Spontaneous chronic subdural hematomas in young adults with a deficiency in coagulation factor XIII

Report of three cases

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Chronic SDHs are lesions that generally occur in elderly patients following head trauma and are characterized by a fluid blood collection or blood products in the subdural space. A negative history of head trauma exists in 20 to 52% of these patients. The incidence of CSH is 58.1 cases/100,000 persons/year in patients older than 65 years and 3.4 cases/100,000 persons/year in those younger than 65 years. In patients with symptomatic chronic SDHs surgical evacuation is the treatment of choice. It is well known that congenital coagulopathy (for example, hemophilia), acquired hematological diseases, and anticoagulation treatment may support the formation and maintenance of chronic SDHs and may influence outcome. To our knowledge the association between an FXIII deficit and chronic SDH has not been described in the literature. An FXIII deficiency may be hereditary or acquired. Hereditary FXIII deficiency is an extremely rare disorder, with an estimated prevalence of only 1 case/5 million individuals. An FXIII deficiency results in a lifelong bleeding tendency.

We report on three cases of chronic SDH in young adults with an FXIII deficiency.

Clinical Material and Methods

In all cases the diagnosis of an FXIII deficiency was made using the urea clot lysis test in combination with a chromogenic quantitative assay. A 5M urea solubility test is based on the chromogenic substrates technique, which offers a very sensible and specific quantitative assay of FXIII levels. The FXIII concentrate was administered in a single 50-U/kg intravenous dose of fibrogammin P (Centeon Aventis, Marburg, Germany). The halflife of FXIII is 6 to 19 days, allowing for the administration of replacement therapy every 4 to 6 weeks if necessary. None of our patients needed additional injections. Furthermore, no adverse effect, allergic reaction, or viral transmission occurred.

Case Reports

Case 1

History and Examination. This 30-year-old man presented with a 1-month history of progressive frontal headache. He had no significant medical history. Physical examination revealed no neurological deficit. The T1-weighted magnetic resonance imaging studies demonstrated bilateral chronic SDH in the parietal region as hyperintense fluid collection related to a high water content (Fig. 1A). Platelet count, PT, and bleeding time were normal. The aPTT was slightly prolonged to 36 seconds. Considering the patient’s young age, clinical history, and aPTT value, the coagulation factors were evaluated and deemed to be normal (factors II, V, VII, IX, X, XI, XII, and FXI), but FXIII deficiency is indicated. Fibrin clot stability is tested by clotting 0.2 ml plasma with 0.2 ml calcium chloride and incubating one clot in 3 ml NaCl solution and the other in 3 ml 5M urea for 24 hours at 37˚C (98.6˚F). Lysis of the clot incubated in the NaCl solution indicates excessive fibrinolysis, whereas lysis of the clot incubated in urea indicates FXIII deficiency. The clot will dissolve within 24 hours if less than 1% FXIII is present. An FXIII activity greater than 60% is considered normal. The chromogenic test is based on the chromogenic substrates technique, which offers a very sensible and specific quantitative assay of FXIII levels.

Abbreviations used in this paper: aPTT = activated partial thromboplastin time; CT = computerized tomography; FXIII = factor XIII; PT = prothrombin time; SDH = subdural hematoma.
Spontaneous chronic subdural hematomas and factor XIII

VIIIc, VIIIr, IX, X, and XI and fibrinogen) except for the FXIII level, which had 25% activity.

The main causes of acquired FXIII deficiency and Lupus anticoagulant syndrome were excluded. Liver disease was excluded on the basis of normal biochemical parameters of liver functionality (aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, alkaline phosphatase, and PT) and on the basis of a negative history of liver disease. Malarial infection was excluded on the basis of a negative history and the absence of suggestive symptoms (no intermittent fever). Inflammatory bowel disease was excluded based on a negative history and the absence of enteric symptoms. Normal results of other coagulation tests excluded the possibility of an FXIII deficiency caused by other coagulopathy (for example, hypofibrinogenemia or dysfibrinogenemia). A disseminated intravascular coagulopathy was excluded on the basis of normal PT, fibrinogen, fibrinogen degradation product, and antithrombin III plasma levels and a normal platelet count. A Henoch–Schonlein purpura was excluded based on the absence of suggestive symptomatology (that is, abdominal pain, renal damage, arthritis, and purpura).

Treatment and Postoperative Course. After the intravenous administration of a single dose of FXIII concentrate (50 U/kg of fibrogammin P), the patient underwent surgery and the hematomas were evacuated. The postoperative course was uneventful with resolution of the preoperative headache. Malarial infection was excluded on the basis of a negative history and the absence of enteric symptoms. Normal results of other coagulation tests excluded the possibility of an FXIII deficiency caused by other coagulopathy (for example, hypofibrinogenemia or dysfibrinogenemia). A disseminated intravascular coagulopathy was excluded on the basis of normal PT, fibrinogen, fibrinogen degradation product, and antithrombin III plasma levels and a normal platelet count. A Henoch–Schonlein purpura was excluded based on the absence of suggestive symptomatology (that is, abdominal pain, renal damage, arthritis, and purpura).

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Case 2

History and Examination. This 35-year-old man presented with a 1-week history of headache and episodic paresthesias in the upper-right extremity. His medical history was not significant. The physical examination was nondiagnostic. A CT scan revealed bilateral chronic SDHs, which appeared mostly hypodense with hyperdense lower components corresponding to a major protein and cellular concentration (Fig. 1B). A coagulation profile showed an increased aPTT (39 seconds); PT, bleeding time, and platelet count were normal. All coagulation factors (factors II, V, VIIIc, VIIIr, IX, X, and XI and fibrinogen) were normal except for an FXIII deficiency (20% activity). The main causes of acquired FXIII deficiency and Lupus anticoagulant syndrome were excluded.

Treatment and Postoperative Course. An FXIII concentrate was administered. The patient underwent complete removal of the hematomas. His postoperative course was uneventful. Deficiency of FXIII was confirmed 1 month after surgery (30% activity). A CT scan excluded recurrence of the SDHs, and the administration of additional FXIII concentrate was not necessary.

Case 3

History and Examination. This 27-year-old man with a 1-month history of severe headache and progressive motor deficit in the left side was admitted to our institution. He had no significant medical history. Physical examination revealed a mild left hemiparesis. A CT scan documented a hypodense right hemisphere chronic SDH (Fig. 1C). Platelet count, PT, aPTT, and bleeding time were normal. The coagulation factors (factors II, V, VIIIc, VIIIr, IX, X, and XI and fibrinogen) were normal except that the FXIII level exhibited 20% activity. The main causes of acquired FXIII deficiency were excluded.

Treatment and Postoperative Course. After the administration of FXIII concentrate, the SDH was evacuated. The patient’s postoperative course was uneventful with complete neurological recovery. In this case the FXIII deficiency was also confirmed with a dosage 1 month after surgery. A CT scan documented complete evacuation of the SDH, and the administration of additional FXIII concentrate was not necessary.

Discussion

To our knowledge the association between subdural...
bleeding and FXIII deficiency has not been described in the literature. Factor XIII is an enzyme (protransglutaminase) that stabilizes fibrin clots in the final stages of blood coagulation, becoming activated by the concerted action of thrombin and Ca$^{2+}$. It circulates in plasma as a heterotetramer composed of two A-subunits and two B-subunits. The A-subunit contains the active site of the enzyme; the B-subunit serves as a carrier for the catalytic A-subunit in plasma and is synthesized by the liver. The most important steps in the activation of plasma FXIII include the proteolytic removal of activation peptide by thrombin, the dissociation of subunits A and B, and the exposure of the originally buried active site on the free A-subunits. The main physiological function of plasma FXIII is to crosslink fibrin and protect it from the fibrinolytic plasmin. The latter effect is achieved mainly by covalently linking alpha-2 antiplasmin, the most potent physiological inhibitor of plasmin, to fibrin.

An FXIII deficiency may be hereditary or acquired. Leukemia, liver disease, malarial infection, inflammatory bowel disease, disseminated intravascular coagulopathy, and Henoch–Schönlein purpura are pathological conditions in which FXIII activity may be decreased approximately 50% or more. Hereditary FXIII deficiency is an extremely rare disorder, with an estimated prevalence of only one case/5 million individuals. This disorder is inherited as an autosomal-recessive trait and results in a lifelong bleeding tendency in homozygotes.

Spontaneous intracranial bleeds may occur in more than 30% of patients and may cause death. The cases reported herein emphasize the role of FXIII deficiency in the pathogenesis of spontaneous chronic SDHs. The patients in our study were all young adults and the SDH represented the first bleeding episode in their life. In two of the men aPTT was prolonged, although other authors have reported a normal aPTT time in patients with an FXIII deficiency.

König, et al. investigated the correlation between postoperative coagulopathy and outcome in patients with chronic SDH and showed that coagulation disorders occurred in 42% of patients. Among all of the patients in that study 61.1% had a postoperative FXIII deficit. These authors did not investigate the preoperative FXIII levels and the potential role of this coagulation factor disorder and/or deficiency in the pathogenesis of chronic SDH in patients with no history of head trauma.

Because presurgical hemostasis testing is generally limited to PT, aPTT, and platelet count, it is likely that not every FXIII deficiency is diagnosed. Perhaps the percentage incidence of this coagulopathy represents an underestimate of its true frequency. Data in our study emphasize the role of coagulation screening in patients with unexplained chronic SDH, especially in young adults with no known risk factors.

**Conclusions**

In cases of chronic SDH with no clear origin, coagulopathy should be suspected. In fact, chronic SDH could be the first expression of a hemorrhagic diathesis due to an FXIII deficiency. These data could be useful in evaluating the need for coagulation factor and fresh frozen plasma support as well as the rebleeding risk. Moreover, when hereditary FXIII deficiency is suspected, additional testing in the family members is required given the potential importance of an enhanced risk for spontaneous bleeding in a heterozygous deficiency.

**References**