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A newborn with a massive subgaleal haematoma and a rare haematological diagnosis

Congenital factor xiii deficiency is an extremely rare bleeding disorder, which is inherited in an autosomal recessive pattern.[1,5] Factor xiii is the key element in the terminal end of the coagulation cascade that ensures the stability of blood clot formation.[1] Delayed bleeding (12 to 36 hours) after trauma or surgery is the pathognomonic feature of factor xiii deficiency.[2] Here, we report on a term neonate with congenital factor xiii deficiency, who was diagnosed following significant delayed bleeding tendencies in the form of subgaleal haemorrhage and subcutaneous bleeding on the dorsum of the left hand, severe enough to drop the haemoglobin drastically to 62g/L, requiring urgent blood transfusion.

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Key points

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1. Subgaleal haematoma usually does not require neurosurgical intervention.
2. Factor xiii is also known as fibrin stabilising factor.
3. Factor xiii deficiency is a rare, autosomal recessive inherited bleeding disorder.

A baby girl was born by emergency caesarean section (CS) at 39^{+2} weeks gestational age due to fetal bradycardia and significant meconium stained liquor (MSL) and no maternal risk factors for sepsis. No instruments were used during CS. She was born in good condition with a birth weight of 3.135kg. Apgars were 8 and 9 at 1 and 10 minutes respectively.

She was subsequently admitted to the neonatal unit due to a dusky episode and oxygen requirement around five minutes of age. Intravenous benzylpenicillin and gentamicin were started after a partial septic screen for suspected sepsis based on the following risk factors: oxygen requirement, meconium stained liquor and dusky appearance.

She was extremely difficult to cannulate and had multiple attempts with no success. Therefore, a decision was made to put in an umbilical venous catheter (UVC). While prepping for the UVC, she was noted to have roving eye movements, downward gazing of eyes and abnormal posturing of limbs (these were more obvious at four hours of age). They were not associated with jerky movements or change in the sensorium. She was kept under hourly neurological observations for six hours and cerebral function monitoring (CFAM) was started. The CFAM did not capture any electrographic seizures, despite having periodic roving eye movements and some posturing of limbs. Her cord gases were reassuring and she did not fulfil the TOBY criteria for cooling.

She continued to have roving eye movements (without posturing) and on day two of life, she was given a loading dose of IV phenobarbitone without any significant change. Lumbar puncture excluded central nervous system infection and initial metabolic work up was normal.

A standard electroencephalogram (EEG) was also carried out on the same day and it captured several typical episodes of downward gaze deviation, often followed by crying, although no definite electrographic seizure pattern was observed during these events. However, there were rhythmical alpha range activities appearing over the right hemisphere and centro-parietal region, which were quite suspicious (but not definite) of subtle right hemisphere electrographic focal seizures.

On the advice of the paediatric neurologist and following review of video images of these abnormal movements, a decision was made not to start on maintenance antiepileptic medication as these were deemed non-seizure-like activity.

On the third day of life, she was noted to have a boggy swelling measuring approximately 6cm x 8cm on the left parieto-temporal region and swelling on the dorsum of the left hand in the area of

several previous cannula attempts. An ultrasound scan (USS) of the brain did not reveal any intracranial bleeding.

The scalp swelling continued to increase rapidly over a short space of time. This also correlated with an increase in the head circumference. An urgent computed tomography (CT) head scan revealed a left sided parietal high density subgaleal fluid collection, with 1.5cm maximum width, possible haematoma.

Intravenous antibiotics were discontinued following a negative infection screen.

On the same day, she was also found to be significantly pale with a haemoglobin of 62g/L, which was a drastic drop from 187g/L within a 36-hour period (**FIGURE 1**). However, she remained asymptomatic with normal observations.

Her basic coagulation profile including prothrombin (PT) and activated partial thromboplastin time (APTT) and platelet count remained within the normal limits for her age while the Clauss fibrinogen level was slightly low.

A repeat cranial USS did not show any evidence of intracranial bleeding. She then received a second dose of vitamin K and was transfused with packed red cells without any complications.

The swelling on the dorsum of the left hand progressively worsened with associated bluish-purple bruising that suggested an expanding haematoma. An orthopaedic review was requested in view of possible fracture and risk of compartment syndrome, both of which were ruled out.

MRI head was performed on day 5 (**FIGURE 2**) revealing a left-sided subgaleal haematoma with diffuse marked scalp swelling/haemorrhage but no intracranial injury, acute abnormality or focal structural cause for seizures demonstrated, with normal myelination in the posterior limbs of the internal capsule bilaterally.

Discussions were held with the regional neurosurgical team, who recommended close monitoring and investigation for bleeding disorder as subgaleal haematoma usually does not require neurosurgical intervention.

In light of significant bleeding tendencies with normal basic coagulation profile, factor xiii deficiency was entertained as the possible diagnosis. Additional request was made to the lab to add in factor xiii assay and von Willebrand (vWD) screening to the bloods already sent on day two of life prior to blood transfusion.



FIGURE 1 Left: Day 3. Right: Day 3 – a few hours later.
Pictures printed with parent consent obtained by author.

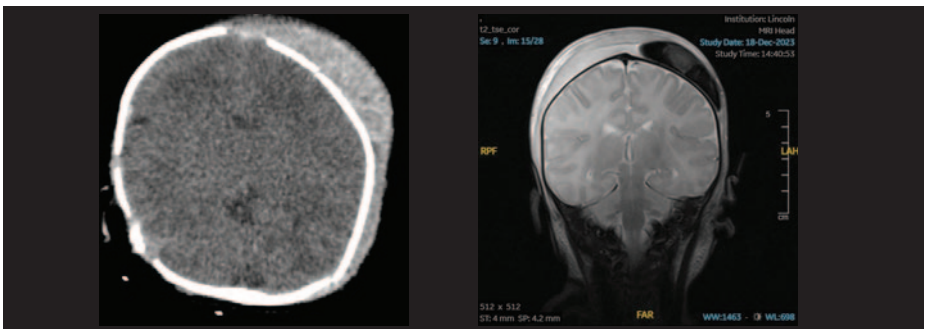


FIGURE 2 Left: CT head on day 3. Right: MRI head on day 5.



FIGURE 3 Left: Resolved hand swelling. Right: At discharge.

Subsequent results revealed a significantly low factor xiii level of 0.06IU/ml (reference range 0.59-1.63IU/ml) while the vWD screen was negative. Hence, the diagnosis of congenital factor xiii deficiency was confirmed.

Over the next couple of days, she remained stable and the swelling continued to spread out around the scalp and face, slowly receding, with the appearance of bruising around both eyes resembling raccoon eyes (**FIGURE 3**).

The left hand swelling also improved significantly without any residual changes.

She was discharged home on day 9 of life, with well-established breast feeding and without any further bleeding complications. Her head circumference decreased as expected with resolution of the subgaleal haematoma.

Upon discharge, she was referred to paediatric haematology following confirmation of the diagnosis.

Congenital factor xiii deficiency

Introduction

Factor xiii is also known as fibrin stabilising factor.[1,5] It was first discovered in 1944 by K.C. Robbins as a coagulation factor[3] and Duckert et al reported the first case of severe factor xiii deficiency in Switzerland in 1960.[3,8]

The incidence of factor xiii deficiency is approximately 1 in 1 to 5 million.[2,5,6]

Factor xiii is a transglutaminase protein heterotetramer composed of two catalytic subunits A and carrier subunits B linked by non-covalent bonds.[1,2,5,9,10] Subunit A is synthesised by megakaryocytes, monocytes and macrophages, whereas subunit B is synthesised by hepatocytes.[3,5]

The function of subunit B is to protect catalytic subunit A from clearance.

The gene responsible for subunit A production is located on the short arm of chromosome 6, whereas the gene involved in subunit B production is located on the long arm of chromosome 1.[4,5] Defects in both genes lead to congenital factor xiii deficiency. Deficiency due to subunit A is more common than that of subunit B.[4,7]

Factor xiii, the proenzyme is activated to xiiia by calcium and thrombin at the terminal stage of coagulation cascade.[1,4]

Factor xiii deficiency can either be congenital or acquired.

Clinical manifestations

The clinical manifestations of congenital factor xiii deficiency include lifelong bleeding diathesis, subcutaneous bleeding, delayed umbilical cord bleeding, muscle haematoma, excessive bleeding following surgery, joint bleeding, mouth and gum bleeding, and spontaneous or traumatic intracranial bleeding. The pathognomonic feature of factor xiii deficiency is delayed (12 to 36 hours) bleeding after trauma or surgery.[2,4]

Bleeding from the umbilicus is the most commonly reported clinical manifestation of factor xiii deficiency.[1,3,7,10] Delayed cord separation is also a presenting feature.

As factor xiii plays a major role in wound healing and tissue repair processes by proangiogenic effect of cross-linking fibrin and fibronectin at the site of injury, enhancing the migration and proliferation of monocytes and fibroblasts, patients with factor xiii deficiency can present with poor wound healing.[1,3,9]

Factor xiii is also essential for the attachment of cytotrophoblasts to the endometrium, therefore deficiency can lead to recurrent spontaneous miscarriages and significant bleeding.[2,3]

Women with factor xiii deficiency can present with menorrhagia.[3]

Learning points

1. Massive subgaleal haematoma can occur from minimal trauma (such as cannula insertion or CFAM needles) when there is an underlying bleeding disorder.
2. A normal basic coagulation profile in the presence of bleeding tendency should prompt the possibility of factor xiii deficiency.
3. An early multidisciplinary approach to care can often help with early diagnosis and avoidance of potentially severe complications.

Acquired factor xiii deficiency

Acquired factor xiii deficiency has been reported with significant reduction in factor xiii levels in conditions like pulmonary embolism, myelodysplastic syndromes, inflammatory bowel disease, leukaemia, erosive gastritis, sepsis, disseminated intravascular coagulation, isoniazid treatment, liver failure, SLE, Henoch-Schonlein purpura, following major surgery, and autoimmune bleeding disorders like anti factor xiii inhibitors.[1,3,5,9]

Diagnosis

Factor xiii deficiency is suspected when bleeding episodes occur with normal basic coagulation tests like APTT, PT, fibrinogen level, platelet count and bleeding time.[1-3,5] The diagnosis is confirmed by either qualitative or quantitative assays.[2,3]

Qualitative assay includes clot solubility testing in concentrated 5M urea, 2% acetic acid, or 1% monochloroacetic acid solution. However, this identifies only very severe factor xiii deficiency.[1,5]

Quantitative factor xiii activity assay identifies all forms of factor xiii deficiencies and therefore it is recommended as the first line screening test.[1]

Management

Minor bleeding can be managed conservatively using ice, applying pressure and oral antifibrinolytic drugs.

Avoidance of trauma, intramuscular injections and nonsteroidal anti-inflammatory drugs would help to minimise the bleeding risk.

Fresh frozen plasma and cryoprecipitate can be used to treat factor xiii deficiency[5,6] but they may carry the risk of transmission of blood borne viruses.[2]

Recombinant factor xiii (rFxiii) is available and is the safer and effective mode of treatment and prophylaxis.[6,7,10]

As factor xiii has a long half-life of 11 to 14 days and factor xiii level of 3% to 5% is usually adequate to prevent spontaneous bleeding, prophylactic therapy is the management of choice.[1] Lifelong prophylaxis every four to six weeks with 10 to 40IU/kg of intravenous rFxiii is recommended in patients with severe factor xiii deficiency to prevent catastrophic, spontaneous bleeding.[2,8]

Plasma factor xiii level should be maintained at more than 5% in major surgery until the wound healing process is complete.[1]

Prophylaxis during pregnancy is essential for women with factor xiii deficiency due to the risk of miscarriage and pregnancy loss and should be commenced as early as possible, ideally before the fifth to sixth week of gestation.[1] Factor xiii level should be maintained at more than 30% at the time of delivery.[3,9] It is also recommended to administer 1,000IU of rFxiii prior to the onset of labour to prevent subsequent postpartum haemorrhages.[9]

Discussion

Our baby was found to have a boggy scalp swelling and a haematoma on the dorsum of the left hand on the third day of life, which were not there initially. Upon reflection, we suspect that minimal trauma from the application of the CFAM needle is the likely cause of the slow and progressive scalp haematoma and subsequent subgaleal haemorrhage. The haematoma on the dorsum of the left hand would have also been caused by multiple attempts at cannulation, considering significantly low levels of factor xiii.

These findings are in keeping with delayed bleeding secondary to trauma, which is the pathognomonic feature of factor xiii deficiency.

Our patient only received a blood transfusion for significant anaemia and additional dose of vitamin K as the initial basic coagulation screen was within normal limits. With supportive care, she gradually improved over time.

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