Recurrent Spontaneous Intracerebral Hemorrhage in a Congenitally Afibrinogenemic Patient: Diagnostic Pitfalls and Therapeutic Options

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Background—Coagulation disorders can cause intracerebral bleeding that may be difficult to detect since subsequent aberrant clot formation may mask early detection. This is an important pitfall because, when diagnosed early, bleeding in these patients is treatable.

Case Description—A patient with congenital afibrinogenemia presented with recurrent hemiparesis. Spontaneous intracerebral hemorrhage was diagnosed, despite an initial negative CT scan. Diagnosis, therapy, and complications of therapy are discussed.

Conclusions—Intracerebral hemorrhage must be strongly suspected in any patient with a coagulation disorder presenting with matching clinical symptoms. Therapy must be installed immediately, before additional investigations, and should be continued even when initial neuroimaging is negative. (Stroke. 1999;30:2479-2482.)

Key Words: afibrinogenemia ■ fibrinogen ■ follow-up studies ■ intracerebral hemorrhage ■ prevention, primary

Congenital afibrinogenemia is a rare autosomal recessively inherited disorder, with an estimated incidence of 2 per million births. The condition is characterized by a complete absence of fibrinogen (coagulation factor I), thus impairing fibrin clot formation. Clinical manifestations range from minor to severe bleeding, often with long asymptomatic intervals. Bleeding may occur spontaneously as well as related to trauma. The incidence of spontaneous intracerebral bleeding in patients with afibrinogenemia is unknown; a small number of case reports have been published. In an older (1971) review, Egbring et al reported intracerebral hemorrhage in 13% of afibrinogenemic patients. Of 12 deaths, 4 were due to intracerebral bleeding.

Case Report

Our patient was diagnosed with congenital afibrinogenemia when she presented with umbilical bleeding in 1972 (prothrombin time and activated partial thromboplastin time immeasurably long; no measurable fibrinogen with both functional [hemagglutination inhibition] and immunological [electrophoresis according to Laucell] assays; no detectable fibrinogen [immunofluorescence] on platelets; platelet aggregation diminished with ADP, absent with adrenalin). Until 1991, only incidental minor bleeding episodes occurred. Menstrual blood loss was normal. In 1991, a bleeding ovarian cyst caused hypovolemic shock, necessitating surgery. Oral contraception was started to inhibit ovulation.

In April 1994, the patient was first seen in the neurology outpatient clinic for examination of a subacutely developed right-sided dropped foot with a diffuse subjective dysesthesia of the right distal leg. CT scanning of the brain was normal, and therefore a bleeding episode was considered excluded. Six days later, she was admitted to the hospital because right hemiparesis had developed. Findings at neurological examination were as follows: global motor weakness assessed on the Medical Research Council (MRC) scale (Table) as grade 4 of the right arm, grade 3 of the proximal right leg, and grade 1 of the distal right leg; a right homonymous hemianopsia; disturbance of pain, light touch, and temperature sense lateral from the tibia diffusely extending over the dorsum and lateral margin of the right foot; and a Babinski reflex on the right. Since at first bleeding was considered to be excluded, other diagnoses were considered, including peroneus neuropathy, multiple sclerosis, partial transverse myelitis, vasculitis, infection, and epilepsy. However, MRI of the cervical vertebral column, electromyography, evoked potentials (visual, brain stem auditory, motor, and somatosensory), immunohistochemical and serological investigations of cerebrospinal fluid and blood samples, and an electroencephalogram (EEG) did not support one of these. Since the a priori chance of intracerebral bleeding was, after all, high, and at that point no alternative diagnosis was likely, substitution therapy was started and continued for an arbitrary time of 2.5 weeks after...
installation (Figure 1; fibrinogen measured by functional assay [Claus method]). The patient was discharged with residual hemiparesis (right arm, grade 4; proximal right leg, grade 4; distal right leg, grade 1). MRI scan at discharge (Figure 2) showed several patchy high-signal areas in the left semioval and parieto-occipital regions on the T2-weighted images; these lesions were hypointense on the T1-weighted images and were considered to exclude a recent bleeding episode. Two weeks later, the patient was readmitted with an acute worsening of hemiparesis (right arm, grade 1; proximal right leg, grade 4; distal right leg, grade 1). Substitution therapy with cryoprecipitate was started immediately after neurological examination. Subsequent MRI and CT scanning demonstrated recent hemorrhage in the left occipital lobe (Figure 3) and left caudate nucleus. Digital subtraction angiography of the vertebral and carotid arteries showed no malformations and a normal venous system. While still on substitution therapy, the patient complained of chest pain.

**Clinical Presentation, Results of Neurological Examination, and Additional Investigations**

<table>
<thead>
<tr>
<th>Date</th>
<th>Presentation</th>
<th>Additional Neurological Investigations</th>
<th>Right Arm</th>
<th>Right Leg, Proximal</th>
<th>Right Leg, Distal</th>
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<tr>
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EMG indicates electromyography; CVC, cervical vertebral column; MEP, motor evoked potentials; VEP, visual evoked potentials; BAEP, brain stem auditory evoked potentials; SEP, somatosensory evoked potentials; LP, lumbar puncture; and DSA, digital subtraction angiography.

**Figure 1.** Intensity and duration of substitution therapy. PE indicates pulmonary embolism; LMWH, low-molecular-weight heparin.

*Fibrinogen level undetectable on admission.*
Multiple pulmonary emboli were demonstrated by lung perfusion scintigraphy. Treatment with low-molecular-weight heparin (15,000 anti–factor Xa activity [aXa] units twice daily) was started. It was stopped at 3 months, while administration of cryoprecipitate was continued at a maintenance dose (Figure 1). Evaluation of antithrombin III, protein C, protein S, plasminogen, and activated protein C ratio showed normal values. The patient made a complete neurological recovery, except for a grade 2 paresis of the foot dorsiflexors (right arm, grade 5; proximal right leg, grade 5; distal right leg, grade 2).

In October 1994, the patient was readmitted with severe headache in the absence of papilledema or retinal hemorrhages. The plasma fibrinogen level was undetectably low, despite maintained substitution with cryoprecipitate. A CT scan of the brain showed no hemorrhage. The headache subsided, and the patient was discharged with dose adjustment of the cryoprecipitate prophylaxis. One month later, she presented with similar headache with normal fundus, concomitant dysarthria, and recurrence of the hemiparesis (right arm, grade 4; proximal right leg, grade 4; distal right leg, grade 2); symptoms had been present for 24 hours. Plasma fibrinogen level was again undetectably low. No recent bleeding was seen on a cerebral CT scan. EEG evaluation did not reveal epileptic activity. Cryoprecipitate infusion, given immediately on admission, was complicated by recurrent pulmonary embolism within 24 hours; treatment with low-molecular-weight heparin was restarted. Fibrinogen antibodies were tested for but could not be detected; a search for thrombophilic defects was negative. At discharge, the paresis of the dorsiflexors of the right foot persisted (right arm, grade 5; proximal right leg, grade 5; distal right leg, grade 2). The low-molecular-weight heparin dosage was tapered at 6 months and stopped at 1 year. Fibrinogen substitution has been continued in a home treatment setting until now. In February 1995, cryoprecipitate was replaced by a heat-treated purified fibrinogen concentrate (Hemocomplettan P, Hoechst). In June 1995, substitution was lowered from 4.5 to 3.5 g fibrinogen twice per week. Plasma recovery of fibrinogen has been measured repeatedly: top levels were approximately 1.7 g/L and trough levels approximately 0.75 g/L. Recurrent bleeding or thromboembolic events have not been suspected after November 1994. The patient has remained negative for antibodies to the human immunodeficiency and hepatitis C viruses. In September 1995, generalized tonic-clonic epileptic seizures were confirmed by epileptic activity on EEG. Phenytoin was started at a dose of 250 mg daily. Outpatient evaluation in October 1995 revealed a marginal right hemihypesthesia and a slight regression of the dorsiflexor paresis that has persisted thus far (right arm, grade 5; proximal right leg, grade 5; distal right leg, grade 4). EEG recordings showed bilateral epileptic activity generalizing over both hemispheres.

**Discussion**

**Diagnosis**

Congenital afibrinogenemia is a rare disorder associated with a high risk of spontaneous intracerebral bleeding. The present case illustrates how unfamiliarity with the disorder may lead to a misinterpretation of the clinical presentation and unnecessary, even contraindicated diagnostic interventions. The diagnosis of intracerebral bleeding as the most likely explanation for the progressive hemiparesis was at first rejected because of an inconclusive CT scan. In patients with a coagulation disorder, abnormal clot formation may lead to an aberrant, eg, isodense appearance of intraparenchymal bleeding on MRI or CT scan. This may explain the absence of detectable bleeding on the initial scans in our patient. Moreover, bleeding was only detected after substitution therapy was given. We therefore hypothesize that administration of fibrinogen leads to a more normal clot composition, which facilitates detection of the bleeding. On the other hand, early
hemostasis by prompt substitution may limit extension of a bleeding episode that consequently remains too small to be detected by CT scan.

An alternative explanation for the negative CT scans may be that there were no hemorrhages at all but rather infarctions or venous thrombosis. This supposition is highly unlikely because of (1) the a priori high risk of cerebral bleeding in afibrinogenemia, (2) the improvement of signs and symptoms observed on substitution therapy, and (3) the recording of 1 intracerebral hemorrhage on CT scan.

Treatment
We gave therapeutic cryoprecipitate infusions to obtain fibrinogen levels of ≥1 g/L (normal range, 1.7 to 3.5 g/L) (Figure 1). This level is usually effective in achieving normal hemostasis. However, since the actual half-life of fibrinogen varies individually, dose adjustments must be made. No data are available on the effective prophylactic levels of fibrinogen. Since cerebral bleeding occurred at a maintenance dose of fibrinogen of 5 g once per week, a dosing scheme of 3.5 g fibrinogen twice weekly was installed. This resulted in fibrinogen levels >0.75 g/L, and no further bleeding occurred. Whether this was cause and consequence or natural history can be debated. Although experience with secondary prophylactic treatment in these patients is very limited,7 we believe that recurrent intracerebral hemorrhage within a time span of several months justifies prolongation of substitution therapy. A formal assessment of the optimal duration of therapy is not realistic in view of the low prevalence of the disorder.

The benefit of continuation of prophylactic fibrinogen substitution should be weighted against the risk of possible complications. In our patient, pulmonary embolism followed substitution therapy with unpurified fibrinogen, ie, cryoprecipitate. Similar findings have been reported in other afibrinogenemia.8,9 Hypercoagulability may be induced by an excess of coagulation factors (factor VIII, von Willebrand factor) due to the infusion of cryoprecipitate or by contamination of the cryoprecipitate with activated coagulation factors.8,10 The continued use of an oral contraceptive may have played a part in this patient; this drug was not stopped to prevent recurrence of ovulation bleeding. Another possibility that we have considered is concomitant thrombophilic defects in the patient, but no lupus anticoagulans or deficiencies of antithrombin, protein C, protein S, or plasminogen could be demonstrated. The risk of thrombosis induced by the presently available, highly purified fibrinogen concentrate is theoretically far smaller. Under frequent monitoring of the fibrinogen level during substitution therapy, neither bleeding events nor thromboembolic complications were observed during a follow-up period of >4 years.

Conclusion
In conclusion, spontaneous intracerebral bleeding must be strongly suspected when an afibrinogenemic patient presents with matching clinical symptoms. CT imaging may fail to detect the hemorrhage, possibly because of abnormal clot forming. Since intracerebral hemorrhage is a life-threatening event, we recommend that substitution therapy be installed promptly at presentation, before additional investigations are made. Early treatment may facilitate detection of the bleeding. In contrast to the earlier described complications of the use of impure concentrates such as cryoprecipitate, long-term secondary prophylaxis with purified fibrinogen in our patient appeared to be both effective and safe.

References
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