successfully treated by burr-hole evacuation with administration of fibrinogen concentrate.

Case Report

A 37-year-old woman was transferred to our hospital because of severe headache, nausea, and somnolence. She had hit her head on the corner of a television during a domestic argument a few weeks previously. She had been diagnosed with congenital afibrinogenemia at 6 days after birth. She had experienced occasional episodes of minor bleeding, and had received fresh frozen plasma (FFP) or plasma-derived fibrinogen concentrate around menstruation. Brain computed tomography (CT) showed a right CSDH with associated midline shift (Fig. 1A). Before the current episode, she had suffered from right ovarian hemorrhage at age 16 years and underwent right adnexitomy. She gave birth to a child through successful pregnancy and cesarean section at age 32 years in our hospital. At that time, she was diagnosed with mutations of the FGA gene. She had also suffered spinal cord infarction due to occlusion of the extracranial right vertebral artery at age 34 years (Fig. 2) and was treated conservatively. Since then, she had been taking eicosapentaenoic acid to prevent the recurrence of stroke.

On admission, no additional neurological deficits were observed other than numbness on the left due to the spinal cord infarction. Laboratory studies showed prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) and the plasma fibrinogen was undetectable. After infusion of 3 g of plasma-derived fibrinogen concentrate (Fibrinogen HT; Benesis, Osaka), PT was 12.6 seconds (69%), aPTT was 29.4 seconds (74%), and fibrinogen level was 93 mg/dl. She was treated by ordinary burr-hole evacuation surgery and the hematoma was co-

![Fig. 1](image1) Brain computed tomography scans on admission (A) and one day after the burr-hole evacuation surgery (B) showing the right chronic subdural hematoma had disappeared and associated midline shift was resolved after the surgery.

![Fig. 2](image2) Sagittal T2-weighted magnetic resonance image of the brain stem and upper cervical cord 3 years before the present episode showing a hyperintense lesion in the upper cervical cord (A), and magnetic resonance angiogram showing occlusion of the right vertebral artery (B).

![Fig. 3](image3) Brain magnetic resonance images one week after the burr-hole hematoma irrigation showing a thin layer of subdural hematoma appearing isointense on T1-weighted (A), hyperintense on T2-weighted (B), and slightly hyperintense on fluid-attenuated inversion recovery images (C), and enhancement of the outer membrane of the hematoma under the dura mater of the right hemisphere on T1-weighted images with gadolinium (D, E).
vered with thin outer membrane which was compatible with CSDH. Hemostasis during the procedure was not difficult using bipolar diathermy. After the hematoma evacuation, headache and nausea disappeared, and the patient became alert and awake.

Brain CT showed disappearance of the hematoma one day after the surgery (Fig. 1B). The draining catheter was removed one day after the surgery. A total of 200 ml of bloody fluid was drained during that period. We administered 1 g fibrinogen concentrate daily for the first 3 days, then 2 g fibrinogen concentrate every other day until 7 days. The serum fibrinogen levels increased to 55–70 mg/dl. Tranexamic acid 3 g was infused during the first day. Brain magnetic resonance imaging one week after the surgery showed a thin layer of subdural hematoma appearing isointense on T1-weighted imaging, hyperintense on T2-weighted imaging, and slightly hyperintense on fluid-attenuated inversion recovery imaging (Fig. 3). The outer membrane of the hematoma under the dura mater of the right hemisphere was enhanced by gadolinium administration. The postoperative course was uneventful and brain CT detected no recurrence of CSDH at 6 months after the treatment.

Discussion

Fibrinogen is a 340 kDa protein that is synthesized in the liver, has a plasma concentration of approximately 150–350 mg/dl, and a half-life of around 4 days. Fibrinogen is important in clot formation through conversion to fibrin by the action of thrombin. Fibrinogen is also important in primary hemostasis for normal platelet aggregation. Afibrinogenemia refers to the total absence of fibrinogen and has an estimated prevalence 1:1000000. The three separate genes encoding FGA, fibrinogen beta-chain, and fibrinogen gamma-chain are involved in causing afibrinogenemia. Homozygous deletion approximately of 11 kb of the FGA gene was first identified as a cause of inherited afibrinogenemia in four members of a Swiss family.

The most common manifestations of afibrinogenemia are umbilical stump bleeding at birth and bleeding from the mucosal surface. Although intracranial hemorrhage can present with rare coagulation disorder, life-threatening intracranial hemorrhage is infrequent in adults, with only 3 cases reported. Two case reports described spontaneous intracerebral hemorrhages which were treated conservatively with the administration of fibrinogen concentrates and the one case report described acute epidural and subdural hematomas which were successfully evacuated via craniotomies using fibrinogen concentrate.

We successfully treated a congenital afibrinogenemic woman with CSDH with burr-hole evacuation and postoperative drainage using fibrinogen concentrate. In patients with coagulation disorder, abnormal clot formation may lead to an aberrant, such as isodense, appearance of bleeding on brain CT. Therefore, it is important to know that isodense subdural hematoma might not be chronic but acute subdural hematoma in a patient with afibrinogenemia. In our case, we diagnosed CSDH because the symptoms gradually became worse after minor head injury.

Our patient had suffered spinal cord infarction caused by right vertebral artery occlusion. We did not confirm whether it was caused by thrombosis or vertebral artery dissection. Although spinal cord infarction is rare, a small number of cases of spinal cord infarction and vertebral artery dissection with afibrinogenemia have been reported. Spontaneous thrombotic complications have also been reported in patients with afibrinogenemia. Fibrin down-regulates thrombin generation by reducing prothrombin activation, and also binds and sequesters thrombin. This anti-thrombin activity of fibrin (antithrombin I) is absent in patients with afibrinogenemia, who exhibit increased prothrombin activation and thrombin generation. Free thrombin stimulates platelets to release several growth factors that induce vascular smooth muscle cell proliferation and intimal hyperplasia. We suspected that the past repeated administrations of fibrinogen concentrate had been the cause of the CSDH in our patient with afibrinogenemia, so coagulation abnormalities might contribute to the development of CSDH.

Fibrinogen concentrate is the treatment of choice for significant bleeding in patients with afibrinogenemia. The fibrinogen level should be maintained above 1 g/l until hemostasis is secure and above 0.5 g/l until wound healing is complete. The suggested amount of fibrinogen is: dose (g) = desired increment in g/l × plasma volume, where the plasma volume is 0.07 × (1 – hematocrit) × weight (kg). Therefore, a dose of 30 mg/kg would be required to raise the fibrinogen concentration up to 1 g/l. We used 3 g of fibrinogen concentrate before the surgery and 1 g of fibrinogen concentrate for the first 3 days, then 2 g of fibrinogen concentrate every other day until 7 days, which was sufficient for hemostasis of the surgical procedure, wound healing, and prevention of the recurrence of CSDH. The alternative protocol is 3 g of fibrinogen concentrate before the surgery and 1 g of fibrinogen concentrate every day until 7 days. Cryoprecipitate and FFP represent alternative replacement therapies and should be given only in emergencies when fibrinogen concentrate is not available. Fibrin glue may be useful to treat superficial wounds. Tranexamic acid may be useful to prevent bleeding for surgical procedures, but should be used with caution in patients with a history of thrombosis because the risk of thrombosis may increase.

The rare heritable coagulation disorders, such as disorders of fibrinogen and deficiencies of prothrombin and coagulation factors, may present significant difficulties in diagnosis and management. Reliable information about clinical management is scarce, but the general recommended protocols for the more common hemostatic disorders are also applicable to the rare coagulation disorders. Recently, a review with guidelines for the management of the rare coagulation disorders was published.

In conclusion, the present case of CSDH in a patient with congenital afibrinogenemia was successfully treated with a burr-hole evacuation and fibrinogen replacement. Although rare coagulation disorders are uncommon, we...
should be aware of the past histories and the family histories of the patients, and the results of the laboratory tests of PT, aPTT, and fibrinogen before neurosurgical procedures to prevent catastrophic bleeding risks in affected individuals.

References


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