Factor IX Deficiency and Bleeding in a Patient With Sheehan’s Syndrome

By Clarence H. Brown, III, Larry K. Kvols, Tah-Hsiung Hsu, and Jack Levin

Factor IX deficiency was associated with a hemorrhagic disorder in a woman who previously had experienced postpartum hypertension resulting in Sheehan’s syndrome. There was no family history of Christmas disease, and other known causes of factor IX deficiency were excluded. Plasma levels of factor IX were partially corrected by therapy with thyroid hormones and completely restored to normal by the administration of cortisone. The response of factor IX to plasma infusion resembled the response of factor VIII in patients with von Willebrand’s disease who receive plasma. Normal hemostasis and levels of factor IX have been maintained by the administration of physiologic dosages of thyroid and adrenal hormones. Blood coagulation was studied in several other patients with pituitary or thyroid dysfunction. All were normal, indicating that this patient represents an unusual example of the effects of an endocrine dysfunction on a single blood coagulation factor.

ALTERATIONS OF HEMOSTASIS have been detected occasionally in patients with a variety of endocrinopathies. Decreased levels of plasma coagulation factors VIII (AHG), IX (PTC), and XI (PTA) have been reported in patients with hypothyroidism. Prolonged whole blood clotting times and increased capillary fragility have been noted in patients with hypopituitarism, and prolonged whole blood clotting times have been observed in patients with Addison’s disease. Elevations of factor VIII may be found in patients with hyperthyroidism and in women taking oral contraceptives. Women in the third trimester of pregnancy often exhibit elevated levels of fibrinogen, factors VII (proconvertin), VIII, IX, and X (Stuart-Prower), and patients with diabetes mellitus have been reported to have increased levels of fibrinogen, factor V (proaccelerin), and factor VIII.

In this report, we describe a patient with a severe hemorrhagic diathesis associated with factor IX deficiency that appeared after the onset of Sheehan’s
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syndrome. This patient’s response to endocrine replacement therapy indicated that the coagulation defect was the result of her endocrine abnormality.

MATERIALS AND METHODS

Measurements of serum thyroxine, ¹³¹I uptake by the thyroid gland (before and after parenteral administration of thyroid stimulating hormone [TSH], 10 U/day for 4 days), and urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids (before and after parenteral administration of adrenocorticotropic hormone [ACTH], 40 U/day for 4 days) were carried out using standard methods. Plasma corticoids and urinary free corticoids (before and after administration of ACTH) were determined by the method of Hsu and Bledsoe. Pituitary secretion of human growth hormone was stimulated by the intravenous administration of arginine monochloride, 500 mg/kg, followed 1 hr later by intravenous insulin, 0.1 U/kg. Levels of plasma growth hormone were determined by the method of Utiger et al. Urinary follicle stimulating hormone (FSH) was measured by the method of Klinefelter et al.

Routine hematologic studies were performed with accepted techniques. For coagulation studies, venous blood was collected in plastic syringes and transferred to plastic or glass test tubes containing 3.8% sodium citrate (9 parts blood: 1 part anticoagulant). Plasma was prepared and either tested immediately or stored at -20°C. Prothrombin times, by the method of Quick, and nonactivated partial thromboplastin times (Thrombofax, Ortho Diagnostics, Raritan, N. J.) were determined within 1 hr of blood collection. Factor II (prothrombin) was measured by the method of Quick et al. Factors VII and X were measured by the ability of the test plasma to correct the prothrombin time of substrate plasma deficient in either factor VII or X. Coagulation factors VIII, IX, and XI were measured by the technique of Hardisty and MacPherson employing factor-deficient plasma as the substrate. Plasmas naturally deficient in factors VII, VIII, IX, and X were obtained from patients with hereditary deficiencies of these factors, and factor XI-deficient plasma was prepared by Filtercel (Johns-Manville, Joliet, Ill.) adsorption of normal human plasma. Normal levels of the plasma coagulation factors in our laboratory are 60 to > 100%. Multiple samples with greater than 100% activity were further diluted with factor-deficient substrate for more precise quantification of the specific factor. This procedure did not reveal levels significantly higher than 100%, and we have reported these samples as “> 100%.” Fibrinogen was measured by the method of Ratnoff and Menzie, fibrinogen degradation products by the hemagglutination inhibition immunoassay of Merskey et al., and the presence of circulating anticoagulants by the method of Margolius and Ratnoff.

CASE REPORT

This 45-yr-old woman had no childhood or family history of abnormal bleeding. Eight years before the present admission, manual removal of the placenta was required during the third stage of labor, resulting in blood loss estimated to be 400 ml. Hypotension persisted for 10 hr. Normal blood pressure was restored with transfusion of 1 liter of whole blood. The patient did not lactate following that pregnancy, and during the next 8 yr experienced amenorrhea, decreased libido, loss of body hair, cold intolerance, and progressive lethargy. Subsequent to the episode of postpartum hemorrhage, serious bleeding did not occur until 3 yr prior to the present admission when dental extraction was followed by bleeding and hypotension. In that same year, she also experienced massive gastrointestinal hemorrhage, during which she received 17 U of whole blood. Radiographic studies and surgical exploration failed to reveal a bleeding site. She did not bleed postoperatively. During these two hemorrhagic episodes the diagnosis of von Willebrand’s disease was considered; however, factor VIII levels and bleeding times were normal.

On the day prior to the present admission, the patient had several teeth extracted from the left maxillary ridge and after initially adequate hemostasis began to bleed copiously. Bleeding continued, and she was admitted the following day, at which time soft tissue
Procedures for endocrine stimulation are described in text. Not determined.

Table 1. Admission Coagulation Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee-White whole blood clotting time</td>
<td>9</td>
<td>9–20</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivy bleeding time</td>
<td>13</td>
<td>2–9</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tourniquet test</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>16</td>
<td>15–20</td>
</tr>
<tr>
<td>(sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>153</td>
<td>65–105</td>
</tr>
<tr>
<td>(sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>295</td>
<td>150–350</td>
</tr>
<tr>
<td>(mg/100 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen degradation products</td>
<td>1.8</td>
<td>≤1.8</td>
</tr>
<tr>
<td>(greatest positive dilution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulating Anticoagulants</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Plasma coagulation factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% of normal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>100</td>
<td>60–&gt;100</td>
</tr>
<tr>
<td>VII</td>
<td>100</td>
<td>60–&gt;100</td>
</tr>
<tr>
<td>VIII</td>
<td>&gt;100</td>
<td>60–&gt;100</td>
</tr>
<tr>
<td>IX</td>
<td>19</td>
<td>60–&gt;100</td>
</tr>
<tr>
<td>X</td>
<td>90</td>
<td>60–&gt;100</td>
</tr>
<tr>
<td>XI</td>
<td>&gt;100</td>
<td>60–&gt;100</td>
</tr>
</tbody>
</table>

Hemorrhage had resulted in swelling and discoloration of the left side of the face. The patient was not taking any medications.

Admission blood pressure was 140/90 mm Hg and the pulse was 80/min. The skin was dry and scaly, and body and pubic hair were sparse. Breast tissue was atrophic, and vaginal mucosa exhibited postmenopausal changes. The relaxation phase of deep tendon reflexes was strikingly prolonged.

Table 2. Studies of Endocrine Function

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Baseline</th>
<th>After Stimulation*</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum thyroxine</td>
<td>1.1</td>
<td>ND†</td>
<td>2.9–6.4</td>
<td></td>
</tr>
<tr>
<td>(µg/100 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>131I Uptake by thyroid (٪)</td>
<td>2 hr</td>
<td>4</td>
<td>8</td>
<td>5–12</td>
</tr>
<tr>
<td></td>
<td>24 hr</td>
<td>8</td>
<td>56</td>
<td>12–35</td>
</tr>
<tr>
<td>Morning plasma corticoids (µg/100 ml)</td>
<td>2.5</td>
<td>ND</td>
<td>8–18</td>
<td></td>
</tr>
<tr>
<td>Urinary free corticoids (µg/24 hr)</td>
<td>3</td>
<td>120</td>
<td>20–70</td>
<td></td>
</tr>
<tr>
<td>Urinary 17-hydroxycorticosteroids (mg/24 hr)</td>
<td>0.7</td>
<td>11.7</td>
<td>2–8</td>
<td></td>
</tr>
<tr>
<td>Urinary 17-ketosteroids (mg/24 hr)</td>
<td>2.6</td>
<td>4.3</td>
<td>4–13</td>
<td></td>
</tr>
<tr>
<td>Urinary follicle stimulating hormone (mouse U/24 hr)</td>
<td>&lt;6.6</td>
<td>ND</td>
<td>12–24</td>
<td></td>
</tr>
<tr>
<td>Plasma growth hormone (ng/ml)</td>
<td>&lt;4</td>
<td>&lt;4</td>
<td>&gt;5 after stimulation</td>
<td></td>
</tr>
</tbody>
</table>

*Procedures for endocrine stimulation are described in text.
†Not determined.
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Laboratory studies included a hematocrit of 31%, white blood cell count of 5300/cu mm, and platelet count of 120,000/cu mm. Serum electrolytes, routine blood chemistries, and a urine analysis were normal. Initial coagulation studies (Table 1) revealed prolongation of the bleeding and partial thromboplastin times. Assays for specific plasma coagulation factors demonstrated a factor IX level of 19% of normal. Other tests, including assays for factors II, VII, VIII, X, and XI, were normal. Qualitative evaluation of clot retraction was normal. Subsequent determinations of bleeding times, factors II, VII, VIII, X, and XI, performed during the course of the patient's hospitalization, were normal.

Endocrine studies during her evaluation are shown in Table 2. The diagnosis of hypopituitarism was confirmed by the demonstration of abnormally low pituitary secretion of growth hormone and FSH, and of TSH-responsive hypothyroidism and ACTH-responsive hypoadrenalism.

SPECIAL STUDIES

Initial Therapy

The prolonged partial thromboplastin time and low factor IX prompted immediate use of fresh frozen plasma (FFP) to control hemorrhage. Approximately 700 ml of FFP were given upon admission, 12 hr later, and then every 24 hr through the seventh hospital day. Because of the past history of postpartum hemorrhage and hypotension, adrenal stimulation and replacement therapy were begun. Intravenous hydrocortisone, 500 mg, and ACTH, 40 U, were given on the day of admission. For therapeutic purposes, intravenous dexamethasone was administered on the second, third, and fourth hospital days in dosages of 4 mg, 6 mg, and 2 mg, respectively. Bleeding ceased after the first transfusion of FFP, and factor IX was 100% by the end of the second day (Fig. 1). Normal levels of factor

Fig. 1. Plasma factor IX levels during initial therapy and response to administration of fresh frozen plasma alone (day 13), ACTH and TSH (days 15-18), and cortisone (days 25 and 26). Dosages of various therapeutic agents are given in text. Ends of the respective days are indicated on abscissa.
IX persisted until the seventh day, when, despite the administration of FFP, levels began to decline reaching 14% on day 12.

Effect of Administration of Fresh Frozen Plasma

To define the role of FFP in the observed rise in levels of factor IX, all therapy was withheld after the seventh day. On day 13 factor IX was 22%. At that time, 650 ml of FFP with factor IX activity of 110% of normal were infused rapidly (Fig. 1). Plasma factor IX levels rose to a maximum of 66% 8 hr after FFP infusion. This peak level was twice as high as that which was predicted on the basis of the patient's calculated plasma volume of 3200 ml and the factor IX content of the donor FFP. Based on the rate of decline after peak levels were attained, the half-life of factor IX was estimated to be 28 hr.

Effect of Administration of ACTH and TSH

The effects of ACTH and TSH on the patient's endocrine function are shown in Table 2. These observations substantiated the diagnosis of Sheehan's syndrome, and factor IX levels rose from 20% to 70% during the period of endocrine stimulation (Fig. 1). Several days after these tropic hormones were discontinued, factor IX levels began to fall.

Effect of Administration of Cortisone

Because of these observations, the effects of separate administration of exogenous adrenal and thyroid hormones upon factor IX were studied. Cortisone, 30 mg by mouth, was given on the 25th and 26th hospital days. All other medications were withheld. After an initial decrease, factor IX levels rose from 55 to 100%, 16 hr after the first dose (Fig. 1). The level of factor IX remained at >100% for 2 days after the second dose of cortisone and then began to decline, reaching 20% on day 31.

Effect of Administration of Thyroid Hormones and Subsequent Maintenance Endocrine Therapy

After the effects of cortisone no longer were evident, thyroid replacement therapy was begun. Triiodothyronine (T-3), in dosages of 25-75 μg/day, was administered for 2 wk. A combination of T-3, 45 μg/day, and thyroxine, 180 μg/day, was then substituted. During the first 3 wk of thyroid replacement therapy, a diurnal variation in factor IX levels was noted. Factor IX levels were obtained in the morning and evening on 15 days; on 11 of these days levels of factor IX were higher in the morning than the evening (the mean difference was 23%). Levels of 100% were occasionally recorded but never were sustained for more than 3 days. On the 56th hospital day, the patient was discharged receiving only thyroid hormones. The level of factor IX remained at 50% of normal. Cortisone, 30 mg/day, was begun, but factor IX did not change. It was learned that the patient was not taking the prescribed dosage of cortisone. For the purposes of controlling her therapy she was readmitted to the hospital, at which time (110th day), there were notable improvements in her clinical appearance. Serum thyroxine was 2.8 μg/100 ml. Morning plasma corticoids were 4 μg/100 ml, urinary 17-hydroxycorticosteroids were 1.4 mg/24 hr, and 17-ketosteroids were 2.2 mg/24 hr. Factor IX was 70% of normal. Thyroid replacement therapy was maintained throughout this hospitalization, but cortisone was withheld until baseline studies were completed. On day 113, 25 mg of cortisone was given. Twelve hours later, factor IX had risen from 70% to >100%. Continuation of thyroid and adrenal replacement therapy has been associated with maintenance of factor IX levels of >100 per cent.

RESULTS AND DISCUSSION

Abnormalities of blood coagulation resulting in hypocoagulability have been reported in patients with hypofunction of the pituitary, adrenal, and thyroid glands. However, significant hemorrhage as a complication of these
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abnormalities is rare. Egeberg described a hypothyroid patient with factor VIII deficiency and prolonged cephalin and bleeding times who had epistaxis, metrorrhagia, and hematuria. Simone et al. reported a patient with myxedema who bled following tonsillectomy and who a year later was found to have low levels of factors VIII and IX. In these and other patients with endocrinopathies and abnormal hemostasis, complete correction of the coagulation defects followed specific endocrine replacement therapy.

Our patient appears to be the first reported case of Sheehan's syndrome associated with an isolated factor IX deficiency. This defect was accompanied by a serious bleeding diathesis. Other disorders might result in factor IX deficiency in a female. For example, a patient with Turner's syndrome and severe factor IX deficiency has been described. Deficiency of this factor has been found in female carriers of the sex-linked deficiency of factor IX (Christmas disease), in women exhibiting increased capillary fragility who perhaps represent a factor IX counterpart of von Willebrand's disease, in a rare female without chromosomal abnormalities or a family history of Christmas disease, and in patients with the nephrotic syndrome. Our patient does not appear to represent any of these varieties of factor IX deficiency. Three of her four living sisters, three of her four living brothers, and six of her seven living children (two sons, four daughters) were studied and were found to have normal coagulation tests.

The slightly prolonged bleeding time recorded during the initial evaluation of hemostatis could have been related to her hypopituitarism and hypoadrenalism and may have contributed to the bleeding tendency. This finding suggested the diagnosis of von Willebrand's disease. Classic von Willebrand's disease was excluded by the normal factor VIII levels and subsequently normal bleeding times. The possibility that the patient represented a factor IX counterpart of von Willebrand's disease was investigated. Patients with classic von Willebrand's disease, i.e., factor VIII deficiency, apparently are stimulated to produce endogenous factor VIII after plasma is administered. Maximum levels of factor VIII are not reached until at least several hours after transfusion, and the subsequent decline of factor VIII to pretreatment levels occurs slowly. A similarity between the type of response of factor VIII to plasma in patients with von Willebrand's disease and the response of factor IX to FFP in our patient was observed. The infused FFP should have produced a maximum acute increment in factor IX levels of 23%, assuming that all of the infused factor IX remained in the intravascular space. However, the observed increment was 44%, and maximum factor IX levels were not reached until 8 hr after FFP infusion. This observation suggested that FFP induced endogenous production of factor IX. The FFP may have contained humoral substances, lacking in the patient because of hypopituitarism, that stimulated the synthesis of factor IX. The concentration of adrenal corticosteroids in the donor FFP was not measured but the concentrations of these hormones in most normal plasma would have been expected to double this patient's plasma corticoids, which might have been sufficient to stimulate factor IX production. A dissimilarity between the response that occurs in von Willebrand's disease...
and that observed in this patient was the normal rate of decline of factor IX after peak levels had been reached. In our patient, factor IX half-life was approximately 28 hr, a value compatible with the reported half-life of 18–29 hr in patients with Christmas disease who receive plasma.29

The effect of administration of corticosteroid and thyroid hormone on factor IX levels indicates that the factor IX deficiency in our patient was the result of hypoadrenalism and hypothyroidism, the latter endocrine dysfunction probably being of lesser significance in this regard. Thyroid replacement therapy alone was not consistently effective in maintaining normal factor IX levels. The observed diurnal variation of factor IX during the early phase of thyroid replacement may have resulted from diurnal fluctuation of residual adrenal function sufficient to elevate levels of factor IX in the morning. Simone et al.2 suggested that coagulation factors are occasionally decreased in hypothyroidism as a result of decreased protein synthesis, an explanation that appears unlikely for our patient in whom only a single coagulation factor was decreased. Exogenous corticosteroid corrected the factor IX deficiency in two controlled trials. In each instance, following a single dose of cortisone, factor IX rose from 55–70% to 100% or greater, within 12–16 hr. It has been reported that corticosteroids or ACTH may affect several tests of hemostatic function, including whole blood clotting time,430 capillary fragility,31 prothrombin time,32 partial thromboplastin time,32 fibrinogen,32 and factors V, VII, VIII, and X.32 Ozsoyulu et al.32 reported rises in factor VIII in patients with hemophilia A receiving adrenal hormones, but other investigators have not reproduced these observations.33 The means by which adrenal and thyroid hormones affect hemostasis and blood coagulation are unclear.

We have studied an additional patient with Sheehan’s syndrome, three patients with hypothyroidism, and one with hyperthyroidism. No abnormalities of blood coagulation were detected in any of these patients. This would suggest that only some patients with endocrinopathies have abnormal hemostasis and that our patient with Sheehan’s syndrome and factor IX deficiency is an unusual example of the association of an endocrine disorder with a significant coagulation defect.

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REFERENCES

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