Progression of Leukoaraiosis and Cognition

Reinhold Schmidt, MD; Katja Petrovic, PhD; Stefan Ropele, PhD; Christian Enzinger, MD; Franz Fazekas, MD

Background and Purpose—Leukoaraiosis is used interchangeably with the term white matter lesions on MRI and seen to some degree in more than half of the routine scans in older persons. Clinicians often struggle to explain the implications of these findings to their patients. Recent data on the progression rate of ischemic white matter damage and its cognitive consequences may help in patient counseling and have implications on treatment trials in vascular cognitive impairment.

Summary of Review—Leukoaraiosis progresses over time. Its extent at baseline is an important predictor for the subsequent rate of lesion progression. Subjects with punctate abnormalities on MRI have a low tendency for progression, individuals with early confluent and confluent changes tend to progress rapidly. Differences in measurement methods and cohort composition make it difficult to compare progression rates reported by different studies. Nevertheless, in community-dwelling cohorts, white matter lesions volume increased by as much as one quarter per year in subjects with confluent abnormalities at baseline. Progression of leukoaraiosis relates to cognitive decline, but this association is complex and modulated by other morphological factors like brain atrophy.

Conclusions—Evidence for rapid progression of widespread leukoaraiosis and the associated cognitive decline in domains particularly affected by cerebral small vessel disease has set the stage for exploratory clinical trials in vascular cognitive impairment using white matter lesions progression as a surrogate marker. (Stroke. 2007;38:2619-2625.)

Key Words: cognition ■ leukoaraiosis ■ MRI

One of the challenges when evaluating patients with cognitive impairment is the interpretation of leukoaraiosis shown by neuroimaging. Stenosis or occlusion of small cerebral vessels with sudden or chronic ischemia leading to incomplete white matter infarction is considered to play a central role in the pathogenesis of leukoaraiosis. Disturbed autoregulation in diseased small vessels and subsequent fluctuations in blood flow in response to changes of systemic blood pressure have also been implicated with complementary factors such as damage to the blood-brain barrier and chronic leakage of fluid to the white matter. So far, it is undetermined how well small vessel pathology maps onto radiological markers such as white matter hyperintensities seen in standard MR sequences. Yet, conventional MRI is unlikely to identify the full spectrum of small vessel disease–related cerebral damage. Diffusion tensor and magnetization transfer–imaging studies indicate that small vessel disease also causes loss of white matter tract integrity in the so-called normal-appearing white matter, a finding that has been related to cognitive decline in elderly individuals. Another pathological correlate of cognitive impairment in subjects with small vessel disease which completely eludes detection by MRI are microinfarcts in the gray matter.

The role of white matter damage as a contributor to vascular dementia is still controversial. This is also evident from the diverging conclusions of the 2 most recent sets of diagnostic criteria on vascular dementia. Both the California and the National Institute of Neurological Disorders and Stroke (NINDS)-Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria consider leukoaraiosis. However, in the former, only research status is attributed to the impact of leukoaraiosis, whereas the latter include it among imaging findings diagnostic for vascular dementia if more than a quarter of the total white matter is affected.

Given the high prevalence of leukoaraiosis in the general elderly population, it is particularly difficult to ascribe a lowest threshold at which these lesions contribute to cognitive impairment. Early cross-sectional studies reported conflicting results probably attributable to low statistical power and the frequent use of insensitive cognitive measures. Meanwhile, large population-based studies clearly support an...
association between leukoaraiosis and cognitive impairment.\textsuperscript{10–12} The multinational Leukoaraiosis and Disability Study (LADIS) also showed a strong association between white matter lesions (WML) and cognitive dysfunction.\textsuperscript{13}

Cross-sectional data cannot prove causality and thus cannot determine whether the relationship between leukoaraiosis and cognitive dysfunction stems from the ischemic white matter damage per se or from coexistent and secondary phenomena also occurring with aging. This prompted a shift from cross-sectional to longitudinal studies to establish a temporal relationship between change in lesion extent and change in clinical presentation.

Recent reports consistently showed that leukoaraiosis progression over time is substantial, particularly in patients with specific phenotypes.\textsuperscript{14} These findings led the European Task Force on Age-Related White Matter Changes to propose WML progression as a potential surrogate marker in therapeutic trials of cerebral small vessel disease.\textsuperscript{15} Nonetheless, WML progression as a potential surrogate marker in therapy on Age-Related White Matter Changes to propose the rate of progression because WML progression from cross-sectional to longitudinal studies to establish a temporal relationship between change in lesion extent and change in clinical presentation.

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Neuropsychological test batteries assessing cognitive effects of leukoaraiosis progression need to be tailored toward the pattern of dysfunction specific for vascular cognitive impairment and distinct from that commonly associated with Alzheimer disease.\textsuperscript{9} A metaanalysis quantified the cognitive sequelae of leukoaraiosis in nondemented subjects and found processing speed, immediate and delayed memory, executive functions, and indices of global cognitive functioning to be especially affected.\textsuperscript{24} It was only recently that the NINDS-Canadian Stroke Network recommended an optimized test protocol covering 4 distinctive cognitive domains including executive control and activation state, language, visuospatial abilities, and memory.\textsuperscript{25}

**Methods to Assess Leukoaraiosis Progression and Related Cognitive Change**

Semi-quantitative visual assessment of leukoaraiosis has proven efficacious and several rating scales with different grades of refinement have been developed and validated to determine leukoaraiosis severity.\textsuperscript{16} These scales demonstrated good interrater agreement and correlated sufficiently with the volume of white matter damage derived from fully quantitative measurements.\textsuperscript{17} Unfortunately, these scales fail to pick up progression.\textsuperscript{17} We adapted the Fazekas scale\textsuperscript{18} and categorized leukoaraiosis progression as minor with 1 to 4 new punctate lesions and as marked with a difference of \textgreater{}2 lesions or a transition to early confluent or confluent white matter abnormalities.\textsuperscript{19} However, by focusing on new lesions and transition to higher grades alone, we probably underestimated the rate of progression because WML progression very commonly means enlargement of already existing changes rather than newly occurring abnormalities.

The Rotterdam Progression Scale considered both new focal lesion occurrence and lesion enlargement, and found good agreement with a volumetric method after the scale had been adapted.\textsuperscript{20} The Cardiovascular Health study investigators calculated a change score by subtracting grades of abnormality on their 10-point scoring system at follow-up and observed modest intrarater reliability for change of 1 or more grades but only fair interrater agreement.\textsuperscript{21} Another group compared visual rating of lesion progression based on the Scheltens scale\textsuperscript{22} with volumetric measurements and concluded that such a quantitative assessment of leukoaraiosis offered a more reliable, sensitive, and objective instrument than visual rating scales in longitudinal studies.\textsuperscript{23} Most researchers consider volumetric assessments superior but very time-consuming and labor-intensive. Current semiautomated methods are mostly based on tissue segmentation and still require considerable operator input. Despite training and guidelines for analysis, some differences between operators are unavoidable. Therefore, most studies have used a side-by-side comparison of lesion-load assessment. This may cause some overestimation of progression rate but is an efficient way of reducing noise and artificial influences on lesion change. Conceptually, techniques of coregistration and image subtraction should also enhance the sensitivity and reliability of detecting lesional changes, but such advantages are frequently offset by a parallel reduction in lesion contrast from image reformatting. Moreover, subtraction techniques rely on identical imaging protocols, a prerequisite that is difficult to fulfill in long-term multicenter studies.

Neuropsychological test batteries assessing cognitive effects of leukoaraiosis progression need to be tailored toward the pattern of dysfunction specific for vascular cognitive impairment and distinct from that commonly associated with Alzheimer disease.\textsuperscript{9} A metaanalysis quantified the cognitive sequelae of leukoaraiosis in nondemented subjects and found processing speed, immediate and delayed memory, executive functions, and indices of global cognitive functioning to be especially affected.\textsuperscript{24} It was only recently that the NINDS-Canadian Stroke Network recommended an optimized test protocol covering 4 distinctive cognitive domains including executive control and activation state, language, visuospatial abilities, and memory.\textsuperscript{25}

**Magnitude of Progression of Leukoaraiosis**

Meanwhile, there is convincing evidence for leukoaraiosis progression from numerous studies using either visual rating or semiautomatic measurement of lesion volume in population-based, community-dwelling and hospital-based studies.\textsuperscript{19,21,26–34} Even CT scanning can demonstrate newly developing leukoaraiosis as shown in a selected cohort from the North American Symptomatic Carotid Endarterectomy Trial. From 596 patients without leukoaraiosis at entry, 18% developed restricted abnormalities and 3% widespread changes during a mean follow-up of 6.1 years.\textsuperscript{35} Similarly, all MRI studies so far also yielded lesion progression over time (Table 1). This table shows great variation in frequencies of progression and volume increases. A direct comparison between studies is difficult because of differences in study groups and analysis techniques. Importantly, all investigations agree that the extent of lesions at baseline is a major predictor of subsequent progression.\textsuperscript{26,27,32,33} Age and conventional risk factors for stroke appear to have relatively little influence, at least over the observational periods reported so far.\textsuperscript{14} In the Austrian Stroke Prevention Study,\textsuperscript{32} there was almost no increase in lesion volume in subjects with punctate abnormalities, whereas participants with a baseline finding of early confluent or confluent changes showed a remarkably rapid increase in lesion volume. After 3 and 6 years of follow-up, subjects with confluent white matter abnormalities at baseline experienced a 5 cm\textsuperscript{3} and 13 cm\textsuperscript{3} increase in lesion volume, respectively. The Figure shows examples of differential lesion progression depending on baseline lesion grade.
Almost two thirds with early confluent and all subjects with confluent lesions demonstrated progression beyond measurement error over 6 years. This was seen in none of the subjects with a normal baseline MRI and only 14% of those with punctate foci. These data together with findings from pathological correlations indicate that punctate WMLs are probably of mixed origin and benign, whereas early confluent and confluent white matter abnormalities are ischemic, progressive, and thus malignant. Progression of white matter abnormalities was also seen in subjects with dementia of various etiologies, but these small studies did not show an effect of the dementing illness per se. Progression rates were again influenced primarily by severity of lesions at baseline rather than by the type of dementia or cognitive decline. A recent investigation showed that leukoaraiosis progression occurs throughout the brain but with some regional variation. Frontal lesions progressed the most, occipital the least. Lesions in the deep white matter progressed more than those in the periventricular white matter, a similar finding was reported by the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study, but only in women.

Cognitive Consequences of Progression of Leukoaraiosis

Reports on the cognitive consequences of lesion progression have been published only recently (Table 2). They consistently demonstrated an association between progression of leukoaraiosis and cognitive decline. In a Danish cohort of people born in 1914 an increase in WML volume correlated with a declining verbal IQ. The Cardiovascular Health Study reported WML progression by at least 1 grade in 28% of study participants. They experienced greater decline on the modified Mini-Mental State Examination and the Digit-Symbol Substitution Test than those without progression. Similar data were seen in the MRI-substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study, but only in women.

Table 1. Leukoaraiosis Progression in MRI Studies in the Elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Subject No.</th>
<th>Follow-Up in Years</th>
<th>Measurement</th>
<th>Progression Frequency</th>
<th>Volume Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahlund</td>
<td>Normals</td>
<td>13</td>
<td>5</td>
<td>Scheltens Scale</td>
<td>92%</td>
<td>4.6 cm³</td>
</tr>
<tr>
<td>Veldink</td>
<td>Normals &amp; cognitively impaired</td>
<td>14</td>
<td>2</td>
<td>Scheltens Scale</td>
<td>57%</td>
<td>...</td>
</tr>
<tr>
<td>Schmidt</td>
<td>Community-dwelling</td>
<td>273</td>
<td>3</td>
<td>Modified Fazekas Scale</td>
<td>17.9%</td>
<td></td>
</tr>
<tr>
<td>Whitman</td>
<td>Normals</td>
<td>70</td>
<td>4</td>
<td>Grid method</td>
<td>...</td>
<td>1.1 cm³</td>
</tr>
<tr>
<td>Schmidt</td>
<td>Community-dwelling</td>
<td>296</td>
<td>6</td>
<td>Semiautomated volume measurement</td>
<td>17.2%</td>
<td>1.4 cm³</td>
</tr>
<tr>
<td>Taylor</td>
<td>Community-dwelling</td>
<td>117</td>
<td>2</td>
<td>Semiautomated volume measurement</td>
<td>...</td>
<td>1.4 cm³</td>
</tr>
<tr>
<td>Van Dijk</td>
<td>Population-based</td>
<td>636</td>
<td>3.3</td>
<td>Modified Rotterdam Scale</td>
<td>27% periventricular, 32% subcortical</td>
<td>...</td>
</tr>
<tr>
<td>Longstreth</td>
<td>Population-based</td>
<td>1919</td>
<td>5</td>
<td>Cardiovascular Health Study Scoring</td>
<td>28%</td>
<td>...</td>
</tr>
<tr>
<td>Ten Dam</td>
<td>Trial cohort</td>
<td>535</td>
<td>2.8</td>
<td>Automated volume measurement</td>
<td>...</td>
<td>1.0 cm³</td>
</tr>
<tr>
<td>Garde</td>
<td>Octogenarians</td>
<td>26</td>
<td>3.8</td>
<td>Semiautomated volume measurement</td>
<td>...</td>
<td>2.4 cm³</td>
</tr>
<tr>
<td>Sachdev</td>
<td>Community-dwelling</td>
<td>51</td>
<td>3</td>
<td>Automated volume measurement</td>
<td>...</td>
<td>6.5 cm³</td>
</tr>
</tbody>
</table>

Baseline (upper row) and 6-year follow-up (lower row) in 3 study participants of the Austrian Stroke Prevention Study. Subject A had punctate lesions at baseline and no change after 6 years. Subjects B and C show early confluent WMLs and confluent abnormalities at baseline, respectively. Typically, these subjects experienced substantial leukoaraiosis progression after 6 years. As shown in B and C, the predominant pattern of progression is lesion growth at the sites of preexisting lesions rather than occurrence of new abnormalities.
cognitive functioning. Increasing volume of leukoaraiosis correlated significantly with loss of brain volume and performance decline in tests of memory, conceptualization, and visuopractical skills. However, the associations between changes in WML load and cognitive functioning were no longer significant when the change in brain volume was added to the models suggesting that cognitive decline related directly to loss of brain substance with progression of lesion burden. One explanation for the mediating effect of brain atrophy in the relation between WML progression and cognitive decline is concomitant Alzheimer disease. However, in the Austrian study, the subgroup of participants with no brain atrophy but extensive white matter changes at baseline experienced a substantially greater loss of brain volume during subsequent years than their counterparts without white matter foci. This supports the view that concomitant Alzheimer pathology is not the sole explanation for increasing loss of brain parenchyma in patients with progressing leukoaraiosis. Interestingly, in the context of subcortical ischemic disease, dementia with substantial cortical and hippocampal atrophy has been shown to occur in the absence of any Alzheimer pathology. There are several mechanisms by which subcortical ischemic disease could lead to loss of brain volume and subsequent cognitive deficits. Among them are chronic functional alterations related to ischemic white matter damage with subsequent structural changes of the cortex. Alternatively, progressing leukoaraiosis might be paralleled by increasing cortical microangiopathy with microscopic infarctions and loss of neurons invisible on conventional MRI. A similar scenario has been suggested in multiple sclerosis where cognitive deterioration also relates more to the magnitude of brain parenchymal loss than to the extent of WML burden. Gray matter pathology beyond the resolution of standard MRI sequences is considered to play an important role. More data are needed on the mechanisms involved in the relationship between evolving leukoaraiosis and cognitive deterioration. Nevertheless, based on current evidence, there is no doubt that, on a group level, leukoaraiosis progression is paralleled by cognitive decline.

### Current Studies Probably Underestimate the Progression of Leukoaraiosis and Related Cognitive Dysfunction

Substantial participant attrition was seen in all longitudinal studies assessing leukoaraiosis progression and requesting study participants to undergo repeat MRIs and complex investigational protocols. In the Rotterdam Scan Study, 38% of participants who underwent brain MRI at baseline did not undergo the 5-year follow-up scan. In the Austrian Stroke Prevention Study, 43% and 52% of participants were lost to the 3-year and 6-year follow-up scanning, respectively. A very similar drop-out rate was seen in the Cardiovascular Health Study in which 42% of subjects did not undergo a second MRI after 5 years. All 3 studies reported that patients who took part in the follow-up examinations were younger, had less vascular risk factors and higher educational levels than the total study population. Therefore, successive evaluations reflect the course of brain changes and the cognitive performance of a progressively more healthy and elite subset of the original sample. It thus appears justified to assume a greater rate of leukoaraiosis progression and its clinical consequences in those study participants who were lost to follow-up.

Also, some underestimation regarding evolving neuropsychological dysfunction may come from practice effects. Repeated confrontation with psychological tests is likely to improve performance and subsequently lead to underestimation of the rate of cognitive deterioration. An analysis of active community residents showed that improvement attributable to retesting can be as large as the average decline between ages 49 and 70, or the average decline between ages 70 and 80. Such effects are of particular importance in studies on elderly populations without dementia from which most current data on the natural course of leukoaraiosis were derived. A time interval of 6 years is needed between test exposures to eliminate practice effects. In the available studies, the intervals between testing were shorter, in part because such long periods between follow-ups pose a serious risk of even higher drop-out rates. It is common practice to use parallel test forms at follow-up in order to reduce practice...
effects. These may, however, not only come from a general familiarization with the examination procedures but also be a consequence of decreased test anxiety. If this is the case, better performance is independent of cognitive test forms used. It is noteworthy that the relevance of practice effects appears to be different for different cognitive domains. They were described to be more pronounced for memory whereas there is little, if any, effect on tests assessing speed.46 Practice effects may also affect randomized trials. It is important that study participants in the control and experimental arm experience identical practice levels.

Conclusions

Significant leukoaraiosis progression is seen in elderly individuals who present with moderate to severe white matter changes irrespective of clinical symptoms.19,21,26–34 Leukoaraiosis progression is accompanied by a modest decline in performance on neuropsychological tests. Future studies will have to better determine the magnitude of cognitive and functional impairment associated with the full range of leukoaraiosis burden in elderly subjects. Currently, it is unknown how often leukoaraiosis is associated with clinically relevant functional deficits. The LADIS project included subjects based on their burden of leukoaraiosis irrespective of their clinical presentation and supports the clinical relevance of these brain abnormalities, because subjects with severe white matter changes performed significantly worse on global cognitive measures such as the Mini-Mental State Examination and showed rapid functional decline as early as after the first year of follow-up in comparison to those individuals with only mild leukoaraiosis at baseline.13,49 The relationship between burden of leukoaraiosis and cognitive functioning is likely to be influenced by other morphological and clinical factors. Evolving brain atrophy mediated the association between leukoaraiosis progression and cognitive deterioration in community-dwelling older persons using automated techniques to study the change of brain morphology over 6 years.40 The existing data cannot rule out that the progression of both leukoaraiosis and related cognitive dysfunction is underestimated because of a selective drop-out of study participants. Other important but underappreciated factors are learning effects and cerebral adaptation to tissue damage, an issue that has attracted little attention in studies on the cognitive sequelae of small vessel disease so far. Consequently, several issues need to be considered when planning interventional therapeutic trials in small vessel disease. Clearly, leukoaraiosis progression represents one of the most convincing and readily measurable markers of progressive small vessel disease.15 It has already been suggested by the European Task Force on Age-Related White Matter Changes that trials on cerebral small vessel disease with primary clinical end points may use lesion load progression as a secondary outcome variable to evaluate therapeutic effects earlier and with higher sensitivity than by clinical observations alone.15 Based on data of the Austrian Stroke Prevention Study, the Task Force estimated that 195 subjects with confluent lesions would be required per treatment arm to demonstrate a 20% reduction in the rate of disease progression over a 3-year period. Only recently has the proposal to use leukoaraiosis progression as a surrogate marker in clinical trials been adopted in the PROSPER trial and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).50 PROSPER did not show any effects of statin treatment on volume change of leukoaraiosis,34 but statin also had no effect on cerebral blood flow and brain volume.51 By contrast, the MRI substudy of PROGRESS revealed a lower incidence of WMLs under angiotensin-converting enzyme inhibitor treatment with the treatment effect being most pronounced in the subgroup of subjects with advanced leukoaraiosis at study entry. The lack of an effect of statin use on progression of morphological and functional variables seen in the PROSPER substudy needs to be considered with caution because patients were recruited irrespective of the presence of white matter lesions at baseline. Also, different from PROGRESS, stratification according to white matter lesion severity was not done.34 Given the complexity of the associations between progression of white matter damage and cognitive decline,40 measuring the increase of leukoaraiosis volume in isolation probably does not suffice to fully determine treatment response in small vessel disease trials. It is equally important to assess other morphological expressions of the disease. Even though changes in brain volume cannot unequivocally be attributed to cerebral small vessel disease, they deserve special attention as possible surrogate markers in treatment trials on this disease as loss of brain parenchyma was found to be more closely related to cognitive decline than the change in leukoaraiosis volume.40 Another focus needs to be put on white matter appearing normal on standard MRI sequences. This will require longitudinal application of techniques to quantify tissue integrity like mean diffusivity, fractional anisotropy or assessment of magnetization transfer ratios.52 A recent longitudinal study in patients with CADA-SIL established correlations between changes of diffusion tensor imaging histogram metrics and clinical measures over time.53 Selection of appropriate patient groups will be an important issue in trial planning. Focus on individuals with already existing substantial leukoaraiosis is mandatory because baseline lesion load is the most significant predictor of lesion progression. Deterioration of neuropsychological performance has also been greater in patients with marked leukoaraiosis at baseline than in those with only mild abnormalities.28 This is further supported by a recent observation of the LADIS study.40 Individuals with severe white matter changes were found to have a 2- to 3-fold increased risk of becoming more impaired as early as after the first year of follow-up in comparison to those individuals with only mild leukoaraiosis at baseline.

Finally, interventional studies will have to concentrate not only on cognitive functions but the entire spectrum of clinical abnormalities potentially attributable to cerebral small vessel disease. This is the only way to attribute adequate importance to an illness that is almost endemically encountered in our older populations and urgently awaits targeted therapeutic measures.

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Disclosures
None.

References


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