Middle Cerebral Arterial Thrombosis in a Patient with Hypofibrinogenemia, 5 Days After rFVIIa and FFP Infusion

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Summary: A 13-year-old female patient is presented who had hypofibrinogenemia diagnosed as von Willebrand disease at 5 years of age at another hospital. She was admitted to the department of pediatric hematology with a severe headache, vomiting, and progressive right flaccid hemiplegia and lethargy. Contrast-enhanced computed tomography scan showed subdural hematoma in posterior parietal region of the brain and impending cerebellar herniation. She was given fresh-frozen plasma (FFP) and then activated factor VII (rFVIIa), $80 \mu g/kg$ was infused for replacement of von Willebrand

factor. The subdural hematoma was emergently drained. The results of coagulation tests before infusion of FFP and rFVIIa revealed hypofibrinogenemia, and FFP was given every 48 hours. The patient recovered dramatically in a few days. Five days after rFVIIa infusion, a magnetic resonance angiography—proven right middle cerebral arterial thrombosis developed. It is an interesting point of discussion whether the middle cerebral arterial thrombosis was provoked as a consequence of rFVIIa and FFP infusion.

Key Words: Hypofibrinogenemia—rFVIIa—FFP—Thrombosis.

The two principal ligands known to mediate platelet adhesion and aggregation are von Willebrand factor (vWF) and fibrinogen (Fg) whose importance is underlined by the bleeding disorders associated with their respective deficiencies, i.e., von Willebrand disease (vWD) and afibrinogenemia. vWD is the most common inherited bleeding disorder. Congenital afibrinogenemia, described in approximately 150 families, also leads to a bleeding diathesis that can be fatal in approximately one third of such patients (1.2).

Another aspect of vWF and Fg are their likely involvement in thrombosis. Thrombosis in coronary or cerebral arteries is the major cause of morbidity and mortality worldwide (1).

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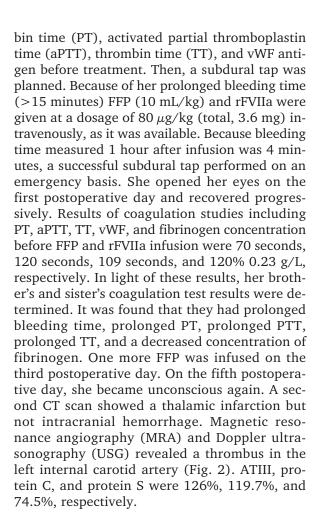
We report a case of inherited hypofibrinogenemia, with middle cerebral arterial thrombosis 5 days after recombinant activated factor VII (rFVIIa) and fresh-frozen plasma (FFP) infusion to stop intracranial hemorrhage.

CASE REPORT

The patient was a 13-year-old girl diagnosed as having vWD at 5 years of age at a different hospital. She was born to second-degree consanguineous parent with a family history of vWD. She had a 6-year-old sister and an 8-year-old brother, in whom intracranial hemorrhage developed 1 year previously. The patient was admitted to our hospital with a serious headache and vomiting for 2 days. Physical examination revealed unconsciousness, right facial paralysis, and flaccid hemiparesis. Cranial contrast computed tomography (CT) scan showed subdural hematoma in the posterior parietal region of the brain and a shift of the intracranial contents (Fig. 1). Blood samples were obtained for prothrom-



FIG. 1. Subdural hematoma and a shift of the intracranial contents on CT (at admission to hospital).



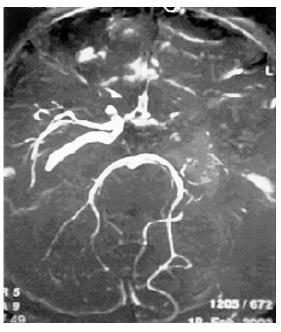


FIG. 2. Infarction area due to obstruction of the middle cerebral artery on MRA.

Physical and supportive therapy were advised for the follow-up period. One year after admission to our hospital, physical examination revealed weakness in the right lower and upper extremities (muscle strength 4/5). Walking and talking disorders did not recover completely.

DISCUSSION

Afibrinogemia is usually responsible for hemorrhagic diathesis. The prolonged bleeding time may be obtained in an afibrinogenemic patient but unexpected ischemic lesions are intriguing (3-5). A congenital deficiency state known to predispose to thrombosis was found in 27.2% of patients. Of these, most were due to deficiencies of protein C (9.2%), protein S (7.6%), ATIII (5%), or to increased plasma PAI-1 concentration (3.1%) (3). Lak and colleagues reported that spontaneous thrombotic episodes developed in two young patients, and three women had recurrent abortions among 55 patients with inherited afibrinogenemia (6). Dupoy and colleagues reported ischemic lesions of the feet related to severe stenosis of the iliac and hypogastric arteries (5). Thrombotic complications are observed frequently in afibrinogenemic patients following replacement of fibrinogen. Therefore, we used a single infusion of fibrinogen at lower doses than usually recommended in afibrinogemic patients (7,8). Our patient was diagnosed as having vWD at 5 years of age in a different hospital, and had severe subdural hematoma and a shift of cerebral content on admission to the hospital. She had a prolonged bleeding time and FFP and rFVIIa (80 μg/kg) were transfused on an emergent basis for subdural tap before results of other coagulation tests were available. Then, our patient was diagnosed as having inherited hypofibrinogenemia based on a family history of bleeding and prolonged PT, aPTT, and TT (109 seconds), and decreased fibrinogen concentration (0.23 g/L). Because the patient lost consciousness again on the fifth postoperative day, it was thought to be caused by recurrent intracranial hemorrhage. But, MRA and Doppler ultrasonography (USG) revealed a thrombus in the left internal carotid artery. The values of protein C, protein S, and ATIII were within normal limits.

Three independent risk factors for arterial thrombotic disease have been reported; namely, fibrinogen, coagulation factor VII, and plasminogen activator inhibitor type 1 (9). FVIIa has been successfully used in patients with hemophilia with inhibitors to factor VIII or IX. As in the case of use of rFVIIa, hemostasis is started by the formation of a complex between tissue factor and activated factor VII following trauma or injury. In vitro studies have shown that rFVIIa can bind to the activated platelet surface with low affinity and induce the thrombin burst for hemostasis. It has also been used for patients with other congenital or acquired functional platelet disorders including Bernard-Soulier syndrome, platelet type vWD, and thrombocytopathies due to uremia or myelodysplastic syndrome (10).

In conclusion, we could not definitively state the cause of the thrombotic complication in this patient with hypofibrinogenemia; it may have been caused by multiple infusion of FFP and rFVIIa.

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