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Case report

# Factor XIII deficiency related recurrent spontaneous intracerebral hemorrhage: A case and literature review

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ABSTRACT

Spontaneous intracerebral hemorrhage (ICH) in young adults under 50 years of age is an uncommon occurrence associated with considerable morbidity and mortality. The differential diagnosis of ICH in this population differs from that of older individuals and includes vascular, toxic, inflammatory, oncologic, infectious and hematologic conditions. We present a case based observation of a spontaneous and recurrent ICH in a 25-year-old female secondary to undetected Factor XIII (FXIII) deficiency with no prior associated stigmata of hematologic disturbance admitted to a tertiary care neuroscience intensive care unit (NICU). Our patient was admitted after spontaneous development of left thalamic hemorrhage with ventricular extension. Initial management included external drain placement (EVD) and fresh frozen plasma administration. Diagnostic evaluation was unrevealing including CT angiography, magnetic resonance imaging (MRI) with venography, conventional cerebral angiogram, and hematologic and rheumatologic screens. Our patient recovered but represented 6 months later with five foci of spontaneous ICH. She underwent vascular, infectious, oncologic, hematologic, and rheumatologic evaluations. She expired secondary to ICH expansion with uncal herniation. The results of our investigation revealed markedly diminished FXIII activity. The pathophysiology, diagnosis and treatment of this disease are reviewed. FXIII deficiency should be considered in a case of cryptogenic ICH presenting with multifocal, recurrent ICH and a normal coagulation profile. Early diagnosis and initiation of factor replacement therapy offer the best strategies to reduce the morbidities associated with this disease.



## 1. Introduction

Intracerebral hemorrhage (ICH) is a common life threatening condition associated with substantial mortality (62% within one year) and disability (31% with functional independence at 3 months) [1]. In the United States and Europe, the incidence rate ranges from 20 to 60 per 100,000 adults ages 45–84 [2]. Studies specifically examining cerebrovascular accidents in adults under the age of 45 demonstrate an incidence of intracerebral hemorrhage of approximately 10 in 100,000 [3]. Spontaneous ICH in older adults is most commonly related to chronic hypertension, cerebral amyloid angiopathy, or rupture of vascular anomalies [4]. Important differences exist, however, between the causes of ICH in those over 50 years of age and that of ICH in younger individuals (Table 1).

The differential diagnosis for spontaneous ICH in young adults can be divided into vascular, toxic, inflammatory, oncologic, infectious, and hematologic conditions. Vascular etiologies include venous sinus thrombosis with secondary hemorrhage, ruptured arteriovenous malformations, saccular aneurysms, cavernous malformations, or telangiectasias [5–6]. Medications and toxic exposures associated with ICH include methanol, carbon monoxide, sympathomimetic agents such as amphetamine, and even herbal energy drinks [7–10]. Systemic and CNS vasculitis can cause ICH [11]. Brain tumors including high grade gliomas or metastasic disease from well vascularized tumors such as lung, renal, thyroid, melanoma, and choriocarcinoma may also result in ICH [12]. Mycotic aneurysms are an infrequent but important cause of ICH particularly in individuals using elicit intravenous drugs [13]. Tobacco use, diabetes, menopause and caffeine ingestion are risk factors for the development of ICH in individuals 18–49 years of

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**Table 1**
Causes of intracerebral hemorrhage in young adults.

| | |
|---|---|
| Vascular | Venous sinus thrombosis (with secondary hemorrhage) |
| | Ruptured AVM |
| | Saccular aneurysms |
| | Cavernous malformations |
| | Telangiectasias |
| Hematologic (hereditary or acquired) | Prothrombin deficiency |
| | Factor X deficiency |
| | Factor XIII deficiency |
| | Factor VII deficiency subsets |
| Infectious | Mycotic aneurysms (IV drug use) |
| Inflammatory | Vasculitis (systemic or CNS) |
| Oncologic | High grade gliomas |
| | Metastatic disease (lung, renal, thyroid, melanoma, choriocarcinoma) |
| Toxic/medications | Methanol |
| | Carbon monoxide |
| | Sympathomimetics (e.g. amphetamine) |
| | Misc |
| | Herbal drinks |
| | Tobacco |
| | Caffeine |
| Trauma | |

age [14]. Hematologic etiologies commonly involve disruption of acquired or inherited coagulation factor production with either a quantitative or qualitative factor deficiency. Life threatening ICH occurs in higher frequency in patients with Prothrombin, Factor X, and Factor XIII deficiencies as well as in subsets of Factor VII deficiency [15].

Here, we present a case of spontaneous and recurrent ICH secondary to Factor XIII (FXIII) deficiency. We accordingly review the pathophysiology, diagnosis, and treatment of this rare disease.

## 2. Case report

A 25-year-old right handed woman of South Eastern European origin with no known personal or family history of hematopathy presented to the Emergency Department with a two month history of intermittent occipital-predominant, pounding headaches and acute onset diffuse headache, nausea, vomiting, lethargy, nonsensical speech, and right lower extremity weakness. Blood pressure was 126/76 at presentation and a non-contrast head CT (NCHCT) revealed a 5.3 cm × 5.4 cm × 7 cm thalamic ICH with ventricular extension and hydrocephalus (Fig. 1a). CT angiography (CTA) was unremarkable. Initial lab studies were unrevealing including: platelet count, prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR). On admission, she underwent right frontal external ventricular drain (EVD) placement and received vitamin K, fresh frozen plasma (FFP), and anti-epileptic therapy. Her hospital course was complicated by elevated intracranial pressures managed with hyperosmolar therapy. Negative studies included brain magnetic resonance imaging with venography, conventional cerebral angiography, hematologic analysis (Fibrinogen, PT/PTT/INR, Factor VIII, Factor IX, Factor XIII, vWF, ristocetin), and rheumatologic evaluation (ANA, ANCA). She was stabilized and discharged to an acute rehabilitation facility.

After rehabilitation, our patient underwent repeated CTA, CT venography and cerebral angiogram with no appreciable vascular abnormality. Approximately 6 months following her initial presentation, she represented with a blood pressure of 120/87 and five foci of spontaneous ICH (L superior frontal gyrus, right

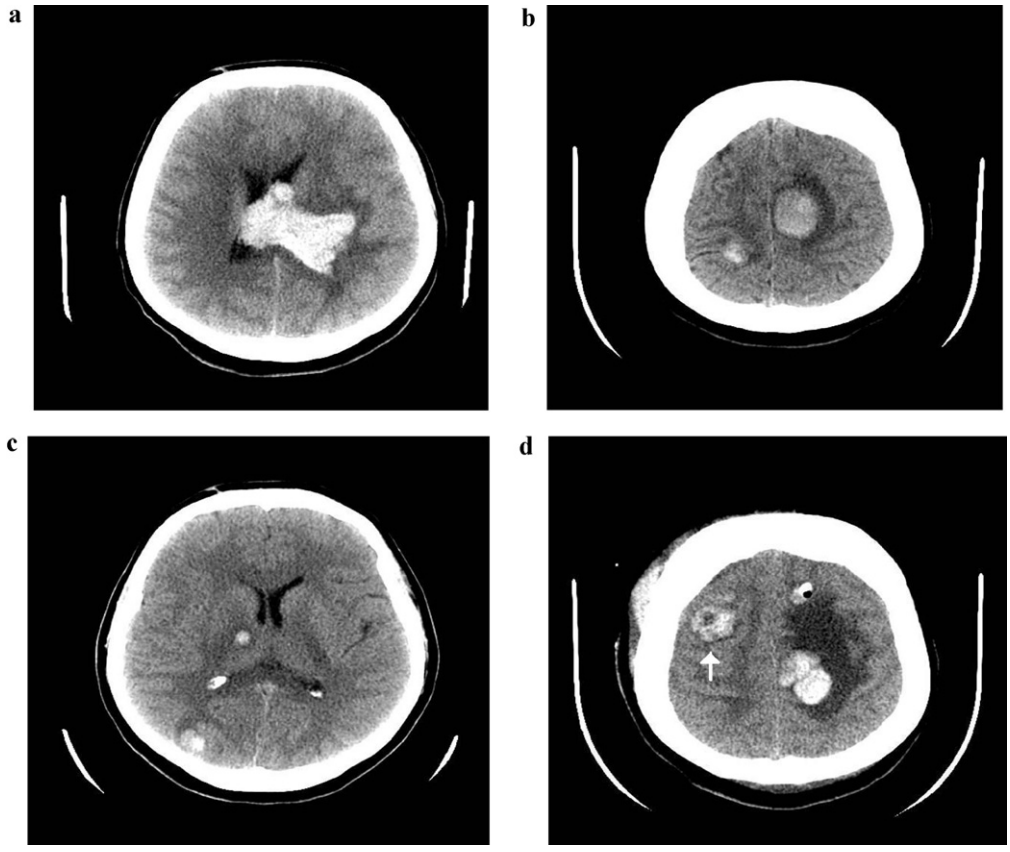


**Fig. 1.** (a) Non-contrast head CT from initial presentation showing thalamic ICH with intraventricular extension of hemorrhage and hydrocephalus. (b) and (c) Non-contrast head CT six months later revealing multifocal hemorrhage in both hemispheres. (d) Right frontal hemorrhage after parenchymal biopsy (white arrow).