Title: A neonatal presentation of factor V deficiency: A case report

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Abstract:

Background: Factor V deficiency is a rare autosomal recessive coagulation disorder. Awareness of presenting features and management is important to avoid bleeding complications associated with mortality and neurodisability.

Case presentation:

A 6-day-old Pakistani boy was admitted with bleeding from the left nipple. His parents were first cousins. A coagulation screen showed a prothrombin time of 41s (control 14s), a partial thromboplastin time of 132 s (control 33s) and a normal thrombin time of 15s (control 14s). Factor V activity was <0.01 IU/ml. Oral tranexamic acid was started. At 5 weeks of age the child presented with irritability, lethargy and reduced feeding and a drop of haemoglobin to 5.6g/dl. A cranial computed tomography scan showed a right intra-cerebral bleed extending from the frontal lobe to the parieto-occipital region with shift of the midline to the left. A regime of 20 ml/kg of fresh frozen plasma four times a week was instituted and has prevented further bleeds up to the present age of 14 months. Neurodevelopment remained normal.

Conclusion: This case illustrates that in an unusually bleeding newborn of consanguineous parents rare severe homozygous bleeding disorders need to be considered. Nipple bleeding may be the first presentation of a congenital bleeding disorder. In cases of factor V deficiency where factor concentrates are not available long term use of fresh frozen plasma can prevent potentially life threatening bleeding.

Keywords: Factor V deficiency, neonatal intracerebral hemorrhage, neonatal nipple bleeding
**Background**

Congenital deficiency of factor V (labile factor, proaccelerin) is a rare hereditary coagulation disorder with an incidence of 1:1000,000 and is inherited as an autosomal recessive trait (1). The active form of coagulation factor V is involved as an essential non-enzymatic cofactor for the activated factor X catalysed conversion of prothrombin to thrombin. Affected patients become symptomatic in early childhood with spontaneous or post-traumatic bleeding complications (2). We present to our knowledge the first case of nipple bleeding as the initial haemorrhagic manifestation of factor V deficiency in the neonatal period. It preceded an intracerebral haemorrhage.

**Case presentation**

A 6-day-old Pakistani boy was admitted to hospital in June 2005 for bleeding from the left nipple. His parents are first cousins. He has two siblings aged 8 and 6 years. There was no family history of bleeding diathesis. The mother had a normal pregnancy with full antenatal care. Mode of delivery at term was an elective Caesarean section due to previous Caesarean sections. His birth weight was 2.7 kg. 1 mg of Vitamin K was given intramuscularly at delivery. His first neonatal check was normal. He had a small amount of self-limiting bleeding from the umbilical cord on day 3 of life. He went home on day 4.

On day 6 of life he had mild spontaneous left sided nipple bleeding (See figure 1), which presented as spots of blood stains on the left side of his baby dress. Over the next 7 days he had two further episodes of a similar nature. Baseline biochemistry and full blood count were normal but a coagulation screen showed a prolonged prothrombin time of 41 s (control 14 s), a prolonged partial thromboplastin
time of 132 s (control 33 s) and normal thrombin time of 15 s (control 14 s). In view
of the mild nature of bleeding, the child was only treated with 1 mg of i.v. vitamin K.
Subsequent coagulation assays revealed a plasma factor V activity of less than 0.01
IU/ml (normal range 0.50-1.50 IU/ml) determined by factor V clotting assay with all
other coagulation factors in the normal range. Hence the diagnosis of congenital
factor V deficiency was made. A cerebral ultrasound done at this stage was within
normal limits. Oral tranexamic acid at a dose of 15 mg/kg/dose 3 times daily was
started.

Mother was found to have a plasma factor V activity of 0.44 IU/ml (normal range 0.5-
1.50 IU/ml) and the father of 0.52 IU/ml by factor V clotting assay. Both levels are
compatible with heterozygous factor V deficiency. The siblings had factor V activities
of 0.61 and 1.1 IU/ml respectively. Genetic analysis at the St. Thomas’s haemophilia
molecular genetics laboratory showed that the affected child is homozygous for a
frame shift mutation resulting in a premature termination sequence at codon 2178 in
exon 25 of the factor V gene and both parents are heterozygous for this mutation.

The infant presented at day 15 of age with a further episode of bleeding from the
umbilical stump. The bleeding stopped promptly following administration of 20ml/kg
of fresh frozen plasma (FFP, methyleneblue sterilized, single donor and US sourced).
Small bruises were noted around the venepuncture sites from the previous admission.

An oval shaped haematoma measuring 2 cm in diameter was noted on the
anterolateral aspect of the left thigh. It was attributed to the intramuscular injection of
vitamin K administered at birth. His head circumference was growing within normal
range and the repeat cerebral ultrasound was normal. Tranexamic acid was continued.
The patient presented again at 5 weeks of age with pallor, irritability, lethargy and
reduced feeding. His anterior fontanelle was bulging and tense. He was
haemodynamically stable and was self-ventilating in air. Blood and urine cultures were taken and intravenous ceftriaxone was started. His haemoglobin was 5.6 g/dl, which represented a significant drop from the previous estimation 3 weeks back. The cerebral ultrasound was repeated and showed a large intracerebral haemorrhage extending from the frontal lobe to the parieto-occipital region. There were a few cystic areas seen within this bleed, which suggested that the bleeding started at least a few weeks ago. The child was immediately transfused with 20ml/kg of FFP and 15ml/kg of packed red blood cells. He had a series of generalized fits within 5 hours of admission. Blood glucose and serum calcium were within normal limits.

The patient was transferred to the regional tertiary referral centre for specialised neurosurgical and haematological management. A cranial computed tomography (CT) scan showed a right, large, intracerebral bleed causing a shift of the midline to the left. The ventricles were not enlarged and the bleed did not extend into the ventricles (See figure 2). A Hickman line insertion was arranged to enable regular FFP infusions.

Preoperatively he was transfused again with 20 ml/kg FFP and 10ml/kg of platelet concentrate to achieve adequate haemostasis. Platelets are known to be a good source of factor V as it is stored in the platelet alpha granules. He was also given 3 given of recombinant factor VIIa (Novoseven, NovoNordisk®) as an empirical adjunctive agent in the peri-operative period in view of the fact that reliably haemostatic levels of factor V levels (0.25-0.30 IU/ml) are difficult to achieve in this condition. Factor VIIa is unlikely to work in the absence of any factor V but can contribute to increased thrombin formation once factor V is present. Postoperatively a regime of FFP (15ml/kg/dose) administration was set up: FFP twice a day for the first 10 days followed by once a day for the next 10 days. This was followed by at least alternate day (every 48hours) of FFP at 20ml/kg/day up to the present. Plasma factor V activity
has been monitored: A maximum factor V level of 0.23 IU/ml was achieved within 20 minutes after transfusion. Trough levels were between <0.01 to 0.05 IU/ml. When undetectable factor V levels were noted inhibitor assays were performed. Inhibitors have not been detected so far. No further bleeding has been noted up to the present day. The infant is up to date with immunisations, which were all given subcutaneously as is normal practice for children with severe bleeding disorders. Hepatitis B vaccination was also given. Follow up until the present (14 months of age) revealed appropriate increment in the head circumference and there has been no abnormality noted with hearing or vision. The neurodevelopmental evaluation has been within normal limits.

**Conclusions**

Our report describes the 6th case of homozygous severe factor V deficiency presenting as bleeding in the early neonatal period reported in the English literature. Clinical and laboratory features of the other cases (1, 2, 3, 4, 5) are listed in table 1. Unilateral nipple bleeding as the first significant bleeding manifestation has not been reported in a coagulation disorder before. The differential diagnosis of nipple bleeding in infancy includes trauma, infection or spontaneous bleeding of a hypertrophic (due to maternal hormones like estrogen, progesterone and prolactin) breast gland (6), papillomas within the breast gland (7) and infantile cystic ductal hyperplasia of the breast gland (8). In our case there were no clinical features supporting any of these diagnoses. Mild haemorrhagic manifestations of coagulation disorders in infants reported previously included umbilical stump bleeding, subcutaneous haematomas, epistaxis and gum bleeding (9). This case illustrates that in an unusually bleeding newborn of consanguineous parents rare severe homozygous bleeding disorders need to be considered. The mild first manifestations need to alert the clinician and lead to the
prompt initiation of coagulation studies bearing in mind that in factor XIII deficiency coagulation tests are normal and factor analysis is required. Even though factor V deficiency can be recognized early prophylaxis of bleeding complications like intracerebral bleeds is difficult in the absence of a factor concentrate and the fact that the risk of intracerebral bleeds for the individual patient is unknown. Intracerebral or subdural bleeds are the most feared complication and have been noted in about 1/10 reported cases in the neonatal period which may be an overestimate due to overreporting (4). In our case, a life threatening intracerebral bleed occurred at 5 weeks of age. Though rare, congenital factor V deficiency should be kept in mind as a differential diagnosis in an otherwise well term infant presenting with catastrophic intracranial bleed, particularly if the parents are consanguineous (2).

Prolonged PT and PTT with normal thrombin time and normal platelet count would be an initial pointer towards an inherited disorder of coagulation. Clotting factor assay revealing markedly reduced plasma factor V activity confirms the diagnosis (4). As there is no specific concentrate available, the mainstay of treatment for severe factor V deficiency is FFP. Platelets also contain factor V, though their use should be reserved for life threatening bleeding and prior to surgery. There is a considerable variation in the volume of FFP and frequency of its administration needed to achieve haemostasis for a particular bleeding episode in the individual patient (4, 10). FFP administration should be titrated according to estimated changes in the plasma factor V activity (5). The half-life of factor V is 12-36 hours and is probably lower in neonates. Therefore regular infusions at least every 48 hours are required in patients with a history of severe bleeding complications. Despite such a regime it is difficult to achieve a factor V level >0.3 IU/ml without encountering problems of fluid overload because of the fact that FFP is not a concentrated treatment.
In our patient one could argue that early institution of regular FFP infusions could have prevented the intracranial haemorrhage and, although it was considered at diagnosis, it is crucial to establish in each case that they have a severe bleeding phenotype before embarking on regular FFP infusions which carry the risks associated with central venous access and FFP and platelet transfusion. Many reported cases of severe factor V deficiency do not have such severe bleeds and may only need treatment at times of surgical challenge (11, 12). At present it is difficult to predict the clinical course with regards to the risk of severe bleeding complications. Future genetic studies may improve our understanding of the risk of developing a severe phenotype associated with a specific genotype. As severe factor V deficiency with a clinically severe phenotype is a very rare disorder of haemostasis the long term prognosis cannot be delineated. It is very likely that cases such as this did not survive infancy in the past and even now the prognosis must be guarded. Detection of the causative mutation is important which facilitates genetic counselling of the parents and prenatal diagnosis in future pregnancies.

The authors declare that there are no competing interests.

Authors contributions:

Amol Chingale, Michael Eisenhut and Anjali Gadiraju have made substantial contributions to conception and design of this report and have been involved in drafting the manuscript and revising it. Ri Liesner has made substantial contributions in acquisition of data and critical revision of the manuscript. All authors have given final approval of the version to be published.

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Written consent was obtained from a parent of the child for publication of this report.

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References:


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Table 1: Cases of neonatal presentations of factor V deficiency reported in the English literature so far.

<table>
<thead>
<tr>
<th>Age at first presentation</th>
<th>Birth</th>
<th>4 Days</th>
<th>10 days</th>
<th>18 Days</th>
<th>Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Hydrocephalous secondary to unilateral subdural haematoma</td>
<td>Large left subdural haematoma causing irritability, pallor, poor feeding</td>
<td>Antenatal diagnosis of increased head circumference and unilateral ventricular dilatation at 32/40, seizure on Day 10</td>
<td>Pallor, excessive crying, bleeding from umbilical stump, Large unilateral intracerebral bleed with intraventricular extension with hydrocephalous</td>
<td>Subdural haematoma</td>
</tr>
<tr>
<td>Family history</td>
<td>Consanguineous parents, no bleeding diathesis in family</td>
<td>Nonconsanguineous parents, no bleeding diathesis in family</td>
<td>Nonconsanguineous parents, no bleeding diathesis in family</td>
<td>Consanguineous parents, no bleeding diathesis in family</td>
<td>Nonconsanguinous, no bleeding diathesis in family</td>
</tr>
<tr>
<td>Clotting screen on presentation</td>
<td>PT: 33 (14) PTT: 87 (33)</td>
<td>PT: Very high PTT: immeasurable</td>
<td>PT: 61s (31s) PTT: 178</td>
<td>Prothrombin ratio: 2.56 (Normal 1-1.2) APTT: &gt;200</td>
<td>PT: 58 s(control 8.7-11.5 s), APTT 198.8 s (control: 29.5-42.7 s)</td>
</tr>
<tr>
<td>Factor V activity in baby (reference 70-120%)</td>
<td>&lt; 1%</td>
<td>&lt; 5%</td>
<td>2 %</td>
<td>3% Presence of Factor 5 inhibitor 2.4 U</td>
<td>&lt;0.4%</td>
</tr>
<tr>
<td>Factor V activity in parents</td>
<td>54%, 42%</td>
<td>35%, 40%</td>
<td>52%, 78%</td>
<td>40%, 63%</td>
<td>59%, 47%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Viral inactivated FFP</td>
<td>Virus inactivated FFP</td>
<td>FFP</td>
<td>FFP, platelet concentrate, activated prothrombin complex, immunoglobulins, single-volume exchange transfusion</td>
<td>No data</td>
</tr>
<tr>
<td>Outcome</td>
<td>Global neurodevelopmental delay</td>
<td>At 6 months, neurologically normal, but recurrent mucosal and soft tissue haemorrhages</td>
<td>VA shunt to drain the hydrocephalous</td>
<td>VP shunt for hydrocephalous, death following another episode of intracranial bleed</td>
<td>No data</td>
</tr>
<tr>
<td>References</td>
<td>(4)</td>
<td>(2)</td>
<td>(3)</td>
<td>(5)</td>
<td>(1)</td>
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