ISSN- O: 2458 - 868X, ISSN –P: 2458 - 8687

International Journal of Medical Science and Innovative Research (IJMSIR)

IJMSIR : A Medical Publication Hub

Available Online at: www.ijmsir.com

Volume – 2, Issue –6, November – December - 2017, Page No. : 455 - 460

An Intriguing Case of Congenital Coagulopathy: Presenting as Intracranial Haemorrhage in a Term Neonate

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Conflicts of Interest: Nil

Abstract:

Congenital coagulopathy leading to intracranial haemorrhage (ICH) is rarepresentation with the overall incidence still unknown, owing to a number of asymptomatic cases and the varying sensitivity of the neuroimaging procedures used for diagnosis. We present a case of ICH in a twenty five day old term neonate who was referred to our institute with complaints of lethargy, fever and vomiting. The patient was markedly pale with tense and bulging anterior fontanelle. Neuroimaging (CT scanbrain) revealed bilateral acute on chronic subdural haemorrhage. Coagulation profile was indicative of an isolated prolongation of prothrombin time (PT) with a normal activated partial thromboplastin time (APTT) signifying an extrinsic pathway disorder following which Factor VII assay clinched our diagnosis of Factor VII deficiency. The patient was treated with intravenous Vitamin K along withfresh frozen plasma transfusions considering the non-availability of Factor VII concentrate or activated recombinant Factor VII concentrate. Preliminary family screening with PT was normal and the child was discharged with counselling regarding immediate home based acute post seizure care and the importance of avoiding even trivial traumatic episodes.

Keywords: Alexander disease, coagulation disorder, factor VII, subdural bleed,

Introduction

Intracranial haemorrhage (ICH) is a major cause of morbidity and mortality in neonates. ICH is relatively uncommon in term neonates resulting mostly due to birth trauma following an instrumental delivery or difficult vaginal delivery. Other important perinatal risk factors include breastfed neonates who didn't not receive vitamin K at birth, newborns with thrombocytopenia, and rarely congenital coagulopathies. Hemophilia A and B are the most common congenital coagulopathy states linked to ICH, alongwith other rare coagulopathies like Factor V, VII or XIII deficiency and congenital afibrinogenemia[(1)]**.** Factor VII deficiency also known as Alexander's disease is a rare congenital coagulopathy, the prevalence being one in 500,000 in general population[(2,3)]. An altered PT level in the setting of normal APTT level raises suspicion for the disease; very low factor VII levels being confirmatory.The spectrum of clinical manifestations ranges from severe life-threatening haemorrhages, like

cerebral, gastrointestinal, and joint haemorrhages, to minor bleeding like epistaxis, easy bruising and gum bleeds.Management options include Factor VII replacement therapy by various modalities, recombinant activated factor VII (rFVIIa) being the best option available currently. In this case report, we present a rare case of Factor VII deficiency which resulted in ICH in a term neonate, its manifestations and the diagnostic and management strategies followed in a tertiary hospital in a developing health care set-up.

Case Report

A twenty five day old, full term male child with birth weight of 2.5 kg, born vaginally to third gravida mother was referred to our hospital with complaints of lethargy and refusal to feed for three days and fever with vomiting for one day prior to admission. The patient was referred with an ultrasound (USG) report of the skull suggestive of suspected intracranial haemorrhage. There was no history suggestive of respiratory distress, cyanosis, sweating over forehead while sucking or any abnormal movements and baby was passing urine and stools normally.Detailed history revealed third degree consanguineous marriage and antenatal / perinatal period was uneventful. The child had two elder siblings who didn't have any significant illness and were developmentally normal for age.

Examination revealed an irritable and lethargic child with a tense, bulging anterior fontanelle. The baby was markedly pale with no organomegaly detected and head circumference showed 3 cmsincreasesince birth. On central nervous system examination (CNS) hypertonia in both upper and lower limbs with brisk reflexes was noted. Our initial differentials were late onset septicaemia with meningitis and/ or intracranial haemorrhage.

On admission at our hospital, the initial USG skull report, was inconclusive of an intracranial bleed and showed only extra-axial hyper-echogenicity. We went ahead with lumbar puncture to rule out meningitis which turned out to be normal. Over the next two days, it was noticed that patient remained lethargic and there was a definite falling trend in haemoglobin with worsening pallor. CT Brain(plain) was done which revealed acute on chronic subdural haemorrhage (maximum thickness 8mm and 4mm on left and right side respectively).

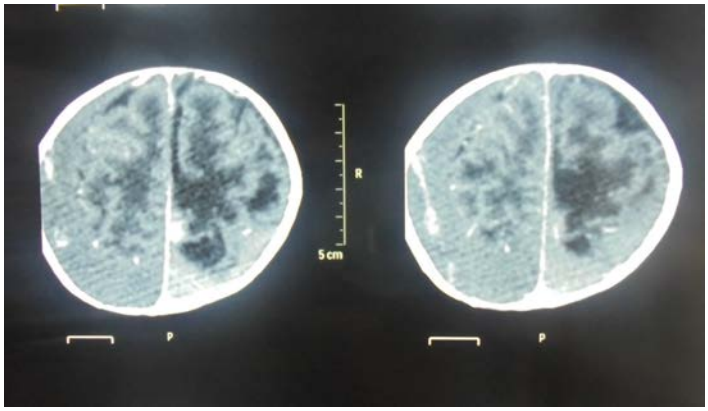

Figure 1: CT Brain (Plain) showing bilateral acute on chronic subdural haemorrhage with maximum thickness of 8mm and 4 mm on left and right side respectively.

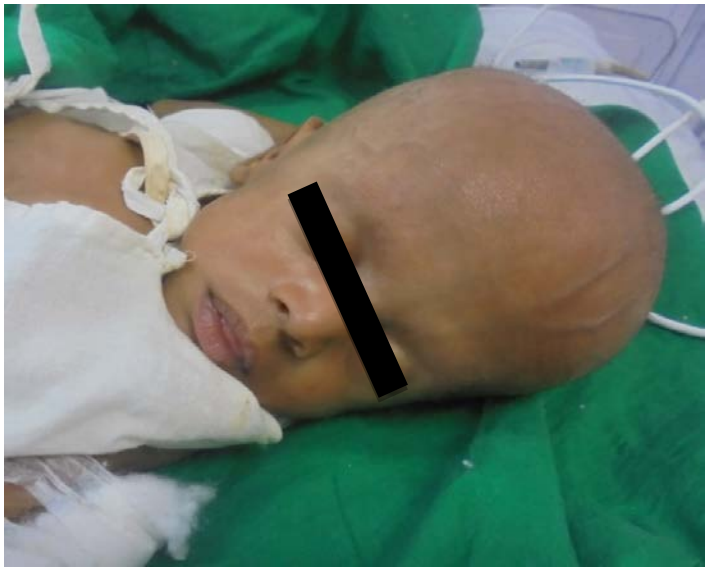

Figure 2: Clinical photograph of thepatient showing a pathologically large head circumference, with prominent scalp veins and bulging anterior fontanelle.

Considering above findings, the diagnostic dilemma was between delayedhaemorrhagic disease of new born(HDN), coagulation disorders or battered baby

syndrome. However, with a history of receiving vitamin K prophylaxis at birth and no hyperbilirubinemia, reticulocytosis or derangements in liver parameters, possibility of delayed HDN was remote. Battered baby syndrome was ruled out as no signs of injury were found externally or on the infantogram and the parents were quite caring towards the child. Coagulation profile was done, which was markedly deranged. The prothrombin time (PT) was grossly prolonged (PT >50 secs), however APTT was normal. Urgently Fresh frozen plasma was started thrice daily with intravenous Vitamin K 1mg daily for 3 days. However, the repeat coagulation profile after 3 days of therapy still persisted to show deranged PT with normal APTT.

In view of isolated prothrombin time prolongation, a strong suspicion of specific intrinsic pathway factor deficiency, namely Factor VII, was thought of and the assay was done. Factor VII assay by thromboplastin dependent one stage clotting revealed markedly low levels (2.5% with the normal range from 50% to 150%) and this clinched our diagnosis of congenital factor VII deficiency. Fresh frozen plasma was continued for 5 days till the PT level normalized. Family screening was advised in the form of factor VII assay, however due to monetary constraints, only PT and APTT levels could be done, the results being normal for both parents and the siblings. The child was discharged on day 47 of life with appropriate counselling with emphasis on avoiding even trivial trauma. Till date (one year old) the child has been readmitted twice for seizure episodes and there was no associated bleeding documented from any site. During both these admissions, neuroimaging did not reveal any fresh ICH. So, theseizure episodes were attributed to sequela of the previous insult.

Discussion

Factor VII was found to be the key initiator of coagulation by Alexander and associates in 1951 who first described factor VII deficiency which was also named as serum prothrombin conversion accelerator (SPCA) deficiency[1,2].

Factor VII is a vitamin K–dependent serine protease glycoprotein which plays a pivotal role following interaction with Tissue Factor (TF) in the extrinsic pathway of the coagulation cascade. It has a circulating half-life of only 3-4 hrs with a plasma concentration of 0.5 mcg/ml[4]. The principal step in the extrinsic pathway comprises of the interaction between activated form of Factor VII(FVIIa) and Tissue Factor (TF) exposed on the vascular lumen after injury. Thisactivates Factor IX (to IXa) and factor X (to Xa) further interacting with factor Va and calcium ions ultimately inducing a stable clot formation[5].

Factor VII deficiency can be inherited or acquired, with the inherited variety further classified as type 1 or 2. Type 1 deficiencies are quantitative defectsand result from reduced synthesis or accelerated destruction or clearance while the type 2 abnormalities represent a qualitative defect in the FVII molecule[6].The genesis of congenital Factor VII deficiency involves abnormalities in the F7 gene located on chromosome 13q34 encoding a 12Kb protein. The protein structure has 406 amino acid composed of two chains; the heavy chain containing the C-terminal serine protease catalytic domain and the light chain comprising of the N-terminal gamma-carboxyglutamic acid (Gla) domain and two epidermal growth factor-like (EGF) domains[7]. Till date, more than 200 mutations scattered along the gene have been reported; with point mutations being the main feature of inherited FVII deficiency and missense mutations being the most frequent. Being a autosomal recessive trait, only homozygotes and compound heterozygotes develop

haemorrhagic manifestations, heterozygotes are usually asymptomatic[8].

Most severe cases of factor VII (FVII) deficiency are diagnosed often during infancy, however neonatal presentation is rare as was seen in our case. In infancy, the gastrointestinal tract (GIT) or centralnervous system (CNS) are most prone for bleeding, accounting for 60-70% of bleeds in this age group.During the neonatal period, bleeding after circumcision or heel stickand in childhood, bleeding after dental procedures are quite common in inherited Factor VII deficiency[9]. The main bleeding sites in FVII-deficient patients occurs intissues in which haemostasis depends on the extrinsic pathway as these are rich in tissue factor (i.e., brain, bowel, uterus, placenta, lungs and heart)[4].

Clinical symptomatology varies from asymptomatic cases to mild muco-cutaneous bleeds such as epistaxis, gum bleeds and may even cause severe life-threatening haemorrhage involving CNS and GIT systems. Clinical signs being extremely variable, no relationship exists between residual Factor VII activity and the risk and severity of bleeding.

The overall clinical presentations considering all age-groups is shown in Table 1:[5,7,10]

Clinical groups	Percentage	Clinical presentation and comments
Asymptomatic	33 %	Diagnosed during haemostatic or family screening
Mild (muco-cutaneous)	52-57 %	Epistaxis (60%), gum bleeding (34%), easy bruising (36%) and menorrhagia (69% of females)
Severe (life-threatening)	10-15%	Haemarthroses(19%), gastrointestinal bleed (15%), intracranial bleed (2.5%), and umbilical cord stump bleeding

Table 1: Table showing clinical groups and presentations among patients with congenital Factor VII deficiency

The severe cases usually present with life-threatening bleedings at FVII levels usually <5%, while cases with moderate-to-mild forms with muco-cutaneous bleeds usually have FVII level ~5–10%[7].

FVII deficiency is suspected when a prolonged PT is associated with a normal APTT as in our patient. FVII assays are performed by using thromboplastin-dependent one-stage clotting assay, normal levels varying on the choice of reagents (mostly between 50-150%).The diagnosis in cases with the presence of anti-FVII antibodies can be made after a mixing test. The sensitivity of factor VII assay varies and decreases when thromboplastins contaminated with even small amount of FVIIa are used. This is of particular importance in diagnosing type II defects like FVII Pandua(Arg304Gln in exon 8) which shows erroneouslynormal results if brain thromboplastin is employed[11].

Molecular diagnosis is based on the conventional polymerase chain reaction(PCR) techniques and is of utmost value for cases in which inheritance pattern is not clear. More complex intragenic rearrangements even undetected by PCR can be detected by semi-quantitative multiplex PCR, thus providing a full mutational status in FVII deficiency[12].Almost 90 % of mutated alleles are detected by direct sequencing; however in 10 % of congenital factor VII deficiencies, still the culprit mutationshaven't been found raising inquisitiveness

towards another gene responsible for the disease warranting further research in this area[13]. Prenatal diagnosis is available and should be proposed when a family history of suspected bleeding disorder is present. Cord blood is usually obtained by either the trans-abdominal or trans-amniotic approach, and genetic analysis remains the gold standard method[14].

Treatment options are challenging as bleeding risk can't be predicted with FVII levels alone and fixed guidelines for the management of this rare disorder are still lacking. Multicentre observational studies like STER and IRF7 have provided evidence regarding the mainstay of treatment which is replacement therapy[15]. Thereplacement therapy options available at present are recombinant factor VIIa infusions, plasma derived FVII, fresh frozen plasma and Prothrombin, Proconvertin, Stuart factor, Antihemophilic factor B concentrate (PPSB). Recombinant factor VIIa(rFVIIa) infusion (15-30 mcg/kg) is the best modalityavailable with advantages like a large volume of distribution and prolonged pharmacodynamics; the only cons being short half- life (4-6 hours), higher cost and a marginally increased risk of thrombosis. In the developing countries, still fresh frozen plasma (30 cc/kg/day) plays a pivotal role owing to its easy availability and lower cost, although multiple transfusions have a risk of volume overload and blood borne pathogen transmission.

Antifibrinolytics such as tranexamic acid can be of help in mild bleeds alone or in combination with replacement therapy. Recent studies have advocated the need for long term recombinant FVIIa(rFVIIa)prophylaxis in patients with severe life-threatening presentations. A weekly dose of 90 mcg/kg weekly in 3 divided doses has shown effective results as per STER studies[16].

Certain aminoglycosides have emerged as a ray of hope to suppress premature termination of translation by non-sense mutation in a number of diseases. Specifically, gentamicin was shown to be most effective of the aminoglycosides and was able to induce in vivo a minimal but clearly noticeable increase of FVIIc[17]. Such non-replacement therapeutic approachesare under research and hopefully will soon revolutionize the management strategies for such coagulation factor deficiencies.

Conclusion

Factor VII deficiency is a very rare congenital coagulopathy and should be suspected in a bleeding neonate with a prolonged PT and normal APTT. Treatment strategies will dependon the availability of newer modalities such as FVII concentrates or rFVIIa and in case of non-availability, cheaper and easily available option like FFP helps to tide over the crisis situations. Expectant parents with a family history of coagulopathy should be counselled regarding availability of prenatal diagnosis and for factors like evading trauma episodes and primary post seizure care.

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