Leukoaraiosis: From an Ancient Term to an Actual Marker of Poor Prognosis

Leonardo Pantoni, MD, PhD

The term leukoaraiosis (from the Greek leuko, white, and araiosis, rarefaction) was introduced in 1986 by Hachinski, Potter and Merskey to designate bilateral and symmetrical areas in the periventricular and centrum semiovale white matter that appeared hypodense on CT scans and hyperintense on T2-weighted MRI. Leukoaraiosis was supposed to be “a neutral term, exact enough to define white-matter changes, sufficient as a description or label, and demanding categorization in vivo of subcortical arteriosclerotic encephalopathy (or Binswanger disease), a form of vascular dementia with predominant involvement of white matter.1,2 It was clear in Hachinski and coworkers’ proposal the aim of contrasting the tendency to immediately identify a radiological aspect with a clinical picture. At that time, changes or lesions of the white matter were recognized with increasing frequency on the brain CT scans of elderly patients,3 and some authors had begun to attribute a clinical significance to these radiological findings, particularly interpreting them as a correlate of cognitive decline. According to some, the introduction of CT had made possible the identification in vivo of subcortical arteriosclerotic encephalopathy (or Binswanger disease), a form of vascular dementia with only few cases reported on pathological grounds until the eighties.4,5 The issue became even more complex after the introduction of MRI in neurological clinical practice because it was soon apparent that this neuroimaging technique was able to detect cerebral white matter changes with much higher frequency than CT.6,7 On MRI, changes of the white matter can be detected even when they are of very small ("punctiform") size.8 A review of the topic published in 1995 concluded that the clinical significance of leukoaraiosis remained incompletely defined, but it also suggested that the presence of the most severe degrees of these changes had an effect on cognitive functions in subjects without or with only minor cognitive impairment.9 The number of studies from which these conclusions were drawn at that time was much smaller than that available today.9

Over the last 10 years, evidence has been mounting on the prevalence, clinical significance, and prognostic value of white matter changes (Table). Nowadays, we know that minimal changes are almost invariably found in the general population.10,11 Data are sufficient to sustain that the mildest degree of leukoaraiosis is to be considered as an almost normal finding in the brain of elderly patients. However, evidence has also accumulated showing that moderate-to-severe white matter changes are not so benign. They are in fact correlated with motor and gait disturbances,12 depressive symptoms,13 urinary disturbances,14 and some cognitive deficits;15 the extent of these latter, however, is likely also influenced by possibly associated lesions such as lacunar infarcts and coexisting degenerative diseases.16–19 Longitudinal studies have outlined also a predictive role of leukoaraiosis in terms of less favorable prognosis in the general population and in a number of clinical conditions (Table). It is therefore essential in studies on white matter changes to abandon the mere assessment of their presence, and it is crucial to recognize their most severe degrees because these are likely the ones bearing clinical consequences. Further studies are needed to determine whether mild-to-moderate changes progress over time to become severe. Most of the studies with a longitudinal assessment of leukoaraiosis, however, have found that the most powerful predictor of progression is indeed baseline leukoaraiosis severity.20,21 Should this be definitely confirmed in the future, it will strongly support the hypothesis that at least 2 different pathological age-related processes of the white matter exist: a first one, more benign and attributable to a quasi-physiological aging process of the brain; and a second one, clearly pathological and associated with clinical disturbances and disease status. This will eventually demonstrate Hachinski and coworkers’ original hypothesis on the heterogeneity of leukoaraiosis.2 Preventive and therapeutic measures will obviously have to focus on the second type of leukoaraiosis.

Perhaps, the most important result in recent years has been the demonstration that leukoaraiosis represents a marker of poor prognosis, particularly in terms of increased mortality and risk of dementia.22–24 In a multicenter study, the severity of white matter changes at baseline was an independent predictor of the transition from a normal functional status to disability already after 1 year.25 The same study showed that this transition was mainly explained by cognitive and motor performances decline. This is of relevance because it suggests that the clinical effect of white matter changes is likely a composite one where different clinical correlates interact to cause loss of independence.

The presence of leukoaraiosis has been identified as a marker of less favorable prognosis also in the acute stroke
settings. In particular, white matter changes have been associated with an increased risk of hemorrhagic transformation of the brain infarct in patients subjected to thrombolysis; this increased risk is probably partially influenced by the copresence of lacunar infarcts. In this issue of *Stroke*, the article by Ay and colleagues adds further evidence about the prognostic significance of leukoaraiosis in this setting. These authors have shown that leukoaraiosis volume at the time of acute ischemic stroke is a predictor of infarct size growth. In this study, leukoaraiosis severity was volumetrically assessed whereas ischemic lesions on admission and follow-up were identified with diffusion and perfusion images. Clearly, this protocol is applicable only in centers with high expertise in neuroimaging techniques and not on a routine basis. But the relevance of the study is to have shown that a neuroimaging correlate of an underlying parenchyma and vessel disease is able to predict outcome in terms of infarct extension. When implemented in clinical practice, these data could provide a basis for a better selection of patients undergoing interventions in the acute phase of stroke.

Taken together, these recently acquired data indicate that the view that white matter changes are an innocuous and incidental finding or a topic to be left to the discussion of a small group of researchers should be now disregarded. Like other biological markers of an underlying disease, leukoaraiosis needs to be carefully looked at, assessed, and quantified; further studies will tell us whether this can be done by using simple visual rating scales or if it requires volume assessment and more sophisticated MRI techniques.

**DISCUSSION**

**Disclosures**

None.

**References**


Key Words: leukoaraiosis ■ white matter changes ■ disability ■ MRI ■ prognosis ■ stroke
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