CASE REPORT

Factor XIII deficiency presenting with intracerebral bleed

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SUMMARY

It has been recognised for some time that many disorders such as vascular malformations, hypertension, collagen vascular diseases, tumours, eclampsia, central nervous system infection, bacterial endocarditis and blood dyscrasias can cause non-traumatic intracerebral haemorrhage in young adults. Factor XIII deficiency is a rare cause of intracranial bleed. The impressive clinical signs with bleeding starting in the neonatal period (prolonged bleeding from the umbilical cord), followed by severe, life-threatening episodes of intracranial haemorrhage should raise the clinical suspicion of factor XIII deficiency. Tests for factor XIII deficiency in high index clinical suspicious cases despite negative coagulative screening tests are essential for diagnosis. The diagnosis of factor XIII deficiency is difficult but has important therapeutic consequences. We are reporting here the clinical outcome of a young woman with intracranial bleed due to factor XIII deficiency. The patient was managed successfully with fresh frozen plasma transfusion and supportive treatments. The prophylactic substitution therapy of factor XIII (recombinant factor XIII, cryoprecipitate and fresh frozen plasma) enables patients to live normal lives, free from catastrophic bleeding episodes.

BACKGROUND

Stroke in young poses a major health problem. Intracerebral haemorrhage (ICH) accounts for 9.9–19.6% of all strokes and results from a wide spectrum of disorders.¹ ICH is more likely to result in death or major disability than ischaemic stroke. The differential diagnosis for spontaneous ICH in young adults can be divided into vascular, toxic, inflammatory, oncological, infectious and haematological conditions.² Non-traumatic ICH most commonly results from hypertensive damage to blood vessel walls but it also may be due to rupture of an aneurysm or arteriovenous malformation, arteriopathy, altered haemostasis, haemorrhagic necrosis or venous outflow obstruction. Factor XIII, the last enzyme in the clotting cascade, catalyses the covalent cross linking of fibrin molecules. It converts the loose fibrin polymer into an organised cross-linked structure with increased tensile strength and makes it relatively resistant to fibrinolysis.³ Young intracerebral bleed with underlying factor XIII deficiency as an important and preventable entity is not yet widely recognised. Not too many cases are reported from different institutes worldwide. Awareness of this condition will enable physicians to suspect and identify it early in the course and

also forms the basis of test for factor XIII deficiency (factor XIII assay/clot solubility test) despite a normal coagulation profile.

CASE PRESENTATION

A 15-year-old girl presented with headache, vomiting for 7 days and altered sensorium for 1 day. She had a history of trivial head trauma 7 days back. She had no history of fever and seizure. She was unmarried, non-vegetarian, had no addiction or history of drug intake. On examination her vitals were stable, Glasgow Coma Score was 7, pupils were normal in size and sluggishly reactive, plantar was extensor bilaterally and power of grade 2/5 in her left half. Her rest of the neurological and systemic examinations were normal. On interrogating her mother, the history of umbilical cord stump bleeding just after birth and prolonged bleeding following minor injuries in her childhood could be retrieved and for which she also required blood transfusions. She has four siblings with one brother who died at an age of 2 years having a similar history of cord stump bleeding.

INVESTIGATIONS

Investigations revealed haemoglobin 10.4 g/dl, total leucocyte count 10 400/mm³, differential count polymorph 68% and lymphocyte count 32%, platelet count 1.29 lacs/mm³. Her coagulation profile revealed prothrombin time 12 s (International Normalised Ratio, INR 1), activated partial thromboplastin time 24 s and bleeding time 3 min 40 s. Her blood sugar, serum electrolytes level, liver and kidney function tests were normal. CT scan head showed intraparenchymal bleed in right temporo-occipital region with intraventricular extension (figures 1 and 2). She was advised for a clot solubility test (5 M urea) which came out positive.

DIFFERENTIAL DIAGNOSIS

- ▶ Other coagulopathies
- ▶ Systemic vasculitis
- ▶ Arterio-venous malformation
- ▶ Oncological and haematological conditions

TREATMENT

The patient received intravenous mannitol and 4 units of fresh frozen plasma.

OUTCOME AND FOLLOW-UP

Her GC score improved gradually and by day 7 she became conscious. She was discharged and advised regular follow-up for prophylactic therapy.

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Figure 1 CT scan head showing intraparenchymal bleed in the right temporo-occipital region.

DISCUSSION

Factor XIII deficiency is inherited as an autosomal recessive disorder and occurs at a frequency of approximately 1 in 1–5 millions. Approximately 200 cases were reported worldwide from the 1960s to 2002.^{4–5} Plasma factor XIII is a heterotetramer composed of two catalytic A subunits and two carrier B subunits linked by non-covalent bonds. Assembly of the A and B subunits probably occurs in the circulation. Factor XIIIa catalyses the formation of peptide bonds between adjacent molecules of fibrin monomer, thus imparting chemical and mechanical stability to a clot.⁶ Patients with factor XIII deficiency have a bleeding tendency that is usually severe. Only homozygous-recessive patients with severe deficiencies have clinical symptomatology, since plasma factor XIII levels of 1–2% or more are adequate for fibrin stabilisation. In one study the most common bleeding symptoms are subcutaneous bleeding (57%), delayed umbilical cord bleeding (56%), muscle haematoma (49%), haemorrhage

Figure 2 CT scan head showing intraparenchymal bleed in the right temporo-occipital region with intraventricular extension.

after surgery (40%), haemarthrosis (36%) and intracerebral bleeding (34%).⁷ Congenital factor XIII deficiency can manifest at any age, but diagnosis is often made during infancy. In most cases, haemorrhages are delayed (12–36 h) after trauma or surgery. Acquired forms of the disease have also been reported in association with hepatic failure, inflammatory bowel disease and myeloid leukaemia. Good history is very important to reach a proper diagnosis. Delayed bleeding tendency with a normal coagulation profile is very suspicious of factor XIII deficiency. Given that the international normalised ratio (INR), prothrombin time (PT) and partial thromboplastin time (PTT) are almost always normal, diagnosis of factor XIII-related ICH can be challenging in the absence of a high clinical suspicion. A prior history of neonatal umbilical bleeding (almost pathognomonic), frequent echymosis, postoperative bleeding, recurrent spontaneous miscarriages and delayed wound healing are all common stigmata of disease.² Our patient had a prolonged history of bleeding and her brother also died due to bleeding disorder. Laboratory diagnosis still relies on the standard clot solubility test because of its high sensitivity and simplicity. If the diagnosis of factor XIII deficiency is suggested by the solubility test, it may be confirmed by estimation of factor XIII activity using one of several quantitative assays.^{8–9} In our case, the obvious history and unwillingness of patient restricted further confirmatory workup. Whole blood, fresh frozen plasma, stored plasma, cryoprecipitate and factor XIII concentrate have all been used successfully in the treatment of factor XIII deficiency and are adequate sources of factor XIII. Traditional treatment for factor XIII deficiency includes cryoprecipitate and fresh frozen plasma. As the half-life of endogenous factor XIII is long, ranging from 5 to 11 days, prophylactic therapy with fresh frozen plasma in doses of 10 ml/kg can be given every 4–6 weeks. Cryoprecipitate can be administered in doses of 1 bag per 10–20 kg every 3–4 weeks.¹⁰ Currently in western countries, most patients are being treated with plasma-derived pasteurised factor XIII concentrate.¹¹ Plasma-derived factor XIII concentrates are superior to fresh frozen plasma (FFP) or cryoprecipitate as these provide reliable and high concentrations of factor XIII in minimum volume, have fewer contaminating substances and are virally inactivated. In view of the high incidence of cerebral haemorrhage it is recommended that all patients with severe factor XIII deficiency (<1 U/dl) should receive prophylactic replacement therapy with factor XIII concentrate from the time of diagnosis. It is recommended that 10 units/kg should be given at intervals of 4 weeks to prevent recurrent clinical problems and bleeding episodes.¹²

A new recombinant factor XIII (rFXIII) has been manufactured in *Saccharomyces cerevisiae* (yeast) and contains no human/mammalian products. Recently it has been demonstrated that rFXIII as a monthly replacement therapy (35 IU/kg intravenous) is efficacious and safe for prophylactic treatment in patients with congenital FXIII-A subunit deficiency.¹³

Learning points

- ▶ Factor XIII deficiency is a dreaded but preventable coagulation factor deficiency disease.
- ▶ In clinically high index suspicion cases, performing only routine coagulation profile is not sufficient.
- ▶ If early detected, and adequately treated, morbidity and mortality may be minimised.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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