 FXIII deficiency due to base exchange Thr 449 (ACT) > Ile (ATT) in exon 11 of the factor 13A gene

A cause of bleeding?

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Summary

A 17-year old man was sent to us for coagulation testing because he suffered from acute bleeding which started immediately after making an incision in the skin for a urological surgery. The patient had a history of mild bleeding symptoms (nose bleeds during the childhood, gingival bleeds). Results of laboratory investigations: Blood group O, closure times (PFA 100): 132 s (ADP/collagen) and 300 s (epinephrine/collagen), VWF antigen 57%, VWF activity 50%, factor VIII activity 66%, factor XIII activity 59%. The results were confirmed by further investigations. Additionally, two relevant genetic findings were obtained: first a heterozygous base exchange in exon 11 of the factor 13A gene -Thr 449 (ACT)>Ile (ATT), not described before the completion of the study, and second the homozygous state of the 807 C-allele within the integrin α2 gene. The patient inherited the base exchange in the factor 13A gene from his mother. Homozygosity of the 807 C-allele in the integrin α2 gene is associated with a very low expression of the platelet collagen receptor. Individuals with low VWF due to blood group O and low platelet collagen receptor density often exhibit a bleeding tendency, e.g. bleedings from mucosal membranes or menorrhagia in females. Conclusion: In our opinion the light factor XIII deficiency in our patient is coincidental and not the sole cause of bleeding.

Keywords

Factor XIII deficiency, low von Willebrand factor, bleeding tendency

Schlüsselwörter

Faktor-XIII-Mangel, niedriger von-Willebrand-Faktor, Blutungstendenz

Zusammenfassung


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Congenital factor XIII deficiency was first described in 1960 by Duckert et al. (3). Its transmittance as an autosomal-recessive trait was detected by McDonagh et al. (8) in 1974. The severe form of the disorder (activity below 1%) is an extremely rare event and affects one out of one to five million people (5).

The majority of cases of factor XIII deficiency are the result of reduced activity of the factor XIII subunit. In such cases the responsible mutation is located in the factor 13A gene. Only 5% of factor XIII deficient patients belong to the subgroup with factor XIIIIB subunit deficiency resulting from mutations in the factor 13B gene. The combined absence of factor XIII subunits A and B is a very rare event (4).

Bleeding symptoms were almost exclusively observed in patients with a residual factor XIII activity lower than five percent (7), resulting from a homozygous or a compound heterozygous state of the causal mutations.

Bleedings typically occur several hours or even several days after an injury.

In 2007 Ivaskevicius et al. (6) presented the results of an international factor XIII registry. This registry comprised information of 104 patients with factor XIII deficiency. Five out of the 104 patients had factor XIII activities between 33 and 53%. From the genetic point of view these patients are heterozygous for any mutation in the factor 13 gene. Four patients were affected by bleeding events. This finding contrasts to the previous assumption that patients bleed only in the case of factor XIII activities below five percent (7). Possibly, in the four symptomatic cases a second defect of the haemostatic system was the cause of bleeding.
We believe that the following case report supports this assumption.

**Bleeding after incision**

In a man (age: 17 years) a severe bleeding occurred on making an incision in the skin for an urgent urological surgery (torsion of a testicle) resulting in a massive haematoma of penis and scrotum. At this time, neither local nor generalized symptoms of inflammation were evident and the course after the surgical procedure was uneventful. In the patient’s history, occasional nose bleeds during his childhood and gingival bleeding after dental care were reported.

The mother of the young man gave birth to four children, one Caesarean section included, without any bleeding complications. Appendectomy and spine surgery were also uneventful. However, a bleeding event occurred during laparoscopic cholecystectomy. This complication was explained as result of an injury, coagulation tests were not performed.

The father, the brother, the patient’s sisters and his nephew reported no bleeding events.

**Diagnosis**

Blood was obtained by clean venipuncture between 8 and 9 hours after a period of overnight fasting. Nine parts of blood were carefully mixed with one part of 0.129 mol/l trisodium citrate solution (BD vacuum). Blood cell count, thromboplastin time (Quick value), activated partial thromboplastin time (aPTT), fibrinogen concentration and the PFA-100 closure times (ADP/collagen and epinephrine/collagen) were determined in the patient and in family members. Coagulation factors II, V, VII, VIII, IX, X, XI, XII, XIII, the von Willebrand factor (activity and antigen concentration), antithrombin, protein C, protein S and the APC-ratio were analyzed in the patient, his parents, his brother, his sisters and his nephew. Finally, their blood groups were determined.

The assays of the coagulation factors were performed with commercially available test kits from IL according to the instructions given by the manufacturer with an automatic coagulation analyzer (ACL Advance, IL).

The factor 13A gene was analyzed after isolation of genomic DNA from leukocytes of the peripheral blood by standard means using micro spin columns (Qiagen, Hilden, Germany). The 15 exons of the factor 13A gene with intron-exon junctions were submitted to polymerase chain reaction (PCR) under standard conditions. Sequencing was performed with an automated coagulation analyzer (ACL Advance, IL)

The polymorphism within the integrin α2 gene (glycoprotein Ia/IIa gene) was detected as homozygous for 807 C. The low factor VIII activity and also low factor XIII activity was determined. Two years after the first investigation, the factor XIII, PFA-100 closure times, von Willebrand factor (VWF), and factor VIII activity were re-examined. The patient (no. 1) exhibited prolonged closure times, low VWF levels, low factor VIII activity and also low factor XIII values.

**Genetics**

The polymorphism within the integrin α2 gene (glycoprotein Ia/IIa gene) was detected as homozygous for 807 C. The low factor XIII activity results from a base exchange Thr 449 (ACT) → Ile (ATT) within

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**Tab. 1 Results of laboratory investigation (patient and his family members)**

<table>
<thead>
<tr>
<th>blood group</th>
<th>closure times (s)</th>
<th>VWF:Ag</th>
<th>VWF:Akt</th>
<th>FVIII:C</th>
<th>FXIII:C</th>
<th>base exchange*</th>
<th>polymorphism integrin α2-gene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADP/collagen</td>
<td>epinephrine/collagen</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>base exchange*</td>
</tr>
<tr>
<td>1. patient</td>
<td>0, Rh pos.</td>
<td>132</td>
<td>138</td>
<td>57</td>
<td>50</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>188</td>
<td></td>
<td>(1)</td>
<td>(3)</td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>2. father</td>
<td>0, Rh pos.</td>
<td>118</td>
<td>127</td>
<td>66</td>
<td>62</td>
<td>63</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>188</td>
<td></td>
<td>69</td>
<td>65</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td>3. mother</td>
<td>0, Rh pos.</td>
<td>90</td>
<td>107</td>
<td>96</td>
<td>113</td>
<td>77</td>
<td>present, heterozygous</td>
</tr>
<tr>
<td>4. sister +</td>
<td>0, Rh pos.</td>
<td>n. d.</td>
<td>n. d.</td>
<td>107</td>
<td>96</td>
<td>113</td>
<td>77</td>
</tr>
<tr>
<td>5. sister</td>
<td>0, Rh pos.</td>
<td>n. d.</td>
<td>n. d.</td>
<td>99</td>
<td>85</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>6. brother</td>
<td>0, Rh pos.</td>
<td>132</td>
<td>192</td>
<td>43</td>
<td>33</td>
<td>47</td>
<td>79</td>
</tr>
<tr>
<td>7. nephew</td>
<td>(son of Nr. 4)</td>
<td>A, Rh pos.</td>
<td>104</td>
<td>138</td>
<td>85</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>reference values</td>
<td></td>
<td>68–121</td>
<td>84–160</td>
<td>60–150</td>
<td>70–150</td>
<td>70–150</td>
<td>70–150</td>
</tr>
</tbody>
</table>

*Thr449(ACY) → Ile (ATT) in exon 11 F13 A gene; + pregnancy (26 weeks of gestation); (1) first, (2) second, (3) third investigation; n. d.: not done
exon 11 of the factor 13A gene. This base exchange has not been described before the completion of the study. We do not know whether this base exchange represents a mutation or a polymorphism as we have not performed studies on its frequency in the general population.

The patient is heterozygous for this base exchange, which is present also in his mother (no. 3), in one of his sisters (no. 4) and in his nephew (no. 7). All family members with the exception of the patient’s nephew (no. 7) have blood group 0 and low levels of VWF with two exceptions: one of the two sisters of the patient was pregnant (no. 4) and the other was using an estrogen containing pill (no. 5).

Prolonged closure times were present in the patient’s brother (no. 6), while in his father only the ADP/collagen closure time was near the upper limit of the normal range.

**Discussion**

We presented a case of an unexpected severe haemorrhage occurring concomitantly with an incision in the skin during an urgent surgical procedure. Concerning the coagulation studies performed four weeks after the bleeding, a mild factor XIII deficiency was obvious and confirmed by further investigations. A hitherto unknown base exchange within the factor 13A gene was identified as the cause of the factor XIII deficiency.

The mild hereditary factor XIII deficiency does not appear to be the sole cause of the bleeding event. The early beginning of the bleeding episode is a typical for disturbed primary haemostasis. In individuals with factor XIII deficiency, however, the primary haemostatic process is disturbed and the late onset of bleeding symptoms after trauma or a surgical procedure is characteristic factor XIII deficiency (5).

Among the disorders of the primary haemostasis, a reduced activity of VWF seems to play an important role. Beck (1) reported the results of a pilot study concerning the influence of reduced VWF activity on bleeding complications. He stated that a VWF activity below 60% increases the bleeding risk after surgical procedures. Low concentrations and activities of VWF and also low factor VIII activities are typical findings in individuals with the blood group 0 (9). A significant influence on the frequency and severity of bleeding symptoms in people with low VWF results without any doubt from an impaired interaction between collagen and platelets (2, 10, 11). The results of prolonged closure times in our patient support this assumption. The patient and the majority of his family members carry blood group 0 and VWF levels were low, with the exception of the patient’s sisters. The patient, his father and his nephew are homozygous for the 807C allele within the platelet glycoprotein IIa-IIa gene (integrin α2 gene). The 807 CC-genotype is associated with a highly reduced expression of the platelet collagen receptor. The patient’s nephew seems to be protected from bleedings by higher VWF values due to the blood group A. The patient’s father reported no bleeding signs, had had no accidents nor had he undergone surgical procedures up to now.

The case described here provides data possibly explaining unexpected bleeding complications in patients with a mild deficiency of any coagulation factor. It should be borne in mind that a disturbed platelet-collagen interaction is not the sole cause in such cases. Bleeding events in this group of patients may be triggered or modulated by a mild deficiency of a second coagulation protein, for instance a mild factor VIII deficiency in association with heterozygous factor XI deficiency (unpublished observation). Therefore, we believe that in cases like the one presented here more detailed studies of several components of the haemostatic system are necessary to protect involved patients from further bleeding events.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**