Risk of Rapid Global Functional Decline in Elderly Patients With Severe Cerebral Age-Related White Matter Changes

The LADIS Study

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Background: Age-related white matter changes (ARWMCs), frequently detected on neuroimaging, are associated with motor, cognitive, urinary, and mood disorders. The LADIS (LeukoAraiosis and DISability) Study primarily aims to assess ARWMCs as a determinant of global functional decline in the elderly population.

Methods: We enrolled 639 patients (mean age, 74.1 ± 5.0 years; 45.1% male) referred for nondisabling complaints, who had ARWMCs detected on brain magnetic resonance imaging (MRI) of mild, moderate, or severe grade according to the Fazekas scale. At the 1-year follow-up, 619 were reassessed using the Instrumental Activities of Daily Living (IADL) scale. Of these, 506 were totally independent at baseline, and 113 were impaired in only 1 item of the IADL scale. We studied the 1-year transition to 2 or more activities limited and selective functional impairments as cofactors of functional decline.

Results: The rate of transition was 9%, 15%, and 26%, in the mild, moderate, and severe ARWMC group, respectively. Comparing the severe with the mild ARWMC groups and adjusting for age and for other predictors of decline, the risk was more than 2-fold higher (odds ratio; 2.38; 95% confidence interval, 1.29-4.38) in patients with 0 or 1 activity limited, and 3-fold higher (odds ratio, 3.02; 95% confidence interval, 1.34-6.78) among patients fully independent at baseline. Both motor and cognitive deterioration predominantly explained the effect of ARWMCs on global functional decline.

Conclusion: Elderly patients who are functionally independent and who have severe ARWMCs are at considerable risk of becoming more dependent in a short period, mostly owing to motor and cognitive deterioration.

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MANY OLDER PEOPLE without major neurological diseases have hyperintensities in the white matter on brain magnetic resonance imaging (MRI), also called leukoaraiosis or age-related white matter changes (ARWMCs).[1] In about one third of cases, these changes are of moderate to severe grade.[2]

Functional problems such as walking difficulties, cognitive impairment, depression, and urinary incontinence are all common among elderly people. These are the deficits contributing the most to loss of independence in everyday life activities and have been consistently reported to be associated with ARWMCs.[3] Transition from autonomous daily living to dependence on others is a crucial event in the personal, family, and social life of an elderly person. Age-related disability is a social and economic challenge that all modern societies are facing.

The LADIS (LeukoAraiosis and DISability) Study is a multicenter collaboration primarily aimed at investigating, through a longitudinal design, whether ARWMCs are an independent determinant of global functional decline in the elderly population.[4]

In this article, we report on global functional decline occurring 1 year after the initial assessment in a cohort of older patients, who, while being evaluated for nondisabling problems, underwent brain MRI and report how much the decline depended on ARWMCs.

METHODS

The rationale of the LADIS Study are fully described elsewhere.[4] In short, the facts that preva-

Author Affiliations are listed at the end of this article.
Group Information: Participating centers and personnel in the LADIS Study are listed on page 87.

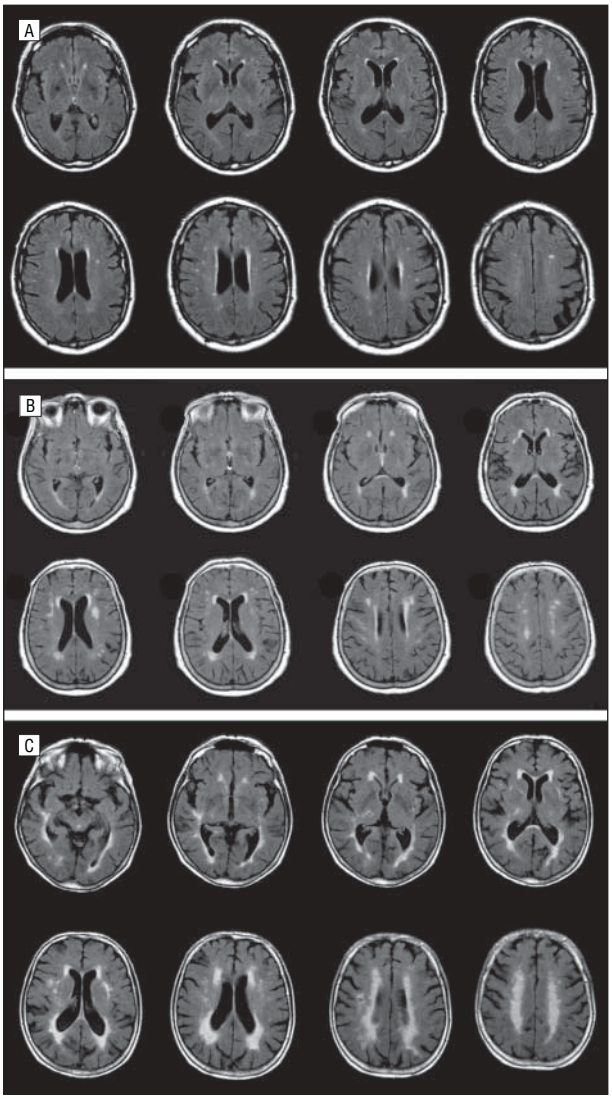

Figure 1. Age-related white matter changes: the 3 severity degrees according to the modified scale by Fazekas et al.[13] Grade 1, mild (A), grade 2, moderate (B), and grade 3, severe (C) white matter changes.

lence and severity of ARWMCs increase with age and that several dysfunctions occurring with age and contributing toward functional disability have been reported as being associated with ARWMCs[5] have raised the hypothesis that these changes may be one of the age-related disease processes involved in the disability transition in the elderly population, independent of other possible determinants of disability. Another unsolved issue is what grade of ARWMCs is able to produce clinical effects. Prespecified objectives of the LADIS Study included the following: (1) to establish whether ARWMCs and their progression play a role as an independent determinant of the transition from functional autonomy to disability in elderly subjects; (2) to confirm whether ARWMCs and their progression predict death from any cause or specific causes, dementia, cardiovascular events, and depression; (3) to examine whether progression of ARWMCs parallels the deterioration of motor and cognitive performances; and (4) to evaluate the impact of ARWMCs on quality of life. According to the activities in the Instrumental Activity of Daily Living (IADL) scale used by Lawton and Brody,[6] the primary end point was the transition from 0 or 1 activity limited at baseline to 2 or more activities limited at follow-up. This corresponds with the transition from no or mild to moderate or severe disability and is the categorization used by longitudinal, population-based studies of disability conducted in similarly aged cohorts.[7-9] The risks estimated by these studies of such transition in the general population were used to estimate the power and sample size of our project.[4]

PARTICIPANTS

The study population comprised patients aged between 65 and 84 years, who, while being investigated for complaints such as mild memory or motor problems, minor cerebrovascular events, mood alterations, or other minor neurological problems (all not interfering with daily life activities), exhibited ARWMCs of any degree on brain MRI at 1 of the 11 collaborating European centers. Subjects in whom ARWMCs were incidentally found were also considered. Patients had to perform without help in all the activities of the IADL scale or to be impaired on just 1 activity. Other inclusion criteria were signed informed consent and having a regularly contactable informant. Reasons for exclusion were (1) severe illnesses (cardiac, hepatic, or renal failure; cancer; or other relevant systemic diseases); (2) unrelated severe neurological diseases; (3) leukoencephalopathy of nonvascular origin (immunologic, demyelinating, metabolic, toxic, infectious, or other); and (4) severe psychiatric disorders.

ASSESSMENT

Subjects were assessed at baseline using a protocol that included a detailed MRI study and several functional and clinical measures.[4] After enrollment, subjects had yearly clinical and functional reassessments. At entry and at each follow-up, patients were administered a structured questionnaire to assess, among other variables, education (expressed as years of schooling), living conditions (alone or with others), history of myocardial infarction and/or angina pectoris (ischemic heart disease), stroke, heart failure, arrhythmias, arterial hypertension, peripheral vascular disease, diabetes mellitus, chronic obstructive pulmonary disease, depression, gait disturbances, osteoarthritis, falls in the last year, visual impairment, hearing loss, and hospital admissions. The definition of each variable was based on updated criteria.[4] All the patients had a standard physical examination, during which body mass index and pulse pressure were also registered.

The IADL scale includes 8 activities: ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibilities for own medications, and ability to handle finances. In the IADL questionnaire, depending on the type of task, questions are asked as to whether the task is accomplished without any limitation or with difficulties or help is needed. The study outcome was the limitation of any type (either difficulty or need of help) presented by the subject in more than 1 activity. The IADL scale was administered from baseline only to the informant because of the expectation of cognitive decline at follow-up. A test of the interrater, intercenter reliability of IADL scoring, performed using descriptions of the performance translated into English, showed good agreement in ratings of each scale item (κ statistic ranging from 0.69 to 0.85). A comprehensive test battery was used to assess global and selected cognitive domains.[4] Of these tests, for the purposes of the present study, ie, determining which functional domains (cognitive, motor, mood, or sphincteral) contributed the most to the possible prediction by degree of ARWMCs with respect to global functional decline, we used the results of the Alzheimer Disease Assessment Scale (ADAS)[10] and those of the 15-item Geriatric Depression Scale (GDS-15)[11] for the cognitive and the mood domain, respectively. Verification of the intercenter agreement on these tests was considered unfair, given the lists of words and questions specifically validated in individual countries. Changes in motor performance were assessed using a modified version

Table 1. Baseline Demographics, Risk Factors, and Comorbid Conditions Across Patients With Different ARWMC Severity

Variable	ARWMC Severity			Total Sample* (n = 619; 100%)	Moderate vs Mild†	Severe vs Mild†
	Mild* (n = 278; 44.9%)	Moderate* (n = 192; 31.0%)	Severe* (n = 149; 24.1%)			
Sex (male)	44.2	39.1	54.4	45.1	0.81 (0.56-1.17)	**1.50 (1.01-2.24)**
Age >75 y	36.3	46.9	52.3	43.5	**1.55 (1.06-2.25)**	**1.92 (1.29-2.88)**
Living condition (with others)	62.2	55.7	68.5	61.7	0.76 (0.53-1.11)	1.32 (0.86-2.01)
Ischemic heart disease	20.3	20.8	18.2	20.0	1.02 (0.66-1.63)	0.88 (0.53-1.46)
Heart failure	2.2	2.6	6.1	3.2	1.21 (0.36-4.01)	**2.92 (1.02-8.38)**
Arterial hypertension	63.5	74.0	77.0	70.0	**1.63 (1.09-2.44)**	**1.92 (1.22-3.03)**
Atrial fibrillation	6.9	6.3	9.5	7.3	0.91 (0.43-1.92)	1.42 (0.69-2.92)
Diabetes	12.2	12.6	17.1	13.5	1.03 (0.59-1.80)	1.48 (0.85-2.60)
Depression	27.3	29.7	26.2	27.8	1.12 (0.75-1.68)	0.94 (0.60-1.48)
Falls in the last year	23.7	29.3	34.9	28.2	1.33 (0.88-2.02)	**1.72 (1.11-2.66)**
Osteoarthritis	31.0	27.7	24.3	28.4	0.85 (0.57-1.28)	0.71 (0.45-1.12)
History of stroke	16.9	30.9	47.7	28.6	**2.20 (1.42-3.41)**	**4.47 (2.85-7.01)**
Chronic obstructive pulmonary disease	9.7	9.4	12.8	10.4	0.97 (0.52-1.81)	1.36 (0.73-2.54)
Complaint of gait disturbances	37.8	36.3	51.7	40.7	0.94 (0.64-1.37)	**1.76 (1.17-2.64)**
Urinary disturbances	39.2	34.4	49.7	40.2	0.81 (0.55-1.19)	**1.53 (1.02-2.28)**
Visual impairment	13.3	17.7	24.2	17.3	1.40 (0.84-2.33)	**2.07 (1.25-3.46)**
Hearing loss	43.5	45.8	49.7	45.7	1.10 (0.76-1.59)	1.28 (0.86-1.91)
Peripheral vascular disease	6.1	7.8	6.2	6.7	1.30 (0.63-2.66)	1.01 (0.44-2.33)
1 IADL impaired at baseline	12.2	20.3	26.8	18.3	**1.83 (1.11-3.02)**	**2.63 (1.58-4.38)**
Age, y	73.3 ± 5.0	74.4 ± 5.2	75.1 ± 4.8	74.1 ± 5.1	**.02**	**<.001**
Education, years of schooling	9.9 ± 3.7	9.6 ± 3.9	9.2 ± 3.8	9.6 ± 3.8	.41	.08
BMI	26.3 ± 4.3	26.1 ± 4.0	26.3 ± 4.5	26.2 ± 4.2	.59	.97
Pulse pressure, mm Hg	64.2 ± 16.8	66.9 ± 16.8	66.2 ± 15.3	65.5 ± 16.4	.09	.21

Abbreviations: ARWMC, age-related white matter change; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IADL, Instrumental Activities of Daily Living.

*Data are given as percentage or mean ± SD.

†Data are given as odds ratio (95% confidence interval) or *P* value (analysis of variance). Boldface values are statistically significant (*P*<.05).

of the Short Physical Performance Battery (SPPB).[12] We also recorded the occurrence of urinary dysfunction (defined as complaints of nocturia, urinary frequency, urgency, or incontinence) during the follow-up period.

Baseline ARWMC severity was rated centrally by 1 rater who was blind to the clinical and functional data, using the visual Fazekas scale.[13] Accordingly, patients were subdivided into 3 severity groups: grade 1, mild ARWMCs (single lesions <10 mm; areas of "grouped" lesions <20 mm in any diameter); grade 2, moderate ARWMCs (single hyperintense lesions between 10 to 20 mm; areas of "grouped" lesions ≥20 mm in any diameter; no more than "connecting bridges" between individual lesions); and grade 3, severe ARWMCs (single lesions or confluent areas of hyperintensity ≥20 mm in any diameter) (**Figure 1**).

We report herein the attainment of the primary study end point (transition to ≥2 IADL activities limited) at 1-year follow-up in the target LADIS population (patients with both 0 and 1 IADL activity limited) and among patients who were fully independent (0 activities limited) at baseline IADL assessment.

STATISTICAL ANALYSIS

In the 619 patients reassessed at the 1-year follow-up, we first examined baseline demographics, risk factors, and comorbid conditions across the 3 ARWMCs severity groups. This was done in a univariate fashion. The net predictive effect of ARWMC severity on the primary study end point, comparing, as preplanned, the severe and moderate groups with the mild one taken as reference,[4] was analyzed using multiple logistic regression analysis (forward stepwise method), controlling for the several baseline factors listed in the assessment section. These were the factors reported as the best predictors of global functional decline in the elderly as evidenced by the meta-analysis by Stuck et al.[14]

By further multiple regression analysis, we evaluated whether acute events occurring during the 1-year follow-up influenced the disability transition. In this model, we entered, together with age and ARWMC severity, living conditions, falls, incidental stroke or myocardial infarction, heart failure, and hospitalization resulting from the 1-year assessment, each of which were studied as a possible confounder of the transition.

To explore which of the dysfunctions (cognitive, motor, mood, or urinary) had the greatest contribution to ARWMC-related functional decline, changes in the ADAS, SPPB, and GDS scores and incident urinary dysfunction were entered as covariates in a logistic regression model, with ARWMCs and age as predictors of the primary study end point. If any of these variables reduced the odds ratio (OR) expressing the amount of the effect of ARWMCs on transition, this was taken as evidence that deterioration in that domain was involved in the prediction of decline by ARWMC severity.

RESULTS

Of the 639 patients (mean ± SD age, 74.1 ± 5.0 years; 45.1% male) enrolled, 619 (96.9%) (mean ± SD age, 74.1 ± 5.1 years, 45.1% male) had their IADL status reassessed at the 1-year follow-up. At entry, 506 of these patients were independent in every IADL activity and 113 were impaired in just 1 activity. Among the 619 subjects reexamined at 1-year follow-up, the distribution of baseline ARWMC severity was as follows: 44% mild, 31% moderate, and 25% severe. Male sex, older age group, history of arterial hypertension, stroke, heart failure, falls

Table 2. Patients by Instrumental Activities of Daily Living Status at Baseline vs 1-Year Follow-up

Activities Limited at 1-y Follow-up, No.	Activities Limited at Baseline, No.		
	0	1	Total
0	423	26	**449**
1	40	39	**79**
>1	43	48	**91**
Total	**506**	**113**	**619**

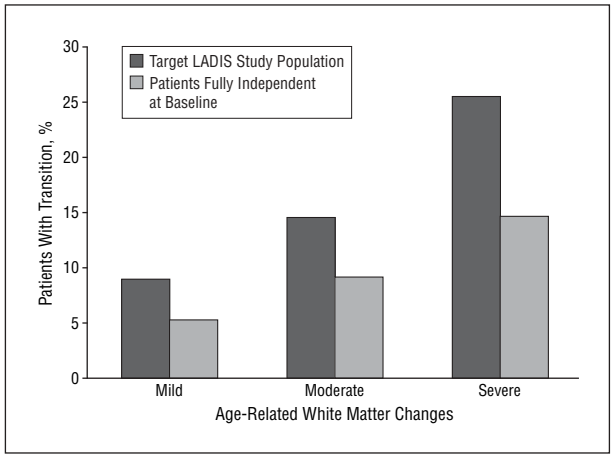

Figure 2. Transition in disability according to the Instrumental Activities of Daily Living scale[6] at 1 year across the 3 age-related white matter change severity groups. LADIS indicates LeukoAraiosis and DISability.

in the last year, complaint of gait disturbance, urinary problems, and visual problems were all more frequent among patients with the most severe degree of ARWMCs (**Table 1**). Subjects with 1 IADL activity impaired at baseline were more prevalent in the moderate or severe ARWMC groups compared with the mild group.

One year after entry, 131 (21.2%) of the 619 subjects had progressed to a lower functional level; of the 506 performing fully independently at baseline, 40 proved to be impaired in 1 activity and 43 in 2 or more activities. Of the 113 limited in 1 activity at baseline, 48 had become dependent on others in 2 or more activities and 26 had returned to normal functioning (**Table 2**). There was a gradient in the risk of reaching the study end point (dependence in ≥2 IADL activities) across patients with mild, moderate, and severe ARWMCs: 9%, 15%, and 26%, respectively, in the target LADIS population and 5%, 9%, and 15%, respectively, among patients who were fully independent at entry (**Figure 2**). After comparing the severe with the mild ARWMC severity group and adjusting for other possible predictors of disability (**Table 3**), the risk of such transition was more than 2-fold higher (OR, 2.38; 95% confidence interval [CI], 1.29-4.38) for target LADIS Study patients and 3-fold higher (OR, 3.02; 95% CI, 1.34-6.78) for patients fully independent at entry (Table 3). Older age, visual impairment, and baseline IADL status (1 vs 0 item altered) were the other independent predictors of transition in the first group of patients; for patients fully independent at entry, this was the case for age and visual impairment. There was no effect related to sex. The severity of ARWMCs also predicted significantly and independently the transition from 0 to 1 activity impaired (adjusted OR, 2.99; 95% CI, 1.26-7.11; severe vs mild ARWMCs). Severity of ARWMCs independently predicted the mean ± SD number of altered IADL activities (0.45 ± 1.24 in the mild group; 0.74 ± 1.60 in the moderate group; 1.33 ± 2.17 in the severe group). The activities that were most frequently limited among patients who declined were housekeeping, shopping, and mode of transportation (**Figure 3**). For comparison, the activities that were limited among the subjects impaired at baseline were mode of transportation (26%), ability to handle finance (23%), housekeeping (18%), responsibilities for own medication (12%), laundry (10%), shopping (7%), food preparation (3%), and ability to use the telephone (2%). After controlling for acute events occurring during the 1 year after initial assessment, the effect of ARWMC severity in predicting functional decline remained significant (OR, 2.71; 95% CI, 1.37-5.34; severe vs mild ARWMCs).

Differences in measures of cognitive or motor performance and mood status at baseline were related to different degrees of ARWMCs. Differences were even more

Table 3. Independent Predictors of 1-Year Transition in IADL Status*

Variables in the Final Model	Patients With 0 or 1 Activity Limited at Entry (n = 619)	Patients With No Activity Limited at Entry (n = 506)
ARWMC Severity		
Mild	1.00	1.00
Moderate	1.26 (0.67-2.37)	1.87 (0.83-4.21)
Severe	**2.38 (1.29-4.38)**	**3.02 (1.34-6.78)**
0 or 1 limited IADL activity at baseline	**6.58 (3.91-11.08)**	**1.11 (1.04-1.19)**
Age, y	**1.09 (1.03-1.15)**	**0.51 (0.26-0.99)**
Visual impairment	**1.98 (1.12-3.49)**	**2.70 (1.31-5.56)**

Abbreviations: ARWMC, age-related white matter change; IADL, Instrumental Activities of Daily Living.
*Multiple logistic regression, stepwise method. See Table 1 for variables in the analysis. Boldface values are statistically significant ($P<.05$).

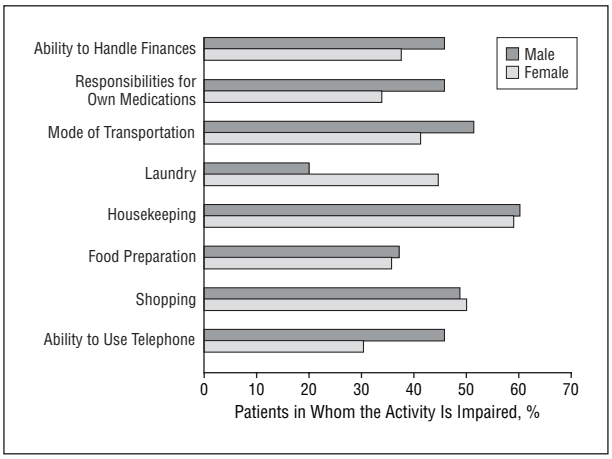

Figure 3. Type of activity changed after 1 year among patients with functional decline according to the Instrumental Activities of Daily Living scale.[6]

Table 4. Baseline, 1-Year Follow-up, and Differences of SPPB, ADAS-Cog, and GDS Scores, According to ARWMC Severity Degree*

Scale	ARWMC Severity			Total	*P* Value (ANOVA)
	Mild	Moderate	Severe		
SPPB					
Baseline	10.3 ± 2.0	10.0 ± 2.0	9.2 ± 2.4	9.9 ± 2.1	<.001
1-y Follow-up	10.0 ± 2.2	9.5 ± 2.6	8.5 ± 2.9	9.5 ± 2.6	<.001
Difference	0.3 ± 1.7	0.5 ± 2.2	0.7 ± 2.1	0.5 ± 1.9	.22
ADAS-Cog					
Baseline	15.2 ± 5.9	16.8 ± 7.5	18.1 ± 8.6	16.4 ± 7.2	.001
1-y Follow-up	15.5 ± 6.7	16.6 ± 7.4	20.0 ± 10.0	16.9 ± 8.0	<.001
Difference	0.3 ± 5.0	0.2 ± 6.1	2.0 ± 6.5	0.5 ± 5.8	.003
GDS					
Baseline	2.8 ± 2.9	3.1 ± 3.0	3.7 ± 3.5	3.1 ± 3.0	.03
1-y Follow-up	2.6 ± 2.9	3.0 ± 2.8	3.5 ± 3.1	2.9 ± 2.9	.03
Difference	0.2 ± 2.3	0.1 ± 2.4	0.2 ± 2.6	0.2 ± 2.4	.92

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; ANOVA, analysis of variance; ARWMC, age-related white matter change; GDS, Geriatric Depression Scale; SPPB, Short Physical Performance Battery.
*Data are given as mean±SD score unless otherwise specified.

apparent at the 1-year follow-up (**Table 4**). Similar trends were shown by urinary dysfunction. Evaluating which of these changes made the greatest contribution to loss of independence in IADL activities, the greatest modification of the prediction of global functional decline by ARWMC severity followed the introduction of the ADAS or the SPPB score changes in the regression model (**Table 5**). This indicates that, among selective functions, impairments occurring in the motor and cognitive domains best explained the effect of ARWMC severity on global functional decline.

Table 5. Modification by Selective Functional Changes of the Prediction by ARWMC Severity of Global Decline*

Variable	Effect on Transition, OR (95% CI)†
ARWMC severity (severe vs mild) (unadjusted)	3.47 (2.00-6.02)
Adjusted for age	3.12 (1.79-5.46)
Adjusted for age plus:	
SPPB	2.49 (1.30-4.74)
Urinary dysfunction	3.00 (1.71-5.27)
GDS	3.25 (1.80-5.86)
ADAS-Cog	2.58 (1.42-4.68)
Urinary dysfunction + GDS	3.09 (1.70-5.60)
Urinary dysfunction + SPPB	2.37 (1.23-4.54)
Urinary dysfunction + ADAS-Cog	2.44 (1.34-4.45)
GDS + SPPB	2.69 (1.39-5.24)
GDS + ADAS-Cog	2.81 (1.53-5.18)
SPPB + ADAS-Cog	2.25 (1.16-4.36)
SPPB + ADAS-Cog + GDS + urinary dysfunction	2.22 (1.12-4.43)

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; ARWMC, age-related white matter change; CI, confidence interval; GDS, Geriatric Depression Scale; OR, odds ratio; SPPB, Short Physical Performance Battery.
*Target LADIS (LeukoAraiosis and DISability) Study population (619 patients).
†$P<.05$ for all.

COMMENT

The LADIS Study shows that elderly people, in whom extensive ARWMCs are discovered by brain imaging while being investigated for nondisabling complaints, are at high risk of declining in global functioning in a period as short as 1 year. Among our patients, ARWMC severity predicted this decline independent of age and of several other factors known to be associated with disability in the elderly. The risk of decline increased with an increasing degree of ARWMC severity, with an apparent dose effect. Also, ARWMC severity predicted independently the number of instrumental activities that were limited after 1 year. The decline occurred mainly through motor and cognitive deterioration.

Some factors may limit our conclusions. The LADIS Study sample is not population based, and, although nondisabled, the majority of subjects were enrolled because they had sought medical attention for symptoms possibly related to ARWMCs. Therefore, in comparison with subjects with ARWMCs who are still free of symptoms, the underlying disease process could have been at baseline in a more advanced stage. The reasons for referral were those commonly leading to discovery of ARWMCs in elderly persons, and thus the LADIS Study sample simply reflects the patient population with ARWMCs that is likely to be encountered in clinical practice. We included subjects with 1 IADL activity limited to reflect the classification strategy adopted by other longitudinal population-based studies on aging. In our study, compared with people performing fully independently in the IADL activities, patients with 1 IADL activity limited at baseline turned out to be more prevalent in the group with severe ARWMCs at entry and more prone to progress to a lower functional level. However, the presence of these subjects in the analysis did not alter the effect of ARWMC severity as an independent determinant of functional decline. Such an effect was equally apparent when considering the transition among subjects who were independent in any IADL activity at entry.

Recent longitudinal studies[15,16] have shown the dynamic nature of the disability process occurring at older ages when progressions in functional dependence over time may alternate with improvements. Indeed, in our study a

limited number of patients recovered to a better functional status after 1 year. Intercurrent reversible events, including acute diseases, hospitalizations, or changes in the psychosocial situation, are the most common causes of reversible transitions.[16,17] We were able to control for some of these events: compared with subjects who remained functionally unchanged, 1-year variation in living conditions, falls, incident stroke or myocardial infarction, heart failure, or hospitalization were all more frequent among subjects who had functional decline. However, after adjusting for these events, the effect of ARWMC severity in predicting functional decline remained significant.

We used the IADL scale as the tool for measuring disability as in previous studies. Reliability and validity of such a scale is considered sufficient to warrant its use in clinical situations.[18] Compared with the Basic Activities of Daily Living scale, the IADL scale may be more sensitive to change in disability status occurring over short periods in highly functioning or in mildly impaired subjects.[19,20] The IADL scale data may be subjected to variability depending on sociodemographic factors.[19] Our assessment of IADL proved to be consistent across several sociocultural settings.

Disability in activities of daily living is common among elderly persons and is associated with adverse outcomes and high health care costs. According to the conceptual model for the disablement process proposed by Nagi,[21] active organ pathologic processes or disease leads to anatomical, physiological, mental, or emotional impairment, loss, or abnormalities, which in turn lead to functional limitations resulting in disability. Disease processes involving various organs may give rise to the chain of events leading to functional dependence in elderly persons. Up to now, clinical and epidemiological research has focused predominantly on demographic, lifestyle, or psychosocial factors of disability. Organ abnormalities involved in the process of disability in the elderly population are still incompletely understood, particularly as far as the central nervous system is concerned. Modern imaging techniques may play a key role in disclosing markers of brain pathologic processes that possibly determine functional dependence in elderly persons. Concerning neurological impairments underpinning disability, a substantial proportion of elderly adults may have walking difficulty or cognitive impairment. Gait abnormalities are a common cause of falls, and slow gait predicts future functional decline[22] and dementia.[23] Cognitive impairment without dementia affects 10% of people older than 65 years.[24] Over 10% of aged people have depression.[25] Urinary complaints are common in elderly people, and sphincteric problems contribute to disability in elderly people.[26] All these conditions have been reported consistently by many retrospective studies to be associated with ARWMCs (for review see Kuo and Lipsitz[3]). Longitudinal data have recently confirmed that ARWMCs predict motor performance decline,[27] the onset of dementia,[28] or deterioration in selective cognitive domains.[29] To our knowledge, no study has hitherto addressed whether, and to what extent, ARWMCs contribute to functional dependence in older adults. Answering this question may shed further light on pathological mechanisms of disability, as well as on potential interventions for preventing or slowing such a process. On the other hand, a recent study showed that white matter changes detected by computed tomography were not associated with an increased risk of mortality when clinical factors were taken into account.[30] Whether this is also the case with respect to global functioning remains to be determined.

In our 1-year follow-up, the LADIS Study has confirmed the hypothesis that ARWMCs affect global functioning in elderly adults independently of and more strongly than many other potential determinants of disability, acting mainly through deterioration of both cognitive and motor function. Because ARWMCs are a marker of small vessel disease associated with arterial hypertension and other vascular risk factors, our observation may be relevant for preventive strategies. Recent observations suggest that, for example, treating hypertension may slow the progression of ARWMCs.[31]

Given the high frequency of ARWMCs among older people, and considering that loss of independence in every day life is an event crucial to the personal and social life of older people, these results might be relevant to the main functional problems related to aging.

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REFERENCES

1. Erkinjuntti T, Pantoni L, Scheltens P; European Task Force on Age-Related White Matter Changes. Cooperation and networking on white matter disorders. *Dement Geriatr Cogn Disord.* 1998;9(suppl 1):44-45.
2. Breteler MMB, Van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology.* 1994;44:1246-1252.
3. Kuo HK, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci.* 2004;59:818-826.
4. Pantoni L, Basile AM, Pracucci G, et al. Impact of age-related cerebral white matter changes on the transition to disability—the LADIS Study: rationale, design and methodology. *Neuroepidemiology.* 2005;24:51-62.
5. Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report: a review. *Stroke.* 1995;26:1293-1301.
6. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9:179-186.
7. Maggi S, Zucchetto M, Grigoletto F, et al. The Italian Longitudinal Study on Aging (ILSA): design and methods. *Aging (Milano).* 1994;6:464-473.
8. Cox CS, Mussolino ME, Rothwell ST, et al. Plan and operation of the NHANES I Epidemiologic Follow-up Study, 1992. *Vital Health Stat 1.* 1997;35:1-231.
9. Van Nostrand JF, Furner SE, Suzman R. Health data on older Americans: United States 1992. *Vital Health Stat 3.* 1993;27:1-5.
10. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry.* 1984;141:1356-1364.
11. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull.* 1988;24:709-711.
12. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994; 49:M85-M94.
13. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol.* 1987;149:351-356..
14. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med.* 1999;48:445-469.
15. Hardy SE, Gill TM. Recovery from disability among community-dwelling older persons. *JAMA.* 2004;291:1596-1602.
16. Hardy SE, Dubin JA, Holford TR, Gill TM. Transitions between states of disability and independence among older persons. *Am J Epidemiol.* 2005;161:575-584.
17. Gill TM, Allore HG, Holford TR, Guo Z. Hospitalization, restricted activity, and the development of disability among older persons. *JAMA.* 2004;292:2115-2124.
18. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc.* 1983;31:721-727.

19. Avlund K. Methodological challenges in measurements of functional ability in gerontological research: a review. *Aging (Milano).* 1997;9:164-174.
20. Ishizaki T, Watanabe S, Suzuki T, Shibata H, Haga H. Predictors for functional decline among nondisabled older Japanese living in a community during a 3-year follow-up. *J Am Geriatr Soc.* 2000;48:1424-1429.
21. Nagi S. Some conceptual issues in disability and rehabilitation. In: Sussman MB, ed. *Sociology and Rehabilitation.* Washington, DC: American Sociological Association; 1965:100-113.
22. Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med.* 1994;38:1-14.
23. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med.* 1995;332:556-561.
24. Di Carlo A, Baldereschi M, Amaducci L, et al. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy: the ILSA Study. *J Am Geriatr Soc.* 2002; 50:41-48.
25. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999;174:307-311.
26. Thom D. Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. *J Am Geriatr Soc.* 1998;46:473-480.
27. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT Jr, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc.* 2005; 53:649-654.
28. Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. *Arch Neurol.* 2004;61:1531-1534.
29. Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain.* 2005;128:2034-2041.
30. Rockwood K, Black SE, Song X, et al. Clinical and radiographic subtypes of vascular cognitive impairment in a clinic-based cohort study. *J Neurol Sci.* 2006; 240:7-14.
31. Schiffrin EL. Blood pressure lowering in PROGRESS (Perindopril Protection Against Recurrent Stroke Study) and white matter hyperintensities: should this progress matter to patients? *Circulation.* 2005;112:1525-1526.