Deep venous thrombosis associated with acquired angioedema type II in a patient heterozygous for the mutation of factor V Leiden: Effective treatment and follow-up for four years

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Deficiency of the C1-inhibitor (C1-INH) is a very rare cause of angioedema. A hereditary (1) and an acquired form (2, 3) of C1-INH deficiency have been described. Two types of acquired angioedema (AAE) exist: type I is associated with lymphoproliferative disorders, whereas type II is characterized by autoantibodies against C1-INH (4).

Clinically, AAE is indistinguishable from hereditary angioedema (HAE) (5, 6). Patients suffer from recurrent edematous attacks that involve subcutaneous or submucosal tissue (of the larynx and gastrointestinal tract). Patients with AAE do not have a family history of angioedema, and their symptoms usually develop after the age of forty. Diagnosis is based on laboratory findings, i.e. decreased complement (C) C2, C4, C1-INH plasma concentrations, decreased C1-INH activity (5, 6) and normal C3 levels, along with low plasma C1q levels [the latter are usually normal in HAE(7)].

In this paper, we report the case of a female patient with type II AAE, where angioedema was associated with recurrent deep venous thrombosis. A review of the literature yielded only one report of two angioedema cases, where AAE type I was associated with thrombotic (both arterial and venous) disorders, as reported by Wautier et al. (8). Our paper discusses the possible relationship between acquired C1-INH deficiency and an enhanced propensity for thrombosis.

Case report

The history of the 66-year-old female patient contains surgery for uterine fibromyoma as well as mild hypertension. Deep venous thrombosis developed in her left lower extremity as a sequel to fracturing her left ankle in 2000. It recurred in February 2001 in her right lower extremity. Acenocoumarol was initiated and effective; however, it was arbitrarily discontinued by the patient on both occasions. Following the first episode of venous thrombosis, the symptoms of angioedema (on the head-neck region, extremities and the laryngeal and gastrointestinal mucosa) recurred eight times between 2000 and 2001. The patient experienced laryngeal edema on two occasions, both diagnoses were confirmed by an ot-rhino-laryngologist. In July 2001, deep venous thrombosis developed again in the right lower extremity, and acenocoumarol therapy was introduced.

The initial step of the diagnostic work-up of angioedema failed to identify an infective focus (dental, urological, gynecological or oto-rhino-laryngological), the presence of sinusitis or tonsillitis was excluded. Leukocyte count (4.51 G/l) and the concentration of C-reactive protein (3.0 mg/l) were within the normal range, while we found increased fibrinogen level (5.12 g/l) in the patient. All the allergy tests yielded negative results. Serological tests were negative for anti-Helicobacter pylori IgG, as well as for human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, hepatitis C virus and hepatitis B virus.

In the Hungarian HAE Center(9) detailed complement analysis was performed to provide the diagnosis. Very low CH50 and C4 concentrations were found with normal C3 levels (Table 1). The serum concentration, as well as the activity of C1-INH was low, suggestive of C1-INH deficiency. Low C1q levels and the presence of both IgG and IgA type autoantibodies were indicative of AAE type II.

Screening for underlying diseases was initiated. Hematology testing, laboratory findings, autoantibody titers, tests against cryoglobulines, CT of the chest and abdomen ruled out the possibility of lymphoproliferative disorders, other malignancies or systemic/organ-specific autoimmune disorders (especially antiphospholipid syndrome). Testing for mutated coagulation factor V (Leiden) by the PCR-RFLP method revealed that the patient was a heterozygous carrier of this abnormality.

Currently, antifibrinolytic agents are the best choice for the long-term prophylaxis of AAE (6, 10). However, in this particular case antifibrinolytics were contraindicated owing to the recurrence of thrombosis. Thus danazol was introduced at an initial dose of 300 mg/day. During the follow-up period, the daily dose of the attenuated androgen was reduced gradually and finally discontinued in July 2003. Captopril was changed to nifedipine immediately after admission, as angiotensin converting enzyme (ACE) inhibitors are known to increase the frequency of attacks in C1-INH deficiencies (6, 11). In addition, the patient received concomitant anticoagulation with 2.5 mg/day acenocoumarol. No manifestations of AAE, such as subcutaneous/
submucosal edema, developed during the 50-month-long follow-up period, and deep venous thrombosis also did not recur.

C1-INH concentration and activity, as well as serum C4, C1q and CH50 levels increased and, eventually, normalized 2–10 months after admission. Specific autoantibodies against C1-INH were invariably present in the patient’s serum. At time of diagnosis, IgG and IgA type autoantibodies were found in high titers. During the follow-up period, IgA type autoantibodies were present in all samples. Slightly elevated titers of IgM type autoantibodies against C1-INH could be detected on four occasions.

Coagulation parameters were determined at regular intervals to monitor the functioning of the coagulation system, and the international normalized ratio (INR) was constantly in the therapeutic range (1.70 to 2.32). During the follow-up period, no hemorrhagic complications developed as a result of the acenocoumarol therapy.

### Discussion

Several serine proteases of the coagulation, fibrinolysis, and contact systems serve as substrates for C1-INH. Thus, the deficiency of C1-INH function leads to hyperactivation of the classical complement pathway and to the formation of C2-kinins. Moreover, activation of the contact system is also observed: plasma kallikrein is protected from inhibition of C1-INH by increased binding to endothelial cells (12), which finally results in enhanced bradykinin formation (13). These two vasoactive mediators – C2-kinin and mainly bradykinin – are believed to play an essential role in angioedema formation, and thereby in the pathomechanism of HAE and AAE.

Thus, the concurrent occurrence of these two diseases raises the question whether there is a link between them – related to their pathomechanisms – or whether it is a pure coincidence only. As the symptoms of angioedema always followed in the wake of the clinical manifestations of DVT in our case, we assume that DVT is a potential triggering factor for AAE. Accordingly, we have hypothesized that a state of hypercoagulation (thrombophilia) and ACE-inhibitor therapy may trigger angioedematous attacks because of the functional deficiency of C1-INH.

Accordingly, ours is probably the first report on the coincidence of type II AAE and recurrent deep venous thrombosis, with the appearance of three different immunoglobulin isotypes against C1-INH during the follow-up period. We discussed that hypercoagulation may precipitate edematous attacks in C1-INH deficiency. Complement testing is necessary to establish the correct diagnosis in coincident cases of thrombosis and angioedema of unknown origin. The control of hypercoagulation and withdrawal of ACE inhibitors were shown to abolish angioedematous symptoms and the need for specific treatment (i.e. danazol) for AAE, even though the antibodies against C1-INH were always present in the patient’s serum. Thus, it is concluded that successful treatment of the underlying disease and elimination of triggering factors are the mainstays of the management of AAE.

### Table 1: Laboratory results of complement parameters of the patient at time of diagnosis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results of the patient</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4, mg/l</td>
<td>7.3</td>
<td>60–180</td>
</tr>
<tr>
<td>anti-C1-INH (IgG), U/ml</td>
<td>65</td>
<td>0–2</td>
</tr>
<tr>
<td>anti-C1-INH (IgA), U/ml</td>
<td>39.4</td>
<td>0–0.6</td>
</tr>
<tr>
<td>anti-C1-INH (IgM), U/ml</td>
<td>4</td>
<td>0–12</td>
</tr>
<tr>
<td>Circulating IC, %</td>
<td>8.1</td>
<td>0–20</td>
</tr>
</tbody>
</table>

Circulating IC: Circulating immune complexes.

### References