CASE REPORT

Congenital Factor VII deficiency: a case report

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Abstract

Factor VII deficiency is a rare congenital blood disorder. Its clinical features are rather variable and ranges from epistaxis to massive intracranial haemorrhage. Treatment involves replacement therapy, which constitutes use of fresh frozen plasma, prothrombin complex concentrates or recombinant activated factor VII. Although it is a rare entity, one still needs to consider it as a probable diagnosis in a newborn with coagulopathy. We report here a case of Factor VII deficiency in a newborn who presented with subdural haemorrhage at day 4 of life.

Key words: Congenital factor VII deficiency, newborn, coagulopathy

INTRODUCTION

The process of haemostasis involves several phases, which include interaction of specific coagulation factors. Inherited disorders of coagulation are a fairly diverse group of which Factor VII deficiency is an entity. Factor VII deficiency is usually suspected if the prolonged prothrombin time (PT) is corrected in a 50:50 mix of test and normal plasma, provided there is no inhibitor present. The clinical spectrum of congenital factor VII deficiency is rather variable; it has been shown that there is a relatively poor correlation between factor VII levels and the risk of bleeding. As this disease is rare, to date, there is no consensus guideline for its overall management. However, it is recommended that recombinant factor VIIa is the treatment of choice in patients with inherited deficiency of moderate to severe level.

CASE REPORT

Baby ‘C’ was delivered via forceps, after two failed vacuum attempts, for poor maternal effort at a private hospital. He was a term baby with a birth weight of 3.26 kg and good Apgar scores. There was bilateral cephalhaematoma with subsequent jaundice but he was otherwise stable. On Day 4 of life, he was noted to be pale with a haemoglobin level of 7.5g/dL and was transfused packed cells. Cranial ultrasound then was normal. He remained relatively well and was discharged on Day 8 of life. Three days later he was readmitted for pallor, which was associated with vomiting, lethargy and poor oral feeds. Clinically he was irritable and had decorticate posture. He was also hypertensive with a blood pressure of 98/60 (mean of 76) mmHg. There was no evidence of any overt bleeding. The anterior fontanelle was full and tense and cranial sutures were separated. There was no significant hepatosplenomegaly. Cranial ultrasound followed by CT brain showed a right subdural bleed with a significant midline shift and compressed ventricles. There was no skull fracture. Initial blood investigations showed: Hb 8.1gm/dL and platelet of 674 x 10^9/L, prothrombin time (PT) 39.0s (control 12.4s, INR 3.49) and activated partial thromboplastin time (APTT) 35.4s (control 32.9s); fibrinogen level was normal. Both fresh frozen plasma (FFP) and packed cells were transfused and intramuscular vitamin K given. He also had an episode of seizure for which intravenous phenobarbitone was loaded. Evacuation of the right subdural haematoma was performed via a right temporo-parietal craniotomy. Both intraoperative and post-operative periods were uneventful. A repeat CT brain was done on postoperative day 2, which showed a residual right subdural haematoma with obliteration of
the ipsilateral ventricle for which evacuation was again performed. Subsequent CT brain on post-operative day 4 showed no evidence of a new bleed.

During this period of time, a series of coagulation profile was done (Table 1) which showed a persistently prolonged PT that was transiently corrected by FFP transfusion; the APTT was prolonged only once. Generally, the time interval between the given treatment (i.e. vitamin K/FFP) and the subsequent PT was between 3 to 4 hours. Liver function test was normal. Further investigation revealed that the PT could be corrected with normal plasma, suggesting an inherent clotting factor deficiency. Clotting factor assay (i.e. factor VII activity) was done. This confirmed that the baby has factor VII deficiency, i.e. <1% (with a normal control of 37.1%). Both parents’ Factor VII assays however showed normal levels. There was no family history of any bleeding disorders and the parents are non-consanguinous. Baby ‘C’ was discharged at day 28 of life after a repeat cranial ultrasound showed resolution of the subdural bleed with a normal brain configuration. Neurologically, he was alert, his tone and reflexes were normal and he sucked well on feeds. Subsequently, he had several admissions for bleeding episodes; at Day 31 of life, (bleeding from the umbilical stump), Day 36 (bleeding from previous venepuncture site) and Day 52 (bleeding from the umbilical stump again). Regular FFP was transfused throughout these admissions. Unfortunately, at Day 60 of life, he was readmitted with pallor, vomiting and seizures. He was opisthotonic, had unequal pupillary response and left fundal haemorrhage. CT scan of the brain showed an extensive left temporoparietal bleed with midline shift. He received FFP transfusion and underwent evacuation of the blood clot. His stay in the intensive care unit was complicated by a pneumonia which recovered thereafter. Unfortunately, on Day 76 of life, he had massive bilateral pulmonary haemorrhage to which he succumbed.

**DISCUSSION**

Factor VII (F VII) is essential for activation of coagulation within the extrinsic pathway. Its concentration within the plasma is very low, and of all the classical coagulation factors, F VII has the shortest half-life of only 3 to 4 hours. Factor VII deficiency is a rare congenital blood disorder, with an estimated incidence of 1 per 500,000 in the western general population. It is inherited in an incomplete autosomal recessive pattern. Consanguinity is an important element in diseases with an autosomal recessive inheritance. However, having said that, in the series of 75 patients reviewed by Ragni et al, only 19% were reported to be consanguinous. In our patient, both parents were non-consanguinous and there was no significant family history of bleeding tendencies. Although their Factor VIIc levels were normal, this condition is known to have a rather variable expression with poor correlation between reported coagulant activity and clinical bleeding tendency. This may well be the explanation for the normal Factor VII assay in the parents. Another possibility is that the parents are gonadal mosaics or alternatively, only one of them is a gonadal mosaic with the other mutation occurring spontaneously in the patient himself.

As with the haemophilia group, Factor VII deficiency may be classified into the severe form (Factor VIIc <1%) and the mild to moderate form (Factor VIIc 5-7%). However, the plasma level of Factor VII that is required for haemostasis is not known and this perhaps contributes to its rather variable expression and poor correlation between reported coagulant activity and clinical bleeding tendency.  

The clinical features range from epistaxis 

<table>
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<tr>
<th>Day of life</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 8</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 14</th>
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</thead>
<tbody>
<tr>
<td>PT (s)</td>
<td>39.0</td>
<td>23.2</td>
<td>29.7</td>
<td>42.2</td>
<td>48.9</td>
<td>22.5</td>
<td>33.6</td>
<td>43.4</td>
<td>44.0</td>
<td>28.1</td>
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<tr>
<td>INR</td>
<td>3.49</td>
<td>1.85</td>
<td>2.44</td>
<td>3.62</td>
<td>4.40</td>
<td>1.83</td>
<td>2.84</td>
<td>3.99</td>
<td>4.10</td>
<td>2.47</td>
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<tr>
<td>APTT (s)</td>
<td>35.4</td>
<td>28.2</td>
<td>32.0</td>
<td>37.2</td>
<td>&gt;180</td>
<td>35.3</td>
<td>35.1</td>
<td>37.5</td>
<td>36.6</td>
<td>35.9</td>
</tr>
<tr>
<td>Intervention</td>
<td>FFP, Vit K</td>
<td>Vit K</td>
<td>– Vit K</td>
<td>FFP</td>
<td>– Vit K</td>
<td>FFP, Vit K</td>
<td>–</td>
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</table>

*Table 1: Serial coagulation profile*

*Note:* The dose of vitamin K given was 1mg and the amount of FFP transfused was 20mls/kg each time.
and post-surgical bleeding to massive haemorrhages involving the central nervous system (CNS); subdural, subarachnoid and intracerebral haemorrhages are amongst those reported. In fact, the incidence of CNS haemorrhages are higher in this condition when compared to other congenital coagulopathies, with the exception of fibrinogen and Factor VIII deficiencies. In the same review of 75 patients by Ragni et al, the incidence of CNS haemorrhage was 16% (12 cases). Of these, 5 occurred in the first week of life and 4 before the age of one year. Unfortunately, only 33% of those with CNS haemorrhage survived. This series also revealed that there was no significant history of preceding trauma or previous underlying CNS abnormality although trauma during delivery was postulated as being a significant risk factor. The fact that this patient underwent instrumental delivery could also be a contributing factor.

Treatment of this condition is mainly by replacement therapy using fresh frozen plasma or prothrombin complex concentrates (PCC). However, as Factor VII has a relatively short half-life, fresh frozen plasma would be required rather frequently within a day, thus a fairly large volume would have to be transfused to the patient. This may be a considerable worry especially in infants. However, though the use of PCC will result in a lower volume of fluid transfused, there will be an unnecessary rise of the other vitamin K dependent factors. In view of all these considerations, plasma derived Factor VII concentrate was developed for use in treating such conditions. Furthermore, as all these products are plasma-derived, the risk of transmitting blood-borne viruses (e.g. Hepatitis B and C) cannot be eliminated entirely. Recently, recombinant activated Factor VII (rFVIIa) has been produced but it is not readily available and is expensive. rFVIIa has been reported to have a high efficacy rate in the treatment of Factor VII deficiency.

Prenatal diagnosis is currently possible especially if the mutation is known for the kindred under study. The human Factor VII gene has been localised to chromosome 13q34. This gene which contains 9 exons separated by 8 introns, covers a span of 12.8 kb. To date, more than 30 different mutations have been identified in these patients. Most have been single base pair substitutions, however, small deletions and splice site abnormalities have also been described. Of the single base pair mutations, a large proportion are missense mutation but nonsense mutation have also been identified. Although there is a recognised ‘hot spot’ for these mutations, unfortunately most of the reported mutations responsible for FVII deficiency have been reported only once. In view of this, direct gene sequencing will probably need to be performed to identify the responsible mutation. Millar et al reported the first successful prenatal exclusion of severe F VII deficiency in an at-risk pregnancy. This was followed by reports from several other centres.

In this case, as the baby’s DNA is not available, the alternative would be to screen both parents instead. If the mutations are discovered, this will then pave the way for a possible prenatal diagnosis in future pregnancies. On the other hand, if the yield is negative, an anticipatory approach with referral to a specialised centre should then be done. In such cases, careful genetic counselling is an important aspect in the overall management.

In conclusion, there are many causes for a newborn who presents with coagulopathy. Although acquired causes such as those related to liver disease should generally be excluded first, one still needs to consider inherited disorders such as Factor VII deficiency, as a possible diagnosis. The variable clinical spectrum and need for specialised therapeutic options are important management issues in this particular disease.

REFERENCES
