New Clinical Relevance of Leukoaraiosis

To the Editor:

Changes in the cerebral white matter are detected with high frequency by CT and MRI in aged individuals.[1] The descriptive term leukoaraiosis, meaning rarefaction of the white matter, was proposed some 10 years ago to describe these radiological changes.[2] Although the mechanism of leukoaraiosis in different clinical conditions such as Alzheimer's disease or stroke remains undefined, vascular mechanisms probably underlie a reasonably large part of these alterations.[3] Leukoaraiosis has been inconsistently associated with cognitive impairment, assorted motor dysfunctions, and gait disturbances, but its contribution to Alzheimer's disease and vascular dementia is controversial.[1] Part of these discrepancies stem from different sensitivities of rating scales for white matter changes, small sample sizes of patients, and use of disparate neuropsychological tests.[1]

Recently, new evidence has suggested that leukoaraiosis may be clinically important. First, patients with leukoaraiosis have a poor prognosis in terms of death, stroke, and myocardial infarction. This has been documented both in patients with motor impairment and extensive leukoaraiosis on CT[4] and in clinically heterogeneous patients with any degree of leukoaraiosis.[5] Second, the results of prospective studies indicate that leukoaraiosis may be an independent and strong predictor of dementia in stroke patients.[6,7] Among 300 patients with TIA, cerebral infarction, or intracerebral hemorrhage, those with poststroke dementia showed leukoaraiosis on their entry CT scan three times more frequently than nondemented patients.[7] Third, and most recent, the presence of leukoaraiosis increases the risk of intracranial bleeding in patients with cerebrovascular diseases treated with anticoagulants.[8] The SPIRIT (Stroke Prevention In Reversible Ischemia Trial) was a multicenter randomized study designed to examine the role of oral anticoagulants and antiplatelet drugs as secondary prevention treatments in sinus rhythm patients with minor cerebral ischemic events of supposed atherothrombotic origin. Anticoagulation was set at a rather high international normalized ratio (INR) level (3 to 4.5), in accordance with Dutch national guidelines. The trial had to be stopped prematurely after the first interim analysis because of the excess of bleeding in the group of anticoagulated patients. Major bleedings were reported in 53 of the 651 patients randomized to warfarin treatment. About one half of all the bleedings were intracranial hemorrhage, which were fatal in 17 cases. Age $\geq$65 years, elevated INR levels, and presence of leukoaraiosis on CT scan were predictors of hemorrhage.[8] The association between white matter abnormalities and cerebral hemorrhage is not new, but it had previously been explained primarily by the common association with arterial hypertension.[9] Since the strongest predictor of leukoaraiosis is advanced age, the SPIRIT results need to be viewed with some caution in the light of the possible confounding effects of age and hypertension. Nevertheless, these data have already had an impact on the scientific community: a second forthcoming randomized trial, the European Stroke Prevention in Reversible Ischemia Trial (ESPRIT), which will evaluate the preventive efficacy of warfarin in patients with noncardioembolic stroke, lists the presence of leukoaraiosis among its exclusion criteria. This will certainly raise the problems of definition and grading of these changes on CT and MRI.

Thus, although much about the pathogenesis and clinical significance of leukoaraiosis remains to be elucidated, white matter changes relate to the prognosis of patients and can no longer be considered a secondary issue. Moreover, the above-mentioned results will require clinicians to examine in greater detail the status of the brain before deciding optimal preventive measures. It is therefore essential that investigators collaborate in the task of harmonizing the classification of white matter changes to better understand the clinical and pathological correlates. An European multinational research group (The European Task Force on Age-Related White Matter Changes) has been recently founded with these aims.

For the European Task Force on Age-Related White Matter Changes*:
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