Coexistence of Cystatin C and β Protein Immunoreactivity

To the Editor:

Maruyama et al 1 have presented an immunohistochemical study of cerebrovascular amyloid in a large number of affected patients with diverse cerebral pathological conditions. One of the most interesting findings was the coexistence of β protein and cystatin C immunoreactivity in nine cases. Seven of the nine patients had suffered a fatal cerebral hemorrhage. The authors present some hypotheses on the potential pathologic role of cystatin C in the development of cerebral hemorrhages.

After the discovery of the role of cystatin C in the pathogenesis of hereditary cerebral hemorrhage with amyloidosis—Icelandic type (HCHWA-I), 2 but before the discovery of β protein in the cerebral blood vessels in patients with hereditary cerebral hemorrhage with amyloidosis—Dutch type (HCHWA-D), 3 it was thought that cystatin C was also involved in HCHWA-D. An immunohistochemical study with anti-cystatin C of three HCHWA-D patients indeed showed a weak immunoreactivity. 4 However, the finding of β protein in HCHWA-D definitely separated HCHWA-I and HCHWA-D as two different diseases, and the cystatin C immunoreactivity was forgotten. 3

The reason multiple cerebral hemorrhages occur at the same time in HCHWA-D patients is still an unsolved question. 2 A circulating serum factor inducing the bleeding may well be a possibility. The suggestion of Maruyama et al 1 that cystatin C may play an additional role in the causation of hemorrhages in cases of cerebral amyloid angiopathy is worth investigating in HCHWA-D since there appears to be combined β protein and cystatin C immunoreactivity in this disease as well. Their article sheds new light on a forgotten finding in HCHWA-D patients. 4

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Sneddon's Syndrome With Negative Antiphospholipid Antibodies

To the Editor:

Sneddon's syndrome is the association of cerebrovascular lesions and idiopathic livedo reticularis. 1 The cerebrovascular lesions usually consist of minor infarctions that occur in the territory of medium-sized cerebral arteries and usually have a favorable outcome; however, this favorable outcome is darkened by the severe mental deterioration that occurs in more than half of the patients. 2,3 Livedo reticularis may appear years before any neurologic symptoms. It involves the trunk and four limbs and worsens with cold. 3 Sneddon's syndrome usually occurs between the second and fourth decades, with a female predominance. 1,3 Computed tomography (CT) generally shows multiple infarcts and diffuse cerebral atrophy. 4 Cerebral angiography frequently discloses multiple stenoses and occlusions located in medium-sized arteries, but may also be normal. Digital artery biopsy shows segmental intimal hyperplasia, which includes fibroelastic proliferation with few smooth muscle cells.

We report a typical case of Sneddon's syndrome that is not associated with the antiphospholipid antibody syndrome. A 43-year-old woman was admitted to the Neurology Service at 12 Octubre Hospital because of an acute speech disorder. Neurologic examination revealed global aphasia, with no other abnormalities. General examination showed livedo reticularis on the trunk and four limbs. One month later, she had improved greatly, and only minor motor dysphasia remained.

Livedo reticularis was first noted by the patient when she was 8 years old. Seven years before admission, she had had a minor right hemispheric ischemic stroke from which she recovered completely in 2 weeks. One month before admission she suffered a thrombosis of the central retinal artery. The patient had no history of miscarriage or deep venous thrombosis. The family history was unremarkable.

The following tests were performed with normal results: erythrocyte sedimentation rate, complete blood count, renal function, liver function, lipogram, serum protein electrophoresis, total cholesterol, HDL cholesterol and LDL cholesterol, triglycerides, serum glucose, complement levels, chest X-ray, electrocardiogram, and echocardiogram. Antinuclear, anti-DNA, and extractable nuclear antibodies; rheumatoid factor; RPR; FTA-ABS; and antibodies to Borrelia burgdorferi were negative.

A CT scan of the brain showed multiple infarcts. Cerebral arteriography demonstrated multiple occlusions and stenosis of medium-sized vessels. A digital artery biopsy revealed intimal hyperplasia consisting of fibroelastic proliferation with small numbers of smooth muscle cells.

The following tests for lupus anticoagulant were performed with negative results: prothrombin time, activated partial thromboplastin time (aPTT), dilute phospholipid aPTT, and tissue thromboplastin inhibition procedure. Anticardiolipin antibodies (IgG, IgM) were not detected by an enzyme-linked immunosorbent assay that has proven to be sensitive in tests conducted against international standards. The tests done for detecting antiphospholipid antibodies were performed 3 days after the stroke when the patient had just begun antiplatelet therapy (aspirin).

The pathogenesis of Sneddon's syndrome is still unknown. After finding positive anticardiolipin antibodies, some authors have linked this disease to the antiphospholipid antibody syndrome 5-7 and antiphospholipid activity. 5 However, cerebral ischemia associated with the antiphospholipid antibody syndrome may have a
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The following is in response:
The Editor

Martinez-Menendez et al report a typical patient with Sneddon's syndrome who had a normal prothrombin time, activated partial thromboplastin time (aPTT), dilute phospholipid aPTT, tissue thromboplastin inhibition, and a single enzyme-linked immunosorbent assay (ELISA) for IgG and IgM anticardiolipin antibodies (aCL). These authors conclude that their patient did not have the antiphospholipid antibody (aPL) syndrome and that cerebral arteriographic findings differ between Sneddon's syndrome and the aPL syndrome. I agree with these authors that Sneddon's syndrome may have multiple causes and that aPL may play a role in some patients with Sneddon's syndrome.1,2 Recently, others have reviewed the literature concerning the relationship between aPL and Sneddon's syndrome.3,4

Clearly, not all patients with Sneddon's syndrome have tested positive for aPL.3,5 Livedo reticularis can be seen and considered to be a nonspecific dermatopathy6 in a large number of diseases, many of which are also associated with ischemic stroke. It therefore stands to reason that Sneddon's syndrome would still exist even if there were no such monster as aPL. It is unclear what the true prevalence of aPL is in the Sneddon's syndrome population, but it would certainly depend on the methods of aPL testing used6 and on concurrent treatment. More sensitive tests for lupus anticoagulants, such as the kaolin clotting time or dilute Russell viper venom test, may yield positive results when other studies for the lupus anticoagulant are negative or normal. Further, it is unclear if one negative assay for aCL truly excludes the presence of aPL since 1) the variability of the current ELISA assays is substantial, 2) the absence of aCL does not exclude the possibility of antibodies to other phospholipids such as phosphatidylethanolamine or phosphatidylethanolamine, 3) levels of aCL may actually drop around the time of a thrombotic event, including stroke,7 and 4) aCL levels fluctuate both spontaneously and in response to treatment.

Both Sneddon's syndrome and the aPL syndrome are associated with cerebral arterial stenosis or occlusion, primarily noninflammatory and intracranial.8,9 It is unclear at this point whether there is a true difference between medium and large cerebral vessel involvement in these two partially overlapping syndromes. Many features of Sneddon's syndrome with aCL are similar to those of Sneddon's syndrome without aCL.4 However, the data of Kalashnikova et al10 suggest that patients with Sneddon's syndrome and aCL have fewer TIA's, are more likely to be disabled, and had shorter disease duration than Sneddon's syndrome patients without aCL. Just as only a fraction of the patients with aPL syndrome have livedo reticularis,9 not all patients with Sneddon's syndrome will have aPL.4 In fact, very few patients with Sneddon's syndrome have had features typical of the aPL syndrome.10 Most reported cases of Sneddon's syndrome were associated with hypertension, cigarette smoking, or both, factors not mentioned in the letter by Martinez-Menendez et al.

Screening all patients with Sneddon's syndrome for aPL is reasonable given that some of these patients do have aPL and their presence may result in a different therapeutic approach. Follow-up testing for aPL may be useful in those patients with Sneddon's syndrome who are initially negative for aPL, but who develop other features of the aPL syndrome.

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Sneddon's syndrome with negative antiphospholipid antibodies.
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