Thyroid Autoimmunity and Spontaneous Cervical Artery Dissection

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Background and Purpose—The possibility that a disorder of immunity might have a role in the mechanism of local inflammatory alterations leading to spontaneous cervical artery dissection (sCAD) has been recently advocated.

Methods—We explored this hypothesis in a case–control study, including patients with sCAD (n = 29) and patients with non-CAD ischemic stroke (non-CAD; n = 29). Serum levels of antithyroperoxidase, antithyroglobulin, and antithyroid-stimulating hormone receptor antibodies, antinuclear antibodies, antineutrophil cytoplasmic antibodies, antidouble-stranded deoxyribonucleic acid antibodies, antiglobulins, complement fraction, and cryoglobulins were measured in all subjects.

Results—Antithyroid autoimmunity was found in 31.0% (9 of 29) of patients with sCAD and 6.9% (2 of 29) of patients with non-CAD ischemic stroke (P = 0.041).

Conclusions—Autoimmunity may be involved in the process of local inflammation related to sCAD occurrence. The hypothesis that the arterial disease might be one phenotypic expression of a generalized activation of immunity warrants further investigations. (Stroke. 2006;37:2375-2377.)

Key Word: cerebral infarction ■ dissection ■ thyroiditis, autoimmune

Increasing evidence supports the assumption that a general susceptibility state may be involved in the pathogenesis of spontaneous cervical artery dissection (sCAD) and that inflammation might have a role in this process. The epidemiology of sCAD with seasonal peaks in autumn and spring, the clinical observation that acute infections may act as triggering factors, the finding of elevated levels of inflammatory markers in serum of patients with sCAD, and the pathologic evidence of inflammatory infiltrates in the wall of intracranial and coronary dissected arteries suggest that local inflammatory alterations might be a crucial step in the cascade of events leading to sCAD in predisposed individuals. Whether this implicates the activation of specific immune-mediated mechanisms is unknown at present. Recently, the hypothesis of an association between sCAD and thyroid disease has been suggested in sparse case reports prompting speculation on the pathogenic role of immunity in such a link. In fact, apart from the well-known association of thyroid dysfunction with vascular diseases, thyroid autoimmunity may lead to peripheral vascular damage independently on thyroid function. To explore the hypothesis of this relation, we search for thyroid autoimmunity, the most common of the autoimmune conditions, in a prospective case–control study, including patients with sCAD and patients with cerebral infarct of different pathogenesis (non-CAD).

Subjects and Methods

Patients consecutively admitted to our department during a 24-month period were included. The diagnosis of CAD was confirmed by magnetic resonance imaging–magnetic resonance angiography or conventional angiography. Dissections occurring as an immediate consequence of a major trauma were labeled “traumatic” and excluded. Patients with non-CAD ischemic stroke, selected from those who experienced first-ever acute cerebral ischemia, after exclusion of the subgroup with CAD-related infarction, served as controls. Only subjects with computed tomography and/or magnetic resonance image-proven cerebral infarction, comparable to sCAD patients on sex and age (±5 years), were recruited.

In all subjects, serum levels of antithyroperoxidase and antithyroglobulin antibodies were measured by microparticle enzyme immunoassay (Abbott Diagnostics) and antithyroid-stimulating hormone receptor antibodies by radioreceptor assay (Brahms). Serum levels of free-thyroxin, free-triiodothyronine, and thyroid-stimulating hormone were measured by routine hospital assays. Antinuclear antibodies and the perinuclear and cytoplasmic patterns of antineutrophil cytoplasmic antibodies were assessed by indirect immunofluorescence (Bio-Rad); antidouble-stranded deoxyribonucleic acid antibodies by radio immunosorbent assay (IBL); antiglobulins, complement fraction, and cryoglobulins were measured by routine hospital assays. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and antidouble-stranded deoxyribonucleic acid antibodies by radio immunosorbent assay (IBL); antiglobulins, complement fraction, and cryoglobulins were measured by routine hospital assays.

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Characteristics of Patients With Cervical Artery Dissection and Immune Activation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age (years)</th>
<th>Site of Lesion</th>
<th>Initial Symptoms</th>
<th>Neuroimaging</th>
<th>tT3–tT4</th>
<th>TSH*</th>
<th>Tg-Ab†</th>
<th>TPO-Ab‡</th>
<th>Other Positive Autoantibodies</th>
<th>Thyroid Disease</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F/43</td>
<td>Multiple vessels</td>
<td>LS, IS</td>
<td>MRI–MRA, DSA</td>
<td>N</td>
<td>14,3</td>
<td>112</td>
<td>129</td>
<td>ANA “speckled” anti-dsDNA</td>
<td>AT</td>
</tr>
<tr>
<td>2</td>
<td>M/62</td>
<td>L ICA</td>
<td>LS</td>
<td>MRI–MRA, DSA</td>
<td>N</td>
<td>9,6</td>
<td>41</td>
<td>N</td>
<td>ANA “speckled”</td>
<td>AT</td>
</tr>
<tr>
<td>3</td>
<td>F/49</td>
<td>L ICA</td>
<td>IS</td>
<td>MRI–MRA, DSA</td>
<td>N</td>
<td>N</td>
<td>200</td>
<td>386</td>
<td>None</td>
<td>AT</td>
</tr>
<tr>
<td>4</td>
<td>F/48</td>
<td>L ICA</td>
<td>LS, IS</td>
<td>MRI–MRA</td>
<td>N</td>
<td>N</td>
<td>168</td>
<td>355</td>
<td>ANA “speckled”</td>
<td>AT</td>
</tr>
<tr>
<td>5</td>
<td>F/51</td>
<td>R VA</td>
<td>LS, TI, IS</td>
<td>MRI–MRA</td>
<td>N</td>
<td>N</td>
<td>154</td>
<td>168</td>
<td>None</td>
<td>AT</td>
</tr>
<tr>
<td>6</td>
<td>F/50</td>
<td>L VA</td>
<td>TIA</td>
<td>MRI–MRA</td>
<td>N</td>
<td>N</td>
<td>39</td>
<td>22</td>
<td>ANA “nucleolar” P-ANCA</td>
<td>GD</td>
</tr>
<tr>
<td>7</td>
<td>M/37</td>
<td>L ICA</td>
<td>LS</td>
<td>MRI–MRA, DSA</td>
<td>N</td>
<td>N</td>
<td>529</td>
<td>622</td>
<td>ANA “speckled”</td>
<td>AT</td>
</tr>
<tr>
<td>8</td>
<td>F/54</td>
<td>L VA</td>
<td>LS, IS</td>
<td>MRI–MRA, DSA</td>
<td>N</td>
<td>N</td>
<td>22</td>
<td>N</td>
<td>ANA “nucleolar”</td>
<td>GD</td>
</tr>
<tr>
<td>9</td>
<td>M/39</td>
<td>L ICA</td>
<td>LS</td>
<td>MRI–MRA, DSA</td>
<td>N</td>
<td>N</td>
<td>46</td>
<td>39</td>
<td>None</td>
<td>AT</td>
</tr>
</tbody>
</table>

*Normal, 0.2 to 4.2 μIU/mL; †Normal, <34 IU/mL; ‡Normal, <12 IU/mL.

T3–T4 indicates free-triiodothyronine–free-thyroxin; TSH, thyroid-stimulating hormone; Tg-Ab, antithyroglobulin; TPO-Ab, antithyroperoxidase; ICA, internal carotid artery; VA, vertebral artery; LS, local signs; IS, ischemic stroke; MRI–MRA, magnetic resonance imaging–magnetic resonance angiography; ANA, antinuclear antibodies; dsDNA, double-stranded deoxyribonucleic acid; ANCA, antineutrophil cytoplasmic antibodies; DSA, digital subtraction angiography; N, normal levels; AT, autoimmune thyroiditis; GD, Graves disease.

Results

The study group was composed of 29 patients with sCAD (male/female, 15/14; median age, 44 years; range, 21 to 64 years) and 29 patients with non-CAD (male/female, 15/14; median age, 45 years; range, 26 to 64 years). Large-vessel or small-vessel atherosclerosis was the presumed cause of infarct in seven non-CAD cases (24.1%), cardiac/transcardiac embolism in 12 cases (41.4%), and other etiologies in the remaining 10 cases (34.5%). Increased levels of thyroid autoantibodies were found in 9 (31.0%) patients with sCAD. Biochemical and ultrasonographic findings were consistent with AT in 7 of these 9 patients. Five were euthyroid with normal circulating thyroid hormone levels, whereas 1 was classified as having a subclinical hypothyroidism and underwent thyroid therapy. In 1 patient (no. 2), the diagnosis of AT had been made 13 years before sCAD occurrence, and he was being treated with hormone replacement therapy (100 μg thyroxine daily) because of overt hypothyroidism. The remaining 2 patients had a 6-year and 1-year history, respectively, of treatment for Graves disease. Of these 9 subjects, 6 were also antinuclear antibodies-positive (4 with a “speckled” pattern), 1 had antibodies to antidual-stranded deoxyribonucleic acid, and 1 was positive for perinuclear antineutrophil cytoplasmic antibodies. In 1 patient (no. 7), the diagnosis of Pemphigus vulgaris had been made 3 years before the vascular event (Table).

Only 2 (6.9%) subjects with non-CAD ischemic stroke had positive antithyroid antibodies titers (P=0.041). AT was the presumed diagnosis in these cases (not shown).

Discussion

Thyroid autoimmunity is the paradigm for autoimmune diseases. In the present study, we observed a higher prevalence of thyroid autoimmunity in the group of patients with sCAD than in the group of patients with non-CAD ischemic stroke, and than that observed in the general population, in which it occurs in a percentage of 10% to 12%. Although the study design does not allow elucidation of the mechanism whereby thyroid autoimmunity is associated with sCAD, our findings suggest the hypothesis of a specific pathogenic relation of these 2 entities. One possible interpretation for such a link is that immunologic mechanisms may contribute to the chronic vascular damage underlying arterial dissection. From this point of view, autoimmunity should be considered a biologic determinant of sCAD. Actually, although AT is traditionally labeled as an “organ-specific” autoimmune disease, a systemic immune dysregulation has been suggested based on the demonstration of activated phenotypes in the peripheral blood of patients with this disease. Therefore, sCAD might be one phenotypic expression of a generalized activation of immunity. According to this view, it might be that antithyroid antibodies do not directly contribute to the pathogenic process, but only serve as indicators of autoimmunity. Alternatively, crossreactivity between thyroid gland and vascular tissues might be operant.

Although a direct relation between AT and sCAD seems the most likely mechanism, the alternative hypothesis of a reverse causation cannot be excluded a priori. In this regard,
the activation of the immune process should be interpreted as the consequence of a primary disorder of the arterial wall.

Apart from the exact mechanism, a number of indirect evidence provides arguments to support our hypothesis of a link between sCAD and autoimmunity. First, inflammatory infiltrates have been described in a substantial percentage of spontaneous coronary dissections at times in combination with cystic medial necrosis. Whether the inflammatory reaction is the cause or the consequence of the dissecting process is difficult to determine from histopathologic changes alone. However, the absence of such infiltrates in cases of iatrogenic–traumatic dissections, the reported association with immune disorders, also including AT, and the rapid disappearance of these arterial abnormalities after immunosuppressive treatment in some cases support the concept of a direct relation between autoimmunity and dissection. Second, autoimmunity has been proposed as a pathogenic mechanism of some disease entities such as segmental arterial mediolysis, related to sCAD occurrence. In line with this hypothesis is the observation that proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, which can be activated by immune mechanisms, may induce the proteolytic process and contribute to the degradation of the extracellular matrix proteins, a crucial process in the pathogenesis of sCAD. Finally, the hypothesis that genetically determined susceptibility to inflammatory stimuli might predispose to sCAD has been recently advocated.

In conclusion, our results provide arguments to the hypothesis that the activation of an immune-mediated process may be involved in the pathogenesis of sCAD probably by determining an underlying susceptibility state to disease occurrence and justify further investigations to clarify the nature of these mechanisms.

References
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