2001–2011: A Decade of the LADIS (Leukoaraiosis And DISability) Study: What Have We Learned about White Matter Changes and Small-Vessel Disease?

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Key Words

White matter changes • MRI • Elderly • Disability • Cognitive decline • Motor disturbances • Depression • Urinary disturbances

Abstract

Over the last 20 years, evidence about the clinical correlates of cerebral white matter changes (WMC; also called leukoaraiosis) has been accumulating. WMC are now listed among the neuroimaging expressions of cerebral small-vessel disease and are no longer considered an innocuous finding because they are associated, in cross-sectional surveys, with various disturbances and, in follow-up studies, with poor prognosis. The Leukoaraiosis And DISability (LADIS) study has contributed substantially to this body of knowledge. LADIS is a European multicenter collaboration that was started in 2001 with the aim of assessing the independent role of WMC in predicting disability in subjects aged 65–84. The main results of the LADIS study have been released in 2009 with the demonstration that severe WMC more than double the risk of transition from an autonomous to a dependent status after 3 years of follow-up. The LADIS study has also

contributed more focused substudies assessing the possible role of WMC in the decline of cognitive and motor performances, depressive symptoms associated with aging and cerebrovascular diseases, urinary disturbances, and also the role of other brain lesions (lacunar infarcts, cerebral atrophy, and corpus callosum morphology). The LADIS study provides a good example of harmonization of instruments (MRI protocol, clinical, neuropsychological, and functional scales) within an international collaboration. Currently, the LADIS study is providing data about the natural history of WMC. In this paper, we review the background and the main results of the LADIS study. This review puts forward some considerations for future studies in the field.

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¹ Authors' Contribution: Anna Poggesi and Leonardo Pantoni drafted the first version of the paper. The paper was then reviewed by the study principal investigator (Domenico Inzitari), the study workpackages coordinators (Franz Fazekas, José Ferro, John O'Brien, and Michael Hennerici), the LADIS Study steering committee members (Philip Scheltens, Timo Erkinjuntti, Marieke Visser and Peter Langhorne), and the remaining center coordinators (Hugues Chabriat, Gunhild Waldemar, Anders Wallin, Anders Wahlund).

Fig. 1. White matter changes: 3 severity degrees (mild, moderate, and severe) according to the modified Fazekas scale.

Introduction

White matter changes (WMC) are frequently observed on CT and MRI in the brains of elderly subjects, particularly in those with vascular risk factors, appearing as bilateral, patchy or diffuse areas of hypodensity on CT or hyperintensities on T₂-weighted MRI scans. These changes involve the periventricular white matter, the corona radiata, and the centrum semiovale with different severity, have irregular margins and do not follow specific vascular territories. WMC are nowadays recognized as one of the manifestations of cerebral small-vessel disease [1]. The clinical and pathologic significance of WMC has been the object of several investigations over the last 30 years. Today, sufficient evidence exists to affirm that, when WMC reach a certain severity degree, they are not an innocuous finding [2–4]. In the 1990s, some data existed about a possible association between WMC cognitive, motor, mood and urinary disorders, but full consensus on their clinical significance was lacking [5].

In order to reach an agreement on the significance of WMC and to harmonize and promote collaborative efforts in this field, the European Task Force on Age-Related White Matter Changes was founded in 1996 [6]. In the following years, the task force setting was the ideal basis for the planning of the Leukoaraiosis and Disability (LADIS) study.

The LADIS study was established as a European multicenter collaboration in 2001 with the support of the European Union (5th European Framework Program ‘Quality of life and management of living resources’) [7]. The study’s main aims were to assess the role of WMC as an independent predictor of the transition from an autono-

mous functional status to disability in elderly subjects and to assess the role of WMC progression in this transition. The study has been carried out in 11 European centers that shared a common interest in the investigation of the clinical consequences of vascular changes in the brain. To tackle specific research questions and to optimize technical aspects, 6 work packages were identified according to the main focuses of the study: (1) methodology, (2) disability, (3) neuroimaging, (4) cognition, (5) mood, and (6) gait, each with one coordinator and collaborators. The enrollment of subjects began in July 2001 and the follow-up ended after 3 years as scheduled. A prolonged follow-up took then part in 2008–2009 based on telephone interviews.

Over the last 5 years the LADIS collaboration has provided a number of publications concerning different aspects of WMC. The aim of this review is to provide an overview of the main results achieved by the collaboration and how these have influenced our understanding and future research efforts.

The LADIS Study: Methods and Sample Characteristics

Six hundred and thirty-nine patients (mean age 74.1 ± 5.0, males 45%) were enrolled in the LADIS study [7]. The enrolled subjects were functionally autonomous elderly patients presenting for medical evaluation for different reasons: (1) mild cognitive complaints, (2) motor disturbances, (3) minor cerebrovascular events, (4) mood disturbances, and (5) other neurological problems. Two other enrollment settings were that of subjects in whom WMC were incidentally identified on brain imaging and

Table 1. Instruments of the LADIS study protocol

	Instruments/methods	Reference No.
Global functioning	IADL	9
	DAD	11
Cognitive performances	MMSE	12
	Stroop Test	13
	Trail Making Test	14
	VADAS-cog	15
Mood	GDS (GDS-15)	16
	Cornell	17
	DSM-IV criteria	18
Motor performances	SPPB	19
	Single leg stance	20
	Gait velocity	20
Quality of life	Euro QoL EQ-5D	21
MRI protocol	WMC	
– Axial/coronal T ₁ , T ₂ , PD, FLAIR sequences	Fazekas Scale	8
	Scheltens Scale	22
– Diffusion tensor and magnetization transfer techniques ¹	European Task Force WMC Scale	23
	Volumetry (semiquantitative measurement)	24
	Infarcts	
	Visual assessment of number and location of lacunar and nonlacunar infarcts	25
	Atrophy	
	Graz Visual Rating Scale (global)	26
	Scheltens Visual Scale (medial temporal lobe atrophy)	27

PD = Proton density.
¹ Available only in selected centers.

subjects participating as controls in other studies. These heterogeneous referral pathways were deliberate so the population recruited reflected the various settings in which patients with WMC can be encountered in clinical practice.

Study inclusion and exclusion criteria are reported in detail in a methodological paper [7]. Subjects were aged 65–84, had to have WMC of any degree on MRI (categorized as mild, moderate, and severe according to a revised version of the scale of Fazekas et al. [8] (fig. 1) and no or only mild disability as assessed by the Instrumental Activities of Daily Living (IADL) scale [9] (no impairment at all or only one item compromised). The distribution of vascular risk factors and diseases and the respective association with WMC severity confirmed the strong association between WMC and age, hypertension and lacunar stroke [10].

Clinical and Instrumental Assessment and Outcome Measures

For baseline and follow-up assessments, structured and standardized protocols were uniformly used in all the participating centers. The clinical instruments were prepared following literature revision and were accepted by consensus among the study principal investigators [for details, see 7]. In table 1 all instruments foreseen by the study protocol are listed.

Patients were followed up for 3 years with a yearly repetition of the baseline clinical and functional assessments. Drop-out and death forms were developed to collect basic information including a phone interview on IADL to be administered to the informant of dropped-out or deceased patients. A checklist to classify causes of death using all available information was used.

The main study outcome was the transition from an autonomous status to disability, defined as the presence of 2 or more impaired IADL activities. Secondary outcomes were dementia, stroke, depression, and quality of life.

MRI Study

All patients underwent an MRI study following a specific protocol. This included T₁-, T₂-, proton density-weighted and FLAIR (Fluid-Attenuated Inversion Recovery) pulse sequences [7]. Diffusion tensor and magnetization transfer techniques were employed by selected centers to further characterize tissue changes [26, 28]. Image analyses of conventional MRI were performed centrally at the Department of Neuroradiology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands, whereas magnetization transfer imaging and diffusion tensor imaging data were analyzed at the Department of Neurology, Medical University Graz, Austria. Corpus callosum assessment was done at the Danish Research Centre for Magnetic Resonance, Copenhagen, Denmark. The analyses included the application of visual rating scales and volumetric analysis of WMC. Other MRI measures were the assessment of lacunar and nonlacunar infarcts, rating of global atrophy and of medial temporal lobe atrophy (MTA), and quantification of the magnetization transfer ratio and of diffusivity in a global and regional manner. The MRI examination was repeated at the end of the 3-year follow-up with the aim of assessing possible progression of WMC and of other lesions.

Validation and Harmonization of Instruments and Procedures

The handling of possible heterogeneity across the different transnational cultural and linguistic settings in the application of the procedures for assessing clinical outcomes was a topic of thorough discussion while finalizing study methods and instruments. The transcultural reliability of the IADL scale (main study instrument) scoring was tested before the start of the study [7]. A good inter-center agreement on each item of the IADL scale was shown (κ ranging from 0.69 to 0.85). A videotape with examples of the motor performance assessments was prepared and distributed to all centers. To check for the correct adhesion to the MRI protocol and the quality of scans, the performance of a dummy run was required before the beginning of the study. Besides the central evaluation, an experienced rater for each participating center independently rated the MRI changes according to pro-

vided illustrative examples in order to carry out an inter-rater trial on the agreement between the single centers and the central rating; the consistency turned out to be good.

The harmonization of cognitive assessment offered particular complexity and led to the construction of a specific neuropsychological test battery [29]. The development of the LADIS battery had to take into consideration that: (1) selected tests had to be available and familiar in the majority of the centers; (2) the tests had to be sensitive to cognitive decline; (3) the battery had to be innovative, easy to administer, comprehensive, but not too long; (4) all centers had to use the same version of each test, and (5) the original English version of tests had to be translated into each local language.

The Contribution of the LADIS Study to the Understanding of the Clinical Consequences of WMC

The main findings of the LADIS study in terms of the impact of WMC and other cerebral lesions on clinical aspects are summarized in table 2.

WMC and Disability

The main objective of the LADIS study was the evaluation of the effects of WMC on the functional status of elderly subjects. A first result of the LADIS study was that already at baseline patients with the highest severity of WMC had a small but measurable degree of functional impairment as measured by the forty-item Disability Assessment for Dementia (DAD) scale despite the independence in everyday life [30]. A trend towards declining performance on the DAD scale was apparent with increasing WMC score severity. The statistical significance of these differences was confirmed in a multiple linear regression analysis, correcting for numerous factors known to influence disability in the elderly. Possible mediators of the relationship between the degree of WMC severity and functional performance were executive functions, which declined with increasing WMC severity and were significantly related to the DAD total score [30].

The hypothesis that WMC have an effect on disability was supported by data from the 1-year follow-up [31]. This interim analysis showed that the rate of transition from a functional autonomous status to disability was 9, 15 and 26%, respectively, in the mild, moderate, and severe group of WMC. Subjects with severe degrees of WMC had a risk of transition more than 2-fold higher compared to that of the mild group and this was indepen-

Table 2. Main findings from the LADIS study concerning the role of neuroimaging features in clinical aspects

Clinical correlates	MRI lesions (parameter)	Results	Reference No.
Functional status	Baseline severe WMC	– Association with worse functional status – Independent predictor of disability	30 31, 32
Cognition	Baseline severe WMC	– Association with worse score on MMSE and ADAS – Association with worse cognitive performances on global tests of cognition, executive functions, speed and motor control, attention, naming and visuoconstructional praxis – Independent predictor of dementia and cognitive impairment	25 33 34
	Progression of WMC	– Association with decrease in executive function score	35
	Number of lacunar infarcts	– Association with worse score on MMSE and ADAS	25
	Location of lacunar infarcts	– Thalamus location associated with worse cognitive performances (MMSE and compound scores for speed and motor control, and executive functions)	36
	Number of new lacunes	– Association with deterioration in executive functions, speed and motor control	35
	SIVD ¹	– Independent predictor of decline in cognitive performances and of dementia	37
	MTA severity	– Association with mild cognitive deficits (MMSE <26); additional effect with severe WMC – Predictor of Alzheimer's disease	38 34
	Corpus callosum atrophy	– Association with worse cognitive performances – Regional association with cognitive performances: anterior with deficits of attention and executive functions, isthmus subregion with semantic verbal fluency – Independent predictor of dementia and motor impairment	39 40 41
	Changes in mean diffusivity of normal appearing white matter	– Association with cognitive dysfunction	26
Mood	Baseline WMC severity	– Association with depressive symptoms – Independent predictor of depressive mood and depressive episodes	42 43, 44
	WMC location	– Deep WMC associated with depressive symptoms – Frontal and temporal regions associated with depressive symptoms	45 45
	Location of lacunar infarcts	– Association of basal ganglia lesions with depressive symptoms	46
Motor performances	Baseline severe WMC	– Association with worse motor performances – Association with falls and balance disturbances	47 48
	WMC location	– Periventricular and deep frontal WMC associated with falls – Deep frontal WMC associated with balance disturbances	48 48
Urinary problems	Baseline severe WMC	– Association with urinary urgency	49

SIVD = Small-vessel ischemic disease.

¹ Defined as severe WMC (Fazekas scale grade 3) plus at least 1 lacune or moderate WMC (Fazekas scale grade 2) plus >5 lacunes.

dent of a large number of other predictors of disability entered in a multivariate model [31].

The analysis of the 3-year follow-up data offered the definite proof of the original hypothesis of the study [32]. After a median follow-up period of 2.9 years, information

on the main outcome was available for 633 (>99%) patients. The annual rate of transition or death was 10.5, 15.1, and 29.5%, respectively, for patients with mild, moderate, and severe WMC (Kaplan-Meier log-rank test, $p < 0.001$). In a Cox model, comparing severe with mild

WMC and adjusting for clinical factors of functional decline, the risk of transition to disability or death was more than 2-fold higher (hazard ratio: 2.43; 95% confidence interval: 1.70–3.47). The effect of severe WMC remained significant independently of the baseline degree of atrophy and the number of infarcts while incident stroke and dementia only slightly modified this effect [32].

WMC and Cognitive Decline

The relationship between WMC and cognitive performance has been explored in the LADIS study under various aspects. Verdelho et al. [33] analyzed the respective role of WMC and vascular risk factors on neuropsychological performance. Severe WMC turned out to be associated with worse performances on global tests of cognition, executive functions, speed and motor control, attention, naming and visuoconstructional praxis. Vascular risk factors, namely diabetes, hypertension, and stroke interfered, independently of WMC severity, with different specific cognitive domains.

Because WMC often coexist with lacunar infarcts, and both can influence cognitive performances, Van der Flier et al. [25] studied their combined effect in the baseline LADIS cohort. Increasing severity of WMC and number of lacunes were each related to worse cognitive performances. When considered together, WMC remained significantly associated with cognitive status, whereas the association with lacunes became less prominent.

The joint effect of WMC and lacunes was further investigated by Jokinen et al. [50]. Patients with a combination of severe WMC and at least one lacune or of a multilacunar state and moderate-to-severe WMC performed more poorly on tests of global cognitive function, psychomotor speed, attention and executive functions, verbal fluency, and working memory compared to those with a combination of less severe changes.

Assessing the topographic distribution of lacunes and their impact on cognitive functions, Benisty et al. [36] found that the presence of lacunes in the thalamus was associated with lower Mini-Mental State Examination (MMSE) scores, and worse compound scores for speed and motor control and executive functions independently of the cognitive impact of WMC. There was also a significant negative association between the presence of lacunes in putamen/pallidum and the memory compound Z score. No significant association was found between cognitive parameters and the presence of lacunes in the internal capsule, lobar white matter and caudate nucleus.

The relationship between vascular and degenerative mechanisms in determining cognitive impairment is a

subject of great interest that has also been tackled in the LADIS study. Van der Flier et al. [38] assessed the respective association of MTA, taken as a marker of Alzheimer-type pathology, and WMC with cognitive functions. While severe WMC and MTA were individually associated with a modest and nonsignificant increase in the frequency of mild cognitive deficits, subjects with the combination of MTA and severe WMC had a more than 4-fold increase in the frequency of mild cognitive deficits. These results suggest a combined involvement of Alzheimer and vascular pathology in the earliest stages of cognitive decline.

Several LADIS papers have focused on corpus callosum morphometry. The interest in this topic derives from the consideration that corpus callosum is the largest interconnecting white matter tract in the brain and that changes in its structure may be related to the presence of WMC. In the LADIS population, corpus callosum atrophy was found to be associated with cognitive and motor performances independently of WMC grade and global atrophy [39, 40], and a predictor of future motor and cognitive decline [41]. Some LADIS data also suggest that WMC might be responsible for corpus callosum tissue loss [51].

Earlier studies have shown that changes in the white matter that are not visualized by conventional MRI techniques might be related to clinical disturbances [52]. The LADIS study has recently provided corroboration of such data. Using diffusion-weighted imaging, Schmidt et al. [26] found that changes in mean diffusivity of whole-brain tissue and normal appearing brain tissue were responsible for cognitive dysfunction (memory performance, executive dysfunction, and speed) and that this effect remained significant after adjustment for WMC lesion volume and brain atrophy. This argues for an additional and independent effect of subtle changes in normal appearing brain tissue on cerebral function in small-vessel disease.

The cognitive performances of the LADIS cohort have also been evaluated in a longitudinal way. The group of patients with a more severe combination of WMC and lacunes presented a significantly steeper decline of cognitive performance and a 3-fold risk of developing dementia during follow-up independently of age, sex, education and MTA [37]. At the end of the 3-year follow-up, 90 patients had developed dementia and 147 cognitive impairment, no dementia [34]. WMC severity turned out to be one of the strongest predictor of cognitive decline (dementia and not dementia), independently of age, education, and MTA. Among considered vascular risk factors, only diabetes independently predicted cognitive decline.

Interestingly, considering subtypes of dementia, Alzheimer disease was predicted only by MTA, while vascular dementia was predicted by previous stroke, WMC severity, and MTA [34]. Another strong clinical predictor of dementia subtype proved to be the presence of baseline self-perceived memory complaints. This turned out to predict Alzheimer disease, independent of other confounders (depressive symptoms, WMC severity, MTA and global cognition status at baseline), but not vascular dementia [53]. A cross-sectional analysis already documented that self-perceived memory impairment was significantly associated with objective memory impairment independently of WMC severity, depressive symptoms and MTA [54].

Jokinen et al. [35] studied the additional effect of incident lacunes on cognitive performances. After controlling for demographic factors, baseline cognitive performance, baseline lacunar and WMC lesion load, and WMC progression, the number of new lacunes was related to a subtle decrease in compound scores for executive functions and speed and motor control, but not for memory or global cognitive function. Irrespective of lacunes, WMC progression was associated with a decrease in executive function score [35]. Thus, the LADIS study data confirm that in addition to WMC, lacunes determine (or modulate the development of) cognitive impairment in small-vessel disease, although the individual contribution of lacunes to cognition is modest.

The LADIS study also offered some additional methodological elements concerning neuropsychological assessment. Ylikoski et al. [55] found that the Alzheimer Disease Assessment Scale – Cognitive Subscale (ADAS-cog) differentiated only between the mild and severe WMC groups, while the differences among the three WMC groups were highly significant with the Vascular Dementia Assessment Scale – Cognitive Subscale (VADAS-cog), suggesting that in patients with vascular lesions a test modified to embrace also mental speed and executive functions (VADAS-cog) is more suited than the original one developed for patients with Alzheimer disease (ADAS-cog). The extent to which the baseline performance in specific neuropsychological tests was able to predict the clinical diagnosis of dementia has also been assessed [56]. As expected, patients with a final dementia diagnosis had lower scores in almost all baseline neuropsychological tests when compared with the participants without dementia. Using logistic regression analyses, controlling for age, education and WMC severity, worse performance on MMSE and VADAS-cog turned out to be independent predictors of dementia. Concerning sensi-

tivity and specificity rates, the VADAS battery turned out to have higher sensitivity and specificity rates (area under the curve = 82%) in this specific population to identify dementia compared with the MMSE and ADAS.

WMC and Depression

At the baseline evaluation, depressive symptoms, as assessed by the Geriatric Depression Scale (GDS), were found to be associated with WMC severity and quality of life, suggesting a causative role of WMC in this regard [42]. When examining the relationship between depressive symptoms and the location of WMC, deep, rather than periventricular lesions, and the frontal and temporal locations proved to have the strongest association [45, 46]. The importance of lacunes as opposed to WMC in relation to depression remains controversial, and both are highly correlated. However, while WMC were strongly associated with GDS score, basal ganglia lacunes were only weakly correlated and lacunes in other regions showed no association [46]. A key issue is whether WMC predate depression, and so are causally related to mood changes, or whether they are a consequence of being depressed. Regarding the predictive role of baseline WMC on the development of depression, the severity of WMC independently and significantly predicted GDS score at 1 year, after controlling for baseline GDS score, quality of life, and worsening disability [43]. More prolonged follow-up analyses corroborated the 1-year follow-up data but also added information about the prediction of depressive episodes [44]. As expected, baseline GDS score significantly predicted future depressive symptoms. When the variable ‘transition to disability’ was included in the regression model, the severity of WMC continued to significantly predict GDS scores at 2 but not 3 years [44]. Furthermore, the baseline severity of WMC no longer predicted incident depression. These findings suggest that the independent effect of WMC on mood attenuates over time as patients in the sample become more disabled. One possible explanation for this could be that, in the more disabled 3-year population, transition to disability is also a driver of depressive outcomes and thus mediates the effect of the other significant covariates from the univariate analysis. Another explanation could be that disability and depression are both so strongly associated with WMC that it is difficult to determine causality using regression techniques.

In conclusion, concerning the mood profile, the LADIS study shows that baseline severity of WMC and lesion progression are both predictive of depressive symptoms, thus supporting the ‘vascular depression hypoth-

esis' and strongly implicating WMC in the pathogenesis of late-life depression.

WMC, Gait and Urinary Disturbances

Gait problems and falls are a major feature of patients with WMC [57] and an important cause of morbidity and mortality in the elderly. Motor, coordination, and gait abilities are based on the integrity of the complex motor circuit network that connects basal ganglia and brain-stem structures with the frontal cortex. This network's function may be challenged by a critical number of lesions in the subcortical regions.

In the LADIS study, in order to quantify motor performance, several clinical measures including the Short Physical Performance Battery (SPPB), single leg stance time, and walking speed were used [47]. A significant difference in SPPB total score for the 3 categories of mild, moderate, and severe WMC was detected. In a logistic regression analysis, using a dichotomized SPPB score as the dependent variable, a significant association was found for all WMC categories (moderate vs. mild, severe vs. mild), pointing at a dose-dependent effect. In the multivariate analysis, adjusting for many possible confounders, the association remained significant when comparing the severe with the mild WMC group. Logistic regression analyses were also performed using pathological single leg stance time and walking speed as the dependent variables. Results were similar to what was found for SPPB scores. Interestingly, regular physical activity was associated with better motor performance and single leg stance time [47].

The study by Blahak et al. [48] has demonstrated the significant association between falls and WMC severity. The rate of falls and the severity of WMC were significantly associated with balance disturbances. WMC location was analyzed with respect to falls and balance performance. In multivariate analysis, periventricular and frontal deep WMC were independently associated with falls. Logistic regression identified frontal deep WMC, but not basal ganglia and infratentorial hyperintensities, as significantly associated with balance disturbances.

In conclusion, the LADIS results corroborate the hypothesis that subcortical vascular changes are among the major determinants of mobility problems in the elderly and also that physical activity might have the potential to reduce the risk of limitations in mobility. The association of frontal and periventricular WMC with falls supports the hypothesis that interruption of frontal-subcortical motor circuits leads to balance disturbances and hence to an increased risk of falls in WMC.

One major determinant of impaired functionality in relation to WMC, in addition to cognitive, motor and depressive disturbances, is represented by continence problems. In the LADIS baseline cohort of nondisabled subjects, severe WMC were associated with urinary urgency, independent of other potential confounders and vascular lesions of the brain [49].

The Role of Neuroimaging in Age-Related Vascular Processes: The Contribution of the LADIS Study

The longitudinal design of the LADIS study, with repetition of MRI examination after 3 years from enrollment, gave us the opportunity to study the natural course of WMC and lacunes over time and the possible predictors of lesion evolution. Progression of WMC, assessed with the modified and validated version of the Rotterdam progression scale [58], developed mostly in the subcortical regions where WMC had also been most prevalent at baseline [59]. New lacunes mostly appeared in the subcortical white matter, mainly of the frontal lobes, whereas the majority of baseline lacunes were located in the basal ganglia. When assessing the contribution of baseline MRI features and clinical characteristics to disease progression, both WMC severity and the number of lacunes, together with previous stroke, were independent predictors of both WMC progression and of the occurrence of new lacunes. Diabetes and blood glucose levels were risk factors for WMC progression, while male sex, hypertension, systolic blood pressure, body mass index, high-density lipoprotein, and triglyceride levels were risk factors for new lacunes [59].

Almost half of the new subcortical lacunes after 3 years had occurred within areas of preexisting WMC or were associated with a significant local development of WMC at follow-up. This was significantly different from lacunes which had occurred in the basal ganglia or in infratentorial regions. Also the risk factors for incident lacunes specifically in the subcortical white matter (history of hypertension and stroke) were different from those predicting new basal ganglia and infratentorial lacunes (atrial fibrillation), hinting at a possibly different pathogenesis [60].

Concerning the evaluation of WMC severity, in the LADIS study both visual rating and semiautomated volumetric methods were implemented [58, 61, 62]. The ability of the two approaches to detecting an association between lesion severity and clinical parameters at baseline was particularly investigated [24]. It was found that, pos-

sibly due to a ceiling effect of visual rating scales, volumetric data were better suited to show differences between subjects regarding memory symptoms whereas associations were similar regarding age and gait disturbances. A clear but nonlinear relationship was established with WMC volume for all rating scales [24].

Regarding nonconventional MRI the LADIS study also explored the contribution of diffusion-weighted and magnetization transfer imaging for the assessment of WMC and normal appearing brain tissue. The severity of WMC and age were significant predictors of both global changes in diffusivity and magnetization transfer ratio and diffusion-weighted imaging appeared more robust for the application in a multicenter setting [28].

Conclusion and Future Directions

The LADIS study is the first international collaboration entirely devoted to the assessment of the clinical impact of WMC in the elderly. The study results have shown that the severity of WMC is a strong and independent predictor of the transition from an autonomous status to disability (main study outcome). The LADIS study has also provided additional data on the specific influence of WMC and lacunar infarcts on other disturbances commonly seen in elderly patients such as cognitive, motor, depressive and urinary problems (table 2). It is to be noted that the LADIS study was mainly focused on WMC; other lesions were also assessed in the study, with the main aim of using them as covariates in the analyses of study outcome. Today, more profound knowledge exists that other lesions such as lacunar infarcts are strictly linked with the same underlying small-vessel pathogenesis of WMC. A more modern view would perhaps suggest considering these two lesion types together.

Despite the somehow heterogeneous study population, which has, however, proved to be no limitation in making important observations, and despite the absence of imaging sequences which now seem to be important in observing other sequels of small-vessel disease, such as susceptibility-weighted imaging and T2*, the LADIS study has made significant contributions to understanding the importance of WMC. The LADIS study represents a successful model of an integrated and collaborative effort among different European countries and, because of the strength of the existing network, provides a platform for subsequent endeavors. Future lines of development of the LADIS experience may be (1) the establishment of clinical trials for small-vessel disease-related functional impair-

ment; (2) furthering the knowledge about the relation between vascular and degenerative changes in terms of cognition and functional outcome; (3) testing the role of new biomarkers (neuroimaging, cerebrospinal fluid components [for a preliminary experience, see 63]) in association with WMC; (4) development of the basis for the definition of vascular mild cognitive impairment criteria, and (5) exploration of the influence of genetic factors in small-vessel disease. The LADIS study group invites colleagues to join and widen the existing collaborative network, to jointly work in the coming 10 years on the elucidation of WMC and related pathology.

Appendix

List of Participating Centers and Personnel

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The *LADIS Steering Committee* is formed by Domenico Inzitari (Study Coordinator), Timo Erkinjuntti, Philip Scheltens, Marieke Visser, and Peter Langhorne, who replaced Kjell Asplund in this role, beginning in 2005.

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