A combination of prednisone, high-dose intravenous immunoglobulin and desmopressin in the successful treatment of acquired hemophilia A with high-titer inhibitor

Sir,

The spontaneous appearance of inhibitory antibodies to factor VIII is a rare and severe condition which is extremely difficult to treat.1,2 There are various therapeutic options available (human or porcine FVIII, activated recombinant human factor VII,3 desmopressin, high-dose intravenous immunoglobulin, prothrombin complex concentrates, plasmapheresis and immunosuppressive agents such as corticosteroids and cytotoxic drugs) depending on the severity of the hemorrhage and levels of inhibition.4

We report the case of an elderly woman with high-titer idiopathic factor VIII inhibitor who was successfully treated with the association of prednisone, high-dose intravenous immunoglobulin (IVIg) and subcutaneous desmopressin.

A 75-year-old woman was admitted to our city hospital in November 1998 because of rectal bleeding and extensive hematomas on the left thigh and right upper arm. There was no family or personal history of congenital bleeding diatheses. The patient had undergone a hysterectomy with no hemorrhagic complications two years previously. On admittance to our hospital, laboratory tests revealed anemia (hemoglobin 9 g/dL), prolonged aPTT at 64 sec, which was not corrected by normal plasma, decreased factor VIII activity (6 IU/dL) and the presence of a high-titer factor VIII inhibitor (30 BU/mL). Platelet count, fibrinogen levels and PT were normal. A search for underlying disorders most frequently associated with the formation of inhibitors (e.g. autoimmune diseases, malignancies, dermatologic disorders, reaction to drugs) was negative. A rectosigmoidoscopy revealed the presence of 3 bleeding rectal polyps.

Given the patient’s age and the severe but not life-threatening clinical presentation, we started therapy with intravenous tranexamic acid 1 g thrice daily until the patient was discharged, oral prednisone 1 mg/kg/day for 5 days starting 60 minutes before the operation, and 6 BU/mL factor VIII inhibitor titer had fallen respectively to 38 sec and to 6 BU/mL while factor VIII activity had increased to 40 IU/dL. Three days later the patient underwent endoscopic resection of the rectal polyps: subcutaneous desmopressin (0.3 µg/kg for 5 days starting 60 minutes before the operation) was added to the ongoing therapy (oral prednisone and tranexamic acid). Blood tests 60 minutes after desmopressin injection showed the normalization of aPTT and factor VIII activity. The patient was discharged 15 days later: the hematomas had disappeared and hemostatic parameters remained within normal ranges. No factor VIII inhibitor was detected in the patient’s serum. She continued with her steroid therapy which was tapered off over the next two months in order to reduce the risk of side effects, which are particularly common in the elderly. A recent check-up (February 1999) confirmed the absence of factor VIII inhibitor.

Since acquired hemophilia A often occurs in elderly subjects, aggressive treatment such as plasmapheresis may be ill-advised.1,5 Our case report shows how a combination therapy of steroid, high-dose immunoglobulin and desmopressin is both an effective and well tolerated treatment for bleeding in an elderly patient with high-titer idiopathic factor VIII inhibitor.

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Key words
Acquired hemophilia, desmopressin, bleeding

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References

Double carriers of the factor V Leiden and prothrombin (FIIG20210A) mutations: a description of four cases

Sir,

The factor V Leiden (FVL or FV R506Q) mutation and the G-A transition at nucleotide 20210 of the prothrombin gene (FII G20210A) have been associated with venous thromboembolism (VTE). Although they
might also be associated with premature onset of the arterial thrombosis,\(^1\) this subject remains highly controversial. Recently, both anomalies have been linked to several clinical events such as cerebral venous thrombosis,\(^2\) superficial thrombophlebitis,\(^3\) venous insufficiency and leg ulcers,\(^4\) complications of pregnancy (pre-eclampsia, abruptio placentae, fetal growth retardation and stillbirth), suprarenal portal or mesenteric vein thrombosis (FII G20210A carriers),\(^5\) or Legg-Perthes disease (FVL carriers). There have also been suggestions that they might be implicated in some other processes, although the evidence is not conclusive, e.g. inflammatory bowel disease, retinal vein occlusion, juvenile ischemic stroke\(^6\) or peripheral arterial disease.\(^6\)

Moreover, these risk factors show only moderate expressiveness, and the heterozygous carrier status could be compatible with an uneventful long life, shown by a cohort of centenarians with FVL,\(^7\) or when death rates were considered.\(^8\) However, perhaps among the rare FVL homozygous patients the clinical situation could be worse. The thrombotic tendency among FII G20210A heterozygotes seems even milder, but among homozygotes, it is less known. The thrombotic profile of FVL-FII G20210A double carriers is beginning to be understood. Some reports have suggested a synergistic effect\(^9,10\) although less severe than that for other thrombophilic defects.

We describe four such double carriers (Table 1) to illustrate both the heterogeneity and moderation of the clinical course. Even the more symptomatic patients (\#1 and \#2) had important acquired risk factors for VTE.

Case \#1. A 68-year old man might have had a pulmonary embolism (PE) at 38 years old; after surgical repair of a left ankle fracture, he developed pulmonary condensation and dyspnea without fever, which was diagnosed as pneumonia. He then suffered several episodes of lower limbs phlebitis (never anticoagulated) and underwent three major surgical procedures without thromboembolic complications (peritonitis, right total knee and left total hip replacements). However, five months after the hip replacement, he developed a left femoropopliteal deep venous thrombosis (DVT). Two years later he suffered a PE on the 35\(^{\text{th}}\) post-operative day after a new hip replacement because of prosthesis dysfunction. His FVL-FII G20210A double carrier status and normality for antithrombin, protein C, protein S, anticardiolipin antibodies, lupus anticoagulant and fasting homocysteine were demonstrated. The C677T polymorphism in the methylenetetrahydrofolate reductase gene, AT: antithrombin deficiency, PC: protein C deficiency, PS: protein S deficiency, HHcy: hyperhomocysteinemia; ACA: anticardiolipin antibodies; LA: lupus anticoagulant, ND: not determined.

Case \#2. A 45-year old woman suffered a DVT/PE on the eleventh day after a road accident complicated by multiple rib and clavicular fractures and hemopneumothorax (therefore she did not receive heparin). The thrombophilia study other than the FVL-F IIG20210A was normal and like the previous case, the MTHFR was 677TT. Her father suffered recurrent PE (at 50, 59 and 69 years) and carries the G20210A allele, whereas her mother (70 years) was an asymptomatic FVL carrier.

Another two patients were symptom-free until advanced age. Case \#3 suffered two transient ischemic attacks (aphasia at 60-years and hemiparesis at 84-years old without cardiovascular risk factors). He did not develop VTE despite undergoing three major surgical procedures (pyloroplasty, cholecystectomy and a fibrohystiocytoma exertion), so we could consider this patient as non-thrombophilic.

Case \#4 was asymptomatic until 87 years old, when she suffered right lower limb phlebitis and afterwards a chronic leg ulcer. Although this could be related with FVL, this presentation is quite natural in elderly and is not necessarily association with these mutations.

We highlight the clinical heterogeneity and the relatively moderate penetrance that seems to be linked with the combined anomaly of FVL and prothrombin mutations.

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**Key words**
Factor V Leiden, prothrombin gene, FII 20210A, thrombosis, mutation

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### Table 1. Description of the four FVL and FII G20210A double carriers.

<table>
<thead>
<tr>
<th>Pt. Age/Sex</th>
<th>Clinical manifestations</th>
<th>FV G056</th>
<th>FII G20210A</th>
<th>MTHFR 677T/T</th>
<th>AT/PC/PS/HHcy/ACA/LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 68M</td>
<td>ST/DVT/PE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
</tr>
<tr>
<td>2 45F</td>
<td>DVT/PE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
</tr>
<tr>
<td>3 69M</td>
<td>Recurrent TIA (CVD)</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4 94F</td>
<td>ST-DVT/Meig ulcers</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

References