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Case report

Recurrent intraparenchymal brain hemorrhage in an infant with factor XIII deficiency

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Abstract

Factor XIII deficiency is an autosomal recessive disorder with an incidence of 1 in 1-5 million. On activation factor XIII stabilizes clot formation by cross-linking fibrin strands. Deficiency is characterized by severe bleeding due to impairment in clot formation. We describe a case of a child presenting with drowsiness following a trivial fall and trauma to the head. An emergency CT scan of the brain was suggestive of acute on chronic (recurrent) hemorrhage. Intraoperatively he was noted to have an intraparenchymal multiloculated cystic cavity with a thinned out cortex in the right frontal region. The child underwent right frontal craniotomy and decompression of an intracerebral hemorrhage. He was subsequently diagnosed to have factor XIII deficiency. He is presently on monthly cryoprecipitate prophylaxis with which he has not experienced a recurrence of a similar episode.

Keywords

Intraparenchymal bleeding, factor XIII deficiency, acute on chronic bleeding, clot solubility test, cryoprecipitate, neurosurgery.

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Introduction

Factor XIII deficiency is an autosomal recessive disorder with an incidence of 1 in 1-5 million [1-3]. This can be congenital or acquired. Congenital factor XIII deficiency can arise due to mutations in catalytic A subunit on chromosome 6 or B subunit on chromosome 1. Factor XIIIA subunit deficiency is more common with 50% of cases being caused by missense mutations. Factor XIIIB subunit deficiency is associated with a milder form of the disease [4]. Rarely both subunits may be absent. Acquired factor XIII deficiency is seen in systemic lupus erythematosus and rheumatoid arthritis. Decreased factor XIII activity is seen in Crohn's disease, ulcerative colitis, pulmonary embolism, leukemia, sepsis, and disseminated intravascular coagulation [4]. On activation factor XIII stabilizes clot formation by cross-linking fibrin strands [1]. The deficiency is characterized by severe bleeding due to impairment in clot formation.

Clinical description

An 8-month-old male child of non-consanguineous parents presented to our clinic with a history of progressively increasing drowsiness for 48 hours following trivial trauma to the head. He was also experiencing recurrent episodes of vomiting. There was no history of seizures, fever or rash.

The infant had normal developmental milestones. No neurological deficit had been noted by the family prior to this episode. The parents reported a history of prolonged umbilical stump bleeding after birth and occasional self-resolving skin bruises with minor trauma.

The child had a Glasgow Coma Score of 8 [E2V2M4]. His pupils were equal and symmetrically reacting to light. The anterior fontanelle was open and full. The baby had diminished power (grade 3/5) and tone in all 4 limbs. A computed tomography (CT) scan showed an atypical large hematoma in the right frontal region, with multiple loculations containing altered blood of different signal intensities, suggestive of long-term recurrent bleeds, with incomplete resolution and membrane formation (**Fig. 1A**). He was hemodynamically stable. Sepsis markers and baseline screening coagulation parameters were normal. Liver and renal function was also normal. There was no history of autoimmune disorders and he was not on any long-term medication.

The child's platelet count was 158 x 10^9/L, the prothrombin time was 14 sec (control 12 sec), the activated partial thromboplastin time was 32 sec (control 28 sec), and fibrinogen was 228 mg/dl. The

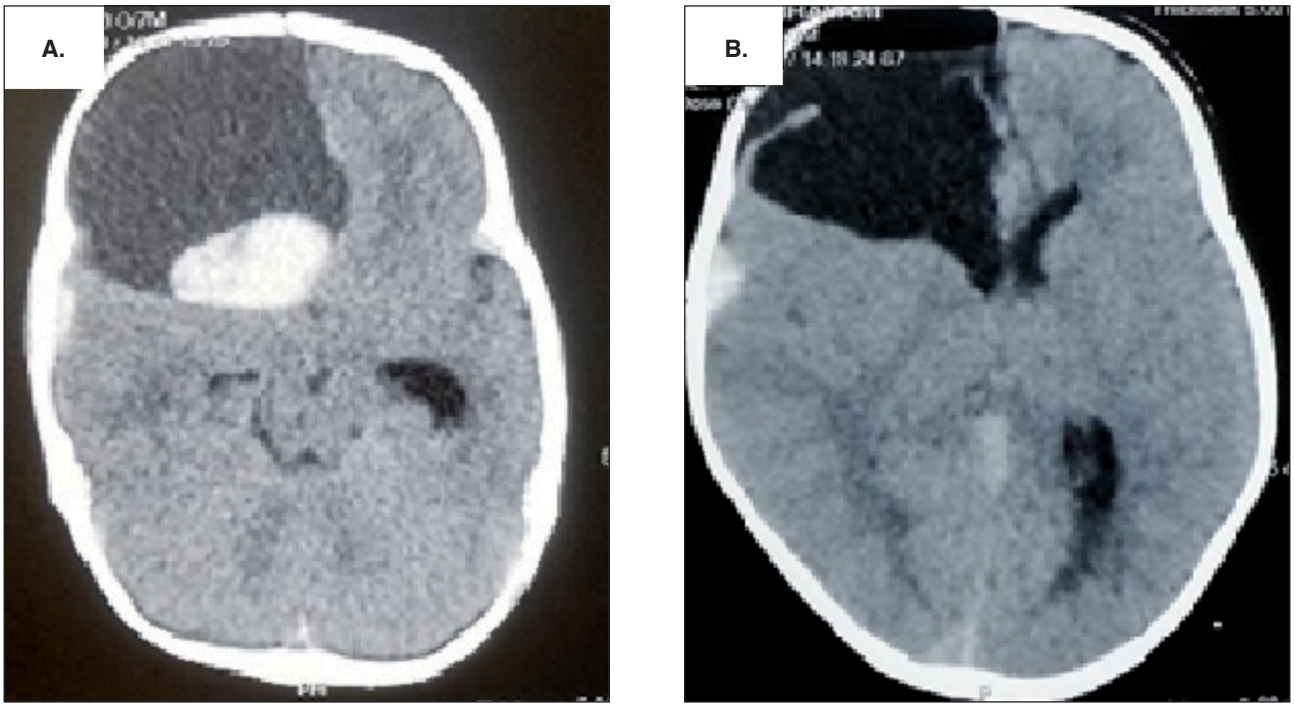

Figure 1. Computed tomography (CT) scans. **A.** Emergency CT scan prior to surgery showed an atypical large hematoma in the right frontal region, with multiple loculations containing altered blood of different signal intensities, suggestive of recurrent bleeds over a long time, with incomplete resolution and membrane formation. **B.** Post-operative CT scan was suggestive of decompressed intracerebral hemorrhage and reduced mass effect.

clot solubility test showed a positive result with dissolution of the stable clot at 24 hours with 2% acetic acid. Factor XIII deficiency was suspected.

As the infant had a hemoglobin of 8.2 gram/dl, he was administered a unit of packed red blood cells. Anemia was possibly due to iron deficiency as noted from his iron profile. The child also received 3 units of cryoprecipitate prior to surgery.

Intraoperatively we observed the child to have an intraparenchymal multiloculated cystic cavity with a thinned out cortex in the right frontal region. The cyst contained dark brown altered blood, with yellow pigmentation of the surrounding brain. There appeared to be multiple cysts arising in a concentric fashion from the basifrontal region, with the deeper cysts having newer bleeds. The cyst wall appeared to be similar to the membrane formation seen in chronic subdural hematoma. The outer layer had older hemorrhages with more fluid content. The inner deeper layers had more viscous blood which was suggestive of a recent bleeding episode. The right frontal lobe was gliotic and underdeveloped (a closed right frontal porencephalic cyst with acute on chronic hemorrhage within). The child underwent right frontal craniotomy and decompression of an intracerebral hemorrhage. A post-operative CT scan was suggestive of a decompressed intracerebral hemorrhage and reduced mass effect (**Fig. 1B**). He received 2 units of cryoprecipitate every day for the following 3 days. At discharge, our patient was alert and conscious with no neurodeficit.

His developmental milestones have been appropriate during follow-up. We performed a definitive quantitative factor XIII assay in follow-up, which confirmed our diagnosis (less than 1% factor XIII activity), and the child is presently receiving 2 units of cryoprecipitate every month as prophylactic therapy. At his 5-month follow-up, our patient had 5% factor XIII activity.

Discussion

Prolonged or delayed umbilical stump bleeding is the most common early presentation and pathognomonic for factor XIII deficiency as we saw in our patient. Factor XIII deficiency is also characterized by recurrent episodes of subcutaneous bleeding, muscle hematoma and intracranial bleeding. Recurrent miscarriage has also been noted. These bleeding episodes can be severe and may be associated with significant morbidity and mortality [2-5]. Severe bleeding with delayed presentation may be noted following trauma or invasive procedures. Our index case presented more than 48 hours after trivial trauma. He was also noted to have recurrent subcutaneous bleeding which had been ignored by the parents and had not been followed up with appropriate investigations and management.

The rarity of the disease and failure of routine coagulation studies to detect it makes diagnosis challenging [2]. The diagnosis is often guided by a detailed history and thorough assessment of clinical presentation, as performed with our patient.

The clot solubility test has a low sensitivity and is not standardized. However, it is often used as the initial screening tool in developing countries [3]. It may underestimate factor XIII level and fail to detect mild or moderate disease. However, quantitative factor XIII assays are not easily available and the blood sample has to be outsourced to a higher center in resource-limited settings of a developing country. As the history obtained for this child was suggestive of factor XIII deficiency, we performed the clot solubility test before deciding on surgical intervention.

Quantitative assays of factor XIII activity are diagnostic for the disease. A quantitative assay by chromogenic method was carried out at his 1-month follow-up visit and showed that our patient had less than 1% factor XIII activity.

Factor XIII concentrate as prophylaxis is the treatment of choice. However, it is not available in our region. Its exorbitant cost also contributes to the difficulty in procuring this product. Cryoprecipitate or fresh frozen plasma (FFP) can be used in resource-limited settings [2, 6]. Plasma-derived factor XIII concentrate is safer than cryoprecipitate and FFP as it has a lesser risk of infection, allergies and reactions. It also provides a more reliable and larger concentration of factor XIII [2, 10]. Patients with less than 1% activity are at risk of serious bleeding while those with 1-4%, of moderate to severe bleeding. It is preferable to maintain levels above 5% to prevent life-threatening bleeding in these patients [3, 7]. A dose of 10-20 IU/kg of factor XIII concentrate or 1-3 units of cryoprecipitate per 10 kg is sufficient as primary prophylaxis. FFP can also be administered every 4-6 weeks as 10 ml/kg. As the half-life of factor XIII is about 11-14 days, once monthly prophylaxis is used in these patients to prevent spontaneous hemorrhages [2, 8-10].

Intraparenchymal bleeding following trivial head trauma in infancy should be investigated appropriately with a proper focused history and followed up with appropriate investigation to diagnose life-threatening hematological conditions.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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