Thromboembolism Complicating the Treatment of Lupus Anticoagulant Hypoprothrombinemia Syndrome

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ABSTRACT. Lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) is a rare disorder characterized by a bleeding tendency due to factor II deficiency associated with the presence of lupus anticoagulant (LAC) autoantibodies. We describe a patient with systemic lupus erythematosus and LAHPS in whom successful treatment of central nervous system bleeding due to severe factor II deficiency was followed by a major thromboembolic complication. Literature review revealed 2 other patients with LAHPS who developed thrombosis resulting from the treatment of factor II deficiency. We suggest that factor II deficiency counterbalances the prothrombotic effect of LAC in LAHPS, and correcting this deficiency may promote thromboembolism. (First Release Aug 15 2006; J Rheumatol 33:2088–90)

Key Indexing Terms:
LUPUS ANTICOAGULANT HYPOPROTHROMBINEMIA SYNDROME
THROMBOSIS
FACTOR II DEFICIENCY
ANTIPHOSPHOLIPID SYNDROME
AUTOANTIBODIES

Lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) is a rare disorder characterized by a bleeding tendency due to factor II deficiency associated with the presence of lupus anticoagulant (LAC) autoantibodies. LAHPS was first described by Rapaport, et al in 19601. Since that time, fewer than 40 cases have been reported2. This syndrome is mostly associated with systemic lupus erythematosus (SLE), but has been described in association with primary antiphospholipid syndrome (APS), drugs, and viral infections3-5. The majority of cases described come from the pediatric population2. Clinical manifestations are variable and range from minor bleeding (such as epistaxis, menorrhagia, and hematia) to life-threatening hemorrhage6. However, despite the presence of LAC, which are marker autoantibodies for a high risk of thrombosis in SLE7,8, thromboembolic complications are rare in LAHPS. No consensus exists on treatment of LAHPS and little is known about therapeutic consequences.

We describe a patient with SLE with LAHPS in whom successful treatment of a bleeding diathesis resulted in a major thromboembolic complication.

CASE REPORT
First admission. A 50-year-old French Canadian woman was admitted for severe headache associated with vertigo, nausea, and vomiting. Her history was remarkable for SLE linked to vertigo, nausea, and vomiting. Her history was quiescent over the past years, requiring no medication. LAHPS was manifested by 2 major episodes of postoperative bleeding associated with severe factor II deficiency. The first episode occurred 20 years prior to admission, consisting of severe bleeding after a dental extraction and requiring blood transfusions. Twelve years later, she underwent an open renal biopsy, which was complicated by hemorrhage requiring treatment with intravenous corticosteroids, fresh frozen plasma, as well as platelet and blood transfusions. Factor II levels normalized momentarily at that time, but rapidly returned to low values after the bleeding had resolved and corticosteroids were tapered.

On physical examination, there was no neurologic deficit. Laboratory investigations (Table 1, first admission) revealed the presence of LAC as defined in the guidelines of the International Society on Thrombosis and Hemostasis9 and abnormal coagulation studies with severe factor II deficiency. Lupus serology was unchanged in comparison with the past 24 months (normal or mildly elevated anti-DNA antibodies and slightly decreased C3). A cerebral computed tomography (CT) scan showed 2 cerebellar subdural hematomas (Figure 1).

She was immediately treated with high-dose corticosteroids and 2 cycles of plasma exchange, followed by intravenous immunoglobulins (IVIG, 1 g/kg for 2 days). Factor II levels normalized and oral cyclophosphamide 2 mg/kg was begun as maintenance therapy. Two weeks later, regression of cerebellar hematomas was seen on a control CT scan (not shown) and she was discharged with no need for surgery.

Second admission. Two months later, she presented with complete aphasia. At that time, she was taking prednisone 75 mg daily, but cyclophosphamide had been stopped 4 weeks earlier for a urosepsis that responded to antibiotics.
Cardiovascular examination was normal and there was no other neurologic deficit. In contrast with her first admission, factor II levels were normal (Table 1, second admission). No acute lesion was identified on brain CT scan. However, cerebral magnetic resonance imaging (MRI) showed acute ischemic lesions in the left middle cerebral artery territory (Figure 2). In search of an embolic source, carotid artery Doppler and thoracic echocardiography were normal. However, transesophageal echocardiography revealed anterior mitral valve thickening highly suggestive of Libmann-Sacks endocarditis.

She was diagnosed with an ischemic stroke secondary to an embolism originating from Libmann-Sacks endocarditis in the setting of a hypercoagulable state due to APS that may have been exacerbated by correction of factor II deficiency. With the underlying bleeding tendency, the therapeutic decision was a dilemma because of concern that treatment of thromboembolism might provoke recurrence of bleeding. She continued to receive prednisone 75 mg daily and was started on clopidogrel a few days after her stroke. Azathioprine 2 mg/kg was begun for long-term maintenance of normal factor II levels. Six months later, azathioprine was replaced by cyclophosphamide 2 mg/kg because of decreasing factor II levels during prednisone tapering. At last followup, 1.5 years after the second admission, prednisone had been completely tapered. She had partially recuperated from aphasia and was stable taking cyclophosphamide 2 mg/kg and antiplatelet agents, with normal factor II levels and without recurrence of bleeding or thromboembolism.

**DISCUSSION**

Thrombosis is a characteristic manifestation of APS. In contrast, LAHPS is associated with a bleeding tendency. The proposed mechanism of bleeding in LAHPS is that antiprothrombin autoantibodies bind prothrombin (factor II) without neutralizing its activity, resulting in rapid clearance of these prothrombin-antibody immune complexes by the reticuloendothelial system. This leads to depletion of prothrombin and ultimately, bleeding. The etiology of antiprothrombin autoantibody production is unknown. In addition, the mechanism by which antiprothrombin and LAC autoantibodies are linked is not understood.

There is no consensus on the optimal treatment of bleeding in LAHPS. Indications for treatment have varied from perioperative prophylaxis of bleeding to life-threatening hemorrhage.

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**Table 1.** Laboratory investigations in a patient with SLE and LAHPS. The prolonged INR was corrected by mixing normal plasma 1:1 with the patient plasma.

<table>
<thead>
<tr>
<th>Variable</th>
<th>First Admission</th>
<th>Second Admission</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>1.9</td>
<td>1.0</td>
<td>0.9–1.1</td>
</tr>
<tr>
<td>Factor II</td>
<td>0.25</td>
<td>1.01</td>
<td>0.70–1.20 µ/ml</td>
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<tr>
<td>PTT</td>
<td>&gt; 100</td>
<td>57</td>
<td>23–34 s</td>
</tr>
<tr>
<td>RVVT</td>
<td>234</td>
<td>–</td>
<td>28–50 s</td>
</tr>
<tr>
<td>Platelet count</td>
<td>279</td>
<td>43</td>
<td>140–450 × 10^9/l</td>
</tr>
</tbody>
</table>

INR: international normalized ratio; PTT: partial thromboplastin time; RVVT: Russell’s viper venom time.

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**Figure 1.** Cerebral CT scan without contrast of a patient with SLE and LAHPS, first admission. The scan reveals bilateral cerebellar subdural hematomas (arrows).

**Figure 2.** Cerebral MRI on second admission, revealing acute ischemic lesions in the left middle cerebral artery territory (arrows).
rhage. Patients do not usually have a complete response to fresh frozen plasma, vitamin K, or blood transfusions. Most cases have been successfully treated with corticosteroids but with reappearance of factor II deficiency after tapering\(^4\). In the setting of acute bleeding, IVIG have been used successfully\(^1,4\). To our knowledge, no report exists on the sequential use of plasma exchange followed by IVIG in LAHPS, an approach used with apparent success in our patient in the setting of acute subdural hematomas. For maintenance therapy aimed at prevention of bleeding, there are only a few case reports using azathioprine and cyclophosphamide with variable results\(^5,15\).

Literature review revealed 2 patients with LAHPS who developed thromboembolic complications resulting from treatment of factor II deficiency. The first patient was a 10-year-old girl with SLE presenting with hematuria who was treated with corticosteroids\(^6\). She developed lower extremity deep venous thrombosis during therapy after normalization of factor II levels. The second patient was a 38-year-old man, with no other medical condition except a positive IgG anti-cardiolipin antibody, who was treated with corticosteroids in the setting of a cerebral hemorrhage\(^3\). While on therapy, and with corrected factor II levels, a fatal ischemic myocardial infarction occurred.

Our experience suggests that treating a severe hemorrhagic complication in LAHPS may offset the fragile balance between prothrombotic LAC and the prohemorrhagic pro-thrombin deficiency and may therefore promote thrombosis. Thus, in the absence of an accepted standard of practice in this situation, we recommend that therapy be reserved for severe cases of bleeding. In minor bleeding, an attempt should be made first with fresh frozen plasma and vitamin K, and then corticosteroids if bleeding does not stop or if transfusions are required. Perioperative prophylaxis should be used in patients with prior episodes of bleeding or very low factor II levels. Our opinion is that close followup should probably be used instead of maintenance immunosuppressive therapy except for patients presenting with life-threatening or severe hemorrhage, or multiple episodes of bleeding.

Our case and the 2 other reported cases suggest that factor II deficiency counterbalances the prothrombotic effect of LAC in LAHPS. Treatment aimed at correcting factor II deficiency may promote thromboembolism. Therefore, caution must be used in selecting which patient to treat and determining the type and duration of therapies.

**REFERENCES**