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Case Report

A Rare Bleeding Disorder with Normal Clotting Profile

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Abstract Haemostasis involves a complex cascade which has various pathways to allow an optimal equilibrium between thrombosis and bleeding. Factor XIII (FXIII) contributes at the end of the coagulation cascade and binds with the unstable fibrin clot to form a stable clot. We hereby report a case of Chinese girl presented with prolonged umbilical cord bleeding with normal coagulation study in the newborn period. She developed intracranial haemorrhage at age of 4 months and was subsequently diagnosed to have FXIII deficiency. This case demonstrates that in any patient presenting with bleeding tendency and seemingly normal blood counts and clotting profile, the diagnosis of FXIII deficiency should be considered.

Key words *Children; Factor XIII deficiency; Intracranial haemorrhage; Neonate; Umbilical bleeding*

Case Report

This baby girl was born at full term by normal vaginal delivery with a birth weight of 3.06 kilogram. She had non-consanguineous Chinese parents and there was no family history of bleeding diathesis. She was admitted to the neonatal unit of a regional hospital on day 3 of life with persistent fresh blood oozing from the umbilical stump. She received vitamin K on day 1 of life uneventfully. Her vital signs were stable and no cutaneous bruises or mucosal bleeding. Her anterior fontanelle was of normal tension. Her blood investigations showed haemoglobin (Hb) of 11.2 g/dl and platelet counts of 356 x 10^9/L. The prothrombin time (PT) was 10.5 seconds, international normalised ratio (INR) was <1.0, activated partial prothrombin time (APTT) was 24.7 seconds, which were all normal (Table 1). Control of her bleeding was attempted by manual compression with pressure gauze, sufratulle dressing and application of silver nitrate but without success. Suturing of the umbilical stump was performed and intravenous tranexamic acid was administered. Owing to the prolonged umbilical bleeding, her haemoglobin dropped to 7 g/dl and blood transfusion was given. The bleeding stopped subsequently. Her ultrasound abdomen revealed no umbilical cord anomaly. The baby was discharged on day 16 of age and was reviewed by paediatric surgeons three weeks later with no documented bleeding from the umbilical cord or other sites.

The baby girl was then admitted for seizure at four months of age. She presented to the emergency department for repeated vomiting and an episode of afebrile

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generalised tonic-clonic convulsion. There was no history of head trauma reported. Computer-tomography (CT) of the brain showed intraventricular haemorrhage at the fourth ventricle without hydrocephalus or parenchymal haematoma (Figure 1). Magnetic resonance imaging and magnetic resonance angiography of the brain showed microbleeds at the frontal lobe while the major intracranial arteries were unremarkable. Ophthalmological assessment did not show any retinal haemorrhage. She did not require any neurosurgical intervention or further transfusion. Seizure was well controlled with levetiracetam and phenobarbitone. Metabolic screening was unrevealing. Further work up on coagulopathy showed very low factor XIII (FXIII) of 1% (reference range: 50-150%) by clot solubility test (Table 1). The thrombin time, von Willebrand factor and most coagulation factors were normal. The diagnosis of severe FXIII deficiency was made. Genetic workup was performed by the Next Generation Sequencing, which detected compound heterozygous variants of the *F13A1* gene: c.2045G>A p.Arg682His and c.1984C>T p.Arg662*. Available literature reported compound heterozygous point mutations involving both alleles c.1984C>T p.Arg662[1] and c.2045G>A p.Arg682His,[2] though old nomenclature might not be identical with the current one. Her parents' clotting profile was normal. However, as her parents resided in mainland China, their FXIII levels and genetic study were not performed.

Our patient was receiving regular cryoprecipitate transfusion every four weeks thereafter as prophylaxis to further bleeding. Her follow-up CT brain at six months old showed complete resolution of intracranial haemorrhage. She did not experience further episodes of bleeding or seizure. She weaned off all the anti-epileptic drugs by two years old and she enjoyed normal growth and development at the time of reporting.

Table 1 Complete blood counts, clotting profile and coagulation factor assay of the patient

CBC & clotting profile (Day 5 of life)	Results	Normal range
WCC	12.7 x 10^9/L	4.0-12.0 x 10^9/L
Hb	11.2 g/dl	15-24 g/dl
Platelet	356 x 10^9/L	152-358 x 10^9/L
PT	10.5	10.5-13.0 ms
INR	<1	/
APTT	24.7	22.8-31.7 ms
Factor assay (4 months old)		
Factor V	129%	50-200
Factor VII	82%	50-200
FVIII:C	134%	50-200
vWF (Ricof) activity	110%	50-200
vWF antigen	137%	50-200
FVIIIC/vWFAg	1.0	Greater than 0.7
Factor IX	74%	40-160
Factor X	91%	50-200
Factor XI	69%	40-160
Factor XII	87%	38-109
Factor XIII	1%	50-150

Discussion

Fibrin-stabilising factor was first reported by Robbins in 1944 and it was named FXIII in 1963.[3] Circulating FXIII consists of two active proenzymes (subunit A) and two carrier-proteins (subunit B). During the coagulation cascade, thrombin cleaves off the activation peptide from subunit A, while calcium-dependent dissociation of subunit B presents the active FXIII. Subunit A contains the active centre and subunit B acts as a carrier protein to stabilise subunit A. Activated FXIII stabilises fibrin into fibrin clots in the final stage of blood coagulation without a role in the extrinsic and intrinsic coagulation pathway.

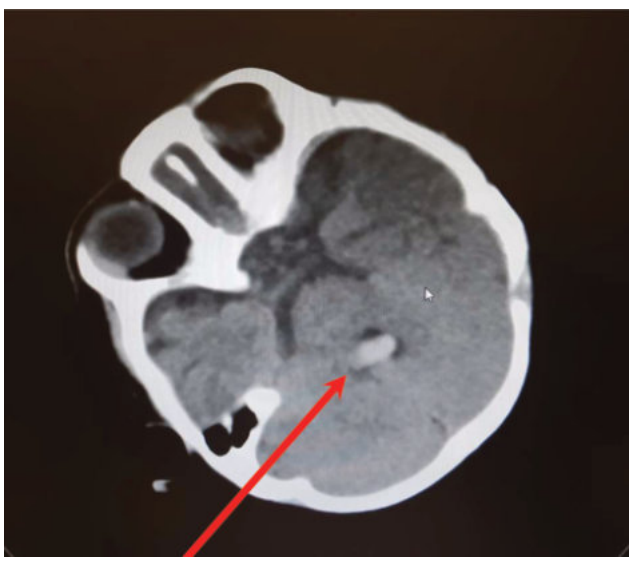

Figure 1 CT scan of brain showed acute haemorrhage in the fourth ventricle.

This accounts for the normal clotting profile in patients with FXIII deficiency as evident in our case.

Clot solubility lysis test is a qualitative screening test. A positive result suggests absent or close to zero FXIII activity. A diagnostic quantitative test involves either a chromogenic assay, which tests for FXIII activity, or an immunological test, which evaluates antigenic concentrations of FXIII and tests for subunits. Coagulation factor activity level correlates with clinical bleeding severity, in which patients with FXIII level less than 1% present with more severe phenotype, as seen in our patient, while moderate cases have FXIII level between 1 to 4%.[4]

Congenital FXIII deficiency is an autosomal recessive disease which could either be FXIII-A, which is the majority of cases, or FXIII-B deficiency. The subunit A is encoded by the *F13A1* gene on chromosome 6 while the subunit B is regulated by the *F13B* gene on chromosome 1. Homozygous mutations are associated with life threatening bleeding episodes.[5] FXIII-A deficiency could be due to quantitative or qualitative defects of subunit A. In FXIII-B deficiency, there is decreased expression of subunit B, which increases the degradation of subunit A and hence a relative deficiency in subunit A. FXIII-B deficiency patients have milder symptoms with a 5 to 10% reduction in FXIII activity.[5]

The diagnosis of congenital FXIII deficiency could be a challenge to physicians and often missed as clinical symptoms can range from mild to severe. Severe symptoms usually present at the neonatal period or early in childhood. The most common presentation is umbilical cord bleeding which could delay up to three weeks after birth, taking up 80% of cases with severe FXIII deficiency.[6] There is a 30% risk of spontaneous intracranial haemorrhage, with this symptom being more frequent in FXIII deficiency than other types of coagulation factors deficiencies.[7] An interesting presentation in female patients is recurrent spontaneous miscarriages, due to poorly formed cytotrophoblasts which affect adhesion of the fetus to the placenta.[8] Menorrhagia was reported as the second most common (26%) bleeding symptom other than umbilical bleeding in women with FXIII deficiency.[9]

Owing to the risk of intracranial haemorrhage, long term replacement is recommended for severe cases of FXIII deficiency. Curative treatment is yet to be developed. Fresh frozen plasma and cryoprecipitate transfusion are the most commonly available replacement therapy to be given every 3 to 4 weeks. FXIII concentrates emerges as a safer and effective alternative.[6] As FXIII has a half-life of 11 to 14 days, replacement is often administered at three to four weeks intervals.[3] The standard dosing for adults is 10 to 20U per kilogram of Fibrogammin P every 4 to 6 weeks. This maintains a FXIII level above 3 to 5%, which is considered adequate in preventing spontaneous bleeding. Plasma-derived FXIII concentrate has evolved to become the mainstay of treatment, while synthetic recombinant FXIII-A subunits (rFXIII) is an even more recent development. The rFXIII minimises pathogen transmission and systemic reactions with smaller transfusion volume, while being free from human products. However, rFXIII is only useful in FXIII-A deficiency, and there is accessibility difficulty and very high costs in developing countries. Plasma-derived FXIII concentrate is now available in Hong Kong and our patient will switch from cryoprecipitate transfusion to receive it. One major concern with the use of replacement therapies is the development of inhibitors or autoantibodies. Low-titer non-neutralising antibodies were detected in some patients after exposure to rFXIII. However, these antibodies were below detection levels four months later without any clinical relevance.[7] This would be one important aspect to monitor in our patient in future follow up.

Clinicians should have a high index of suspicion of FXIII deficiency upon managing a case of prolonged umbilical cord bleeding with normal clotting profile. Early suspicion and diagnosis could enhance prompt commencement of factor replacement, and prevent morbidity as seen in untreated patients. Future direction should put forth resources in improving the accessibility and cost.

Conflicts of Interest

All authors have disclosed no conflicts of interest.

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