Case Report

Hereditary Prothrombin Deficiency

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Abstract

Hereditary prothrombin deficiency is one of the rare congenital coagulation defects. We report a case of 4 months old child who initially presented at 1½ month of age with high-grade fever, generalized convulsions and brownish aspirate through nasogastric tube, diagnosed and managed as meningitis and sepsis. He was readmitted at 4 months of age with bruises over legs. Coagulation profile was suggestive of common pathway defect. Further evaluation revealed absent prothrombin level while other factors were within normal limits.

Introduction

Prothrombin is synthesized in the liver as pre-propeptide. Prothrombin gene is located on chromosomes 11 near centromertes.[1] Thrombin is necessary for proper homeostasis. This powerful protease is at the core of the coagulation cascade.[2] Prothrombin is a precursor to thrombin, which converts fibrinogen into fibrin, which in turn strengthens a protective clot.[3]

There are two types of prothrombin deficiencies, hereditary and acquired. Hereditary hypoprothrombinemia is an autosomal recessive inheritance and is rare, only 100 cases are reported world wide,[4] the estimated incidence is 1

in 2 million.[3] Local data is scarce, a study in Karachi revealed only one case of prothombin deficiency out of 1100 cases of inherited coagulopathies.[5] Type I prothrombin deficiency (hypoprothrombinemia) is the result of decreased prothrombin production. Factor levels of 4-10% have been reported. Type II prothrombin deficiency (dysprothrombinemia) is due to inadequate function of the prothrombin protein.[2]

A significant haemostatic defect is not induced unless prothrombin level is less than 25 percent. Homozygous usually have prothrombin activity less than 10 percent of normal, whereas heterozygous have 40 to 60 percent of normal activity.[4] Severity depends on prothrombin activity, patient with prothrombin activity of 5 to 50 percent usually bleed following trauma and surgery, while in patients with prothrombin activity of 2 to 5 percent of normal, bleeding may be quite variable and in patients with activity less than 1 percent of normal, presents with severe bruising, bleeding from the nose and mouth, menorrhagia, muscle bleeds and intracranial haemorrhages but joint bleeding is rarely reported.[1,3]

Diagnosis is suspected with a prolonged prothrombin time (PT) test and an activated partial thromboplastin time (APTT) test whereas definite diagnosis depends upon specific enzyme assay. Acquired form of Factor II deficiency is also associated with bleeding. The differential diagnosis of acquired hypoprothrombinemia includes liver disease, vitamin K deficiency and inhibitors to prothrombin as in Systemic Lupus Ergthromatosus (SLE). Studies of family members and measurement of vitamin K dependent coagulation factors helps to distinguish acquired from inherited prothombin deficiency.[2]

Bruises and mild superficial bleeding do not generally require replacement therapy. The biological half-life of prothrombin is approximately 3 days; in many cases single treatment is necessary.[1] Infusion of fresh frozen plasma (FFP) is usually sufficient to treat most cases of bleeding. Plasma exchange transfusion may be used to increase factor II levels before surgery.[2] Prothrombin complex concentrates (PCCs) dosage 1 IU/kg augments upto 1.6% blood level.[6]

Case Report

A 4-months-old male presented with complaint of bruises over lower limbs and back. There was a past history of admission at 1½ month of age with fever and fits, right-sided facial nerve palsy, bulging fontanelle and brownish aspirate in nasogastric tube. Investigation revealed prolonged prothrombin time (PT), activated partial prothrombin time (APTT) and CT scan brain showed subdural haematoma. Baby was managed as a case of septicaemia and discharged after recovery.

The patient was a second issue of consanguineous marriage; born at a hospital and received intramuscular vitamin K at birth. His elder brother expired at 3 months of age with similar complaint of multiple bruises over the body. Diagnosis was not established because he expired before reaching the hospital.

In the present admission the child came with acute respiratory tract infection and few bruises on the back and thigh, there was no lymphadenopathy and visceromegaly. The child was febrile and tachypnoeic with mild wheeze bilaterally. His anthropometrics measurements were with in normal limit.

Initial investigations showed normal complete blood counts and peripheral blood smear. Both PT and APTT were prolonged. Other relevant investigations like liver function test, blood culture were also done which were unremarkable. On the basis of prolonged PT and APTT, common pathway defect was suspected. Clotting factor assay including fibrinogen, prothrombin, factor V and factor X were done which revealed absent prothrombin level while other factors were within normal limit.

Patient was treated for acute respiratory infection and was transfused fresh frozen plasma. Prothrombin complex concentrate was not given to the patient because of non-affordability and patient was discharged on request after respiratory tract infection and bruises had resolved. Patient is being followed at the outpatient department, is thriving well and has not bled again to date.

Discussion

Patients with inherited severe hypoprothrombinaemia present early in life, whereas a patient with mild form may present later at any age. Severe life-threatening haemorrhage, including intracranial haemorrhage, is found in neonates with severe prothrombin deficiency. Severe prothrombin deficiency leads to spontaneous abortion and foetal demise in some cases. Complete prothrombin deficiency has not been reported; suggesting that this condition is incompatible with life. In both acquired and inherited hypoprothrombinaemia, the morbidity and mortality risks are related to the circulating level of factor II. The risks are <2% with severe deficiency, 2-10% with moderate deficiency, and 10-40% for mild deficiency.[2]

Despite having absent prothrombin level in our patient, he had only two episodes of bleeding one major as subdural bleed during neonatal life and one minor as subcutaneous bruises. He is not on prophylaxis treatment and is coming regularly for follow up. Now he is six months old.

Case report of two infants of consanguineous marriage showed that these patients presented with acute

subdural haematoma. Investigations revealed a bleeding diathesis due to a prothrombin deficiency. DNA analysis of the prothrombin gene showed homozygosity for a novel mutation, substituting Lys for Glu at codon 7 and resulting in decreased specific clotting activity.[7]

Another case of a male infant showed that he experienced several life-threatening bleeding episodes. Standard coagulation tests revealed that the patient's plasma prothrombin activity was 8%, while his father's and mother's levels were 74% and 62%, respectively.[8]

Severe hereditary prothrombin deficiency was reported in a 14-year-old girl first diagnosed 4 years of age. Treatment included repeated FFP after bleeding events to prophylactic home infusions with the prothrombin complex concentrate. The patient has been essentially free of abnormal bleeding while on this prophylactic regimen for 17 months, with no toxicities and with a much-improved quality of life.[9]

Moderate bleeding can be treated with Fresh Frozen Plasma. Correction of prothrombin can also be achieved with the use of Prothrombin complex concentrates (PCCs).[3] PCCs contain factors II, VII, IX and X. However, there are differences in the amount of factor II present in PCCs, depending upon the product. The major disadvantage of PCCs is a potential for thrombosis, presumably because of contamination of factors such as FXa and FIXa. The dose of infused product should not exceed 100 units/kg, and the frequency of infusion should be adjusted to maintain homeostasis but not excessive level of prothrombin.[10]

References

1. Selighsohn U, White GC. Inherited deficiency of coagulation factor. In: Brutler E, Lichtman MA, Coller BS, Kipps TJ, Selighsohn U Eds. William Heamatology 6th ed. McGraw Hill 2001; pp 1617-19.
2. Excerpts from Hypoprothrombinemia. (Online) 2008 (Cited 2008 Nov 10). Available from URL: http:://emedicine.medscape.com/article/956030-overview.
3. Factor II deficiency. National Hemophilia foundation (Online) 2008 (Cited 2008, Nov 10). Available from URL: http:/www.hemophilia.org/NHFwebN/pgs/NHFaspmenird=1185&contenid =488rptname=bleeding.
4. Freidmen KD, Ridgers GM. Inherited coagulation disorders. In: Greer JP, Foerster J, Lukens JN, Rodgers GM Eds. Wintrobe's Clinical Heamatology. 11th ed. Philadelphia:Lippencott William & Wilkins 2004; pp 1642-43.
5. Khalid S, Bilwani F, Adil SN, Khurshid M. Frequency and clinical spectrum of rare inherited coagulopathies - a tricenter study. J Pak Med Assoc 2008; 58: 441-4.
6. Factor II deficiency (Prothrombin deficiency). (Online) 2006 (Cited 2009 Apr 15). Available from URL: http;//www.hemophilia.ca/en/bleeding-disorder/others-factor-deficiency.prothrombin.deficiency # C343.
7. Strijks E, Poort SR, Renier WO, Grabeels FJ, Bertina RM. Hereditary Prothrombin deficiency presenting as intracranial hematoma in infancy. Neuropediatrics 1999; 30: 320-4.
8. Wong AY, Hewitt J, Clarke BJ, Hudson DM, Krisinger MJ, Dower NA, et al. Severe prothrombin deficiency caused by prothrombin-Edmonton (R-4Q) combined with a previously undetected deletion. J Thromb Haemost 2006; 4: 2623-8.
9. Lobel JS, Majumdar S, Kovats-Bell S. Successful prophylactic treatment for bleeding in a girl with severe hereditary prothrombin deficiency using a prothrombin complex concentrate. J Pediatr Hematol Oncol 2004; 26: 480-3.
10. Blanchette VS, Dean J, Lillicrap D. Rare congenital hemorrhagic disorders. In: Lilleyman JS, Hann IM, Blanchette VS Eds. Pediatric Hematology 2nd ed. Churchill Livingstone 1999; pp 619-20.