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Self-Perceived Memory Complaints Predict Progression to Alzheimer Disease. The LADIS Study

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Abstract. Memory complaints are frequent in the elderly but its implications in cognition over time remain a controversial issue. Our objective was to evaluate the risk of self perceived memory complaints in the evolution for future dementia. The LADIS (Leukoaraiosis and Disability) prospective multinational European study evaluates the impact of white matter changes

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(WMC) on the transition of independent elderly subjects into disability. Independent elderly were enrolled due to the presence of WMC. Subjects were evaluated yearly during 3 years with a comprehensive clinical protocol and a neuropsychological battery. Dementia and subtypes of dementia were classified. Self perceived memory complaints in independent elderly were collected during the interview. MRI was performed at entry and at the end of the study. 639 subjects were included (74.1 ± 5 years old, 55% women, 9.6 ± 3.8 years of schooling). At end of follow-up, 90 patients were demented (vascular dementia, 54; Alzheimer's disease (AD) and AD with vascular component, 34; frontotemporal dementia, 2). Using Cox regression analysis, we found that self perceived memory complaints were a strong predictor of AD and AD with vascular component during the follow-up (β = 2.7, $p = 0.008$; HR = 15.5, CI 95% [2.04, 117.6]), independently of other confounders, namely depressive symptoms, WMC severity, medial temporal lobe atrophy, and global cognition status at baseline. Self perceived memory complaints did not predict vascular dementia. In the LADIS study, self perceived memory complaints predicted AD but not vascular dementia in elderly subjects with WMC living independently.

Keywords: Aging, Alzheimer's disease, dementia, memory complaints, white matter changes

BACKGROUND

Memory complaints are frequent among elderly subjects, but there is no consensus on the implications of memory complaints [1]. Previous studies suggested that memory complaints are associated with depressive symptoms [1–3], anxiety [4], psychological traits and stress [4], but also with brain morphological changes such as white matter changes (WMC) [5–7], hippocampal volume [6–9], and Alzheimer's disease (AD) pathology in postmortem studies [10, 11]. Some studies tried to correlate subjective memory complaints with memory objectively tested changes and controversial results have been published [2, 4, 12–14]. The implications of self reported memory complaints in the future evolution for cognitive decline and dementia are as well under discussion, as several studies found memory complaints to be a predictor of future dementia [12, 15–17] but others did not [14, 18, 19]. A recent study showed that half of the AD patients followed in the Kungsholmen project had no subjective memory complaints three years before diagnosis of AD [20].

We aimed to study the implications over time of self reported memory complaints in elderly subjects with cerebral WMC who seek medical assistance due to minor complaints but were otherwise independent in daily living activities.

METHODS

The LADIS (Leukoaraiosis and Disability) study is a prospective multinational European project investigating the independent impact of WMC on the transition to disability in the elderly. The rationale, methodology, baseline assessment, and cognitive outcomes have been described previously [22, 23]. Inclusion criteria for the study were: (i) 65–84 years of age; (ii) changes in WMC on MRI of any degree, according to the scale of Fazekas [24]; and (iii) no disability, as determined by the Instrumental Activities of Daily Living scale (IADL) [25]. Patients were enrolled if they were independent in daily living activities, and they could have minor neurological, cognitive, mood or motor complaints, or incidental findings on cranial imaging caused by non-specific events, or otherwise volunteers, as detailed elsewhere [21]. Irrespectively of the referral cause, a question about memory complaints was done in all patients ("do you have memory problems?"), with a single answer (yes or no). Subjects were evaluated at baseline and yearly during 3 years with a comprehensive clinical and functional protocol that included registry of demographic factors, vascular risk factors, co-morbidities potentially implicated in dependency in the elderly, evaluation of depression and quality of life, and neuropsychological evaluation [21]. For those patients who could not attend the visit, a phone interview was performed with the patient and the caregiver, vital status, clinical data, IADL was collected and the Telephone Interview for Cognitive Status (TICS) [26] was done with the patient, whenever possible. Investigators were provided with a specifically developed handbook with guidelines for applying criteria and tools including the phone interview and TICS. Depression was considered according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria [27], and severity of depressive symptoms was classified using the Geriatric Depression Scale (GDS) [28].

Neuropsychological evaluation and cognitive criteria

The LADIS neuropsychological battery has been described in detail elsewhere [22]. In short, the neu-

ropsychological battery included the Mini-Mental State Examination (MMSE) [29] as a global measure of cognitive function; the VADAS-Cog (Alzheimer's Disease Assessment Scale (ADAS-Cog) plus delayed recall, symbol digit, digit span, mazes, digit cancellation and verbal fluency) as a comprehensive instrument to assess orientation, language, ideational and constructional praxis, immediate memory and delayed recall) [30]; and the Stroop [31] and Trail Making (TM) test [32] as measures of executive function. In the follow-up clinical visits patient cognitive status was classified by the investigators into the following groups: 1) demented; 2) cognitive impairment not demented; 3) no cognitive impairment. We considered two types of cognitive decline not dementia: 1) amnestic mild cognitive impairment (MCI), according to Petersen et al. [33] (defined as memory complaint, preferably corroborated by an informant; impaired memory function for age and education, preserved general cognitive function, intact activities of daily living and no dementia); and 2) vascular cognitive impairment without dementia (VCIND) (defined as evidence of cognitive impairment and clinical consensus to identify significantly related vascular features; exclusion of dementia when impairments were not sufficiently severe to interfere with social or occupational functioning or when impairments were more focal than the global requirement for a diagnosis of dementia) [34]. We considered the following criteria for subtypes of dementia: 1) probable AD according to the NINCDS-ADRDA Work Group [35]; 2) probable vascular dementia according to NINDS-AIREN criteria [36], subtype of subcortical vascular dementia according to Erkinjuntti et al. [37]; 3) frontotemporal dementia according to McKhann et al. [38]; and 4) dementia with Lewy bodies [39]. The criteria for AD with vascular component was made when the investigator judgment considered that the clinical picture presented both aspects of AD and vascular dementia.

MRI study

MRI was performed at entry and at the end of the study, following a protocol previously described [21]. The degree of WMC severity was rated on FLAIR sequences by central readers blind to the clinical data using the three severity classes in the revised version of the visual scale of Fazekas and colleagues [24]. Volumetric analysis of WMH was performed by a single rater on the same axial FLAIR images, including the infratentorial region, as detailed previously [40]. Medial temporal lobe atrophy was assessed on coronal T1 weighted sequences using the medial temporal atrophy (MTA) scale [41].

Statistical analysis

The influence of self reported memory complaints on the evolution for dementia was assessed using the Cox proportional hazards model. As dependent variable, we considered the last cognitive evaluation as described in the methods section. We calculated three different Cox proportional hazards model, the first intended to evaluate if self reported memory complaints predicted dementia of any type. In the second and third regressions we considered as dependent variables the subtypes of dementia (vascular dementia on the second analysis, and AD and AD with vascular component on the third model). Time of last observation for the survival analysis was measured in months (12, 24 or 36 months). We adjusted survival analysis for age, education, medial temporal lobe atrophy, WMC severity, GDS score and MMSE at baseline, according to significant variables found in previous publications [23]. In order to reduce the number of variables in study, we disregard gender for the present publication due to the lack of influence in cognitive performance in all exploratory cognitive analysis performed (data not shown, available if requested). In our findings of baseline, similarly, gender did not influence cognition [22, 23]. Age, educational level, GDS score, and MMSE were considered continuous variables. MTA and WMC severity and self reported memory complaints were considered categorical. We performed the same analysis considering other global measures of cognition (ADAS-Cog or VADAS).

We repeated all analysis using volume of WMC (continuous) variable, instead of severity of WMC (categorical). Data were analyzed using SPSS 16.0 software.

Since conversion to the different types of dementia is treated in the Cox proportional hazard model as censored data, and survival analysis relies on a non-informative censoring process, competing risks could affect our results. In fact, the potential interference of different event of interests could cause a competitive risks conflict in dementia subtypes analysis (for instance, subjects who died were not allowed to develop any dementia subtype or subjects having one subtype of dementia diagnosed could not have other subtype of dementia). So, we repeated the analysis considering as dependent variables vascular dementia in one hand and AD and AD with vascular component

on the other hand, using the methodology dealing with modeling with competitive risks. For independent variables we used the same variables described for the Cox proportional hazard model. We used R 2.10.1 software, package cmprsk designed for dealing with competitive risks.

RESULTS

638 subjects were included (74.1 years, SD 5; 55% women, 9.6 years of educational level, SD 3.8), (one subject excluded to the present study due to missing data in baseline evaluation). Characteristics of study sample at baseline are presented in table 1.

From the total sample, 168 (26%) subjects were referred to the study due to minor cognitive complaints. When the direct question about self perceived memory complaints was asked, 63% (399 patients) of the sample complained from memory at baseline. Among subjects without self perceived memory impairment at baseline ($n = 239$), only 3% were referred to the study for cognitive complaints, while among patients with self perceived memory complaints (399 patients), 40% ($n = 168$) were referred to the study due to minor cognitive complaints.

89% (568), 78.4% (501), and 75% (480) of the subjects from the initial sample were followed-up in clinical visit at month 12, 24, and 36. At end of follow-up vital status or IADL was possible to ascertain in 633 patients (99.1% of initial sample). Fifty-one patients missed complete cognitive evaluation in any follow-up clinical visit, for those 51 patients no cognitive diagnosis was attributed.

Considering the cognitive diagnosis performed in the last clinical visit, dementia was diagnosed in 90 patients all over the study (vascular dementia, 54; AD, 22; AD with vascular component, 12; Frontotemporal dementia, 2), and 147 patients had cognitive impairment not dementia (VCIND, 86; MCI, 61). Using Cox regression analysis we found that self reported memory complaints predicted dementia (all demented subjects) independently of WMC severity, MTA, GDS score at baseline, and MMSE at baseline (table 2). Considering subjects with vascular dementia in last clinical evaluation (table 3), we found that MTA and WMC predicted vascular dementia, but self reported memory complaints did not. Considering last diagnosis of AD and AD with vascular component, self reported memory complaints at baseline were a strong predictor of AD and AD with vascular component (table 4), with a 16-fold higher risk, controlling for GDS score and MMSE at baseline. The same results were obtained considering other global measures of cognition (ADAS-Cog or VADAS), with similar increase risk, measured by the HR (results not shown, available if requested).

Repeated analysis using volume of WMC instead of WMC severity had similar results (results not shown, available if requested).

In order to solve the potential competitive risks conflict in dementia subtypes analysis, and taking into account the wide confidence interval obtained in the proportional hazard model, we re-analyzed data using the methodology dealing with modeling with competitive risks in order to confirm if our Cox proportional hazards model was valid. Using vascular dementia (54 subjects) as event of interest, against all possible competitive risks (death, AD, AD with vascular component and frontotemporal dementia), we obtained a true convergence of the model, and we were able to confirm that self reported memory complaints did not predict vascular dementia. Using AD and AD with vascular component (34 subjects) as event of interest, against all possible competitive risks (death, vascular demen-

Table 1
Baseline patient characteristics ($n = 638$)

	Total	With memory complaints ($n = 399$)	Without memory complaints ($n = 239$)	p
Age (years old; mean ± sd)	74.1 ± 5	74.23	74.00	0.6
Female/male	351 (55%)/287(45%)	219 (55%)/180 (45%)	132(55%)/107 (45%)	0.9
Educational level (years of schooling)	9.6 ± 3.8	9.36	10.02	0.03
GDS score (mean ± sd)	3.16 ± 2.9	3.74 ± 3.1	2.20 ± 2.3	0.000
MMSE score (mean ± sd)	27.36 ± 2.4	27.23 ± 2.6	27.58 ± 2.0	0.06
WMC severity				
Mild	283 (44%)	174 (44%)	109 (46%)	0.8
Moderate	197 (31%)	127 (32%)	70 (30%)	
Severe	158 (25%)	98 (25%)	60 (25%)	
MTA score (mean ± sd)	1.03 ± 0.8	1.25 ± 0.92	1.00 ± 0.8	0.001

Legend: GDS: Geriatric depression scale; MMSE: Mini-Mental State Examination; WMC = white matter changes; MTA = medial temporal atrophy.

Table 2
Cox proportional hazards model. Dependent variable: dementia in last clinical evaluation (90 subjects)

	B	HR	*p*	95.0% CI	
Age	0.045	1.046	0.080	0.995	1.1
Educational level	0.045	1.046	0.157	0.983	1.113
WMC severity			0.097		
WMC severity (moderate vs. mild)	0.017	1.017	0.958	0.541	1.914
WMC severity (severe vs. mild)	0.539	1.714	0.066	0.965	3.045
MTA			0.006		
MTA (1 vs. 0)	0.146	1.157	0.741	0.488	2.742
MTA (2 vs. 0)	0.873	2.394	0.053	0.987	5.803
MTA (3 vs. 0)	1.360	3.895	0.006	1.486	10.208
MTA (4 vs. 0)	0.908	2.478	0.201	0.617	9.963
GDS-15 total score	0.022	1.022	0.574	0.948	1.102
MMSE baseline	−0.214	0.807	0.000	0.755	0.863
Self reported memory complaint	0.790	2.204	0.012	1.187	4.095

Legend: WMC = white matter changes; MTA = medial temporal atrophy; GDS: geriatric depression scale; MMSE: Mini-Mental State Examination.

Table 3
Cox proportional hazards model. Dependent variable: vascular dementia in last clinical evaluation (54 subjects)

	B	HR	*p*	95.0% CI	
Age	0.029	1.030	0.373	0.966	1.098
Educational level	0.054	1.055	0.173	0.977	1.140
WMC severity			0.069		
WMC severity (moderate vs. mild)	0.494	1.638	0.265	0.688	3.903
WMC severity (severe vs. mild)	0.940	2.559	0.023	1.136	5.766
MTA			0.015		
MTA (1 vs. 0)	1.719	5.581	0.097	0.732	42.576
MTA (2 vs. 0)	2.337	10.347	0.026	1.328	80.632
MTA (3 vs. 0)	2.953	19.162	0.006	2.326	157.853
MTA (4 vs. 0)	2.528	12.524	0.052	0.973	161.180
GDS-15 total score	0.066	1.068	0.174	0.971	1.174
MMSE total	−0.175	0.839	0.000	0.768	0.916
Self reported memory complaint	0.263	1.301	0.473	0.634	2.671

Legend: WMC = white matter changes; MTA = medial temporal atrophy; GDS: geriatric depression scale; MMSE: Mini-Mental State Examination.

Table 4
Cox proportional hazards model. Dependent variable: Alzheimer disease with vascular component in last clinical evaluation (34 subjects)

	B	HR	*p*	95.0% CI	
Age	0.080	1.083	0.064	0.995	1.179
Educational level	0.042	1.042	0.454	0.935	1.162
WMC severity			0.283		
WMC severity (moderate vs. mild)	−0.625	0.535	0.257	0.182	1.577
WMC severity (severe vs. mild)	0.241	1.273	0.595	0.522	3.103
MTA			0.133		
MTA (1 vs. 0)	−1,249	0.287	0.045	0.085	0.971
MTA (2 vs. 0)	−0.052	0.950	0.929	0.305	2.960
MTA (3 vs. 0)	0.309	1.363	0.643	0.368	5.052
MTA (4 vs. 0)	−0.270	0.764	0.782	0.113	5.171
GDS-15 total score	−0.050	0.952	0.452	0.836	1.083
MMSE baseline	−0.258	0.773	0.000	0.692	0.863
Self reported memory complaint	2.741	15.504	0.008	2.045	117.563

Legend: WMC = white matter changes; MTA = medial temporal atrophy; GDS: geriatric depression scale; MMSE: Mini-Mental State Examination.

tia, and frontotemporal dementia), we obtained a true convergence of the model, and we were able to confirm that self reported memory complaints (coefficient 2.82; standard error 1.06; two-sided *p*-value 0.007) were independent predictors of AD and AD with vascular component.

DISCUSSION

Our study showed that among elderly living independently, with age-related WMC, memory complaints are a strong predictor of AD and AD with vascular component during the follow-up, independently of other confounders, namely depressive symptoms, WMC severity, and global cognition status at baseline. Results were quite similar considering the different global measures of cognition (MMSE, ADAS-Cog, and VADAS), confirming the high consistency of this finding. Modeling in the presence of competitive risks confirmed survival analysis findings and reinforced our results.

Significance of self perceived memory complaints in the elderly has been an issue of highest interest, and controversial results have been published [1, 2, 4, 12–14]. A recent study found that memory complaints predicted AD but not vascular dementia, but in that study neuroimaging variables were not considered [42]. Several explanations have been proposed regarding the discrepancies found. One of the differences rely on methodological differences between studies, as some data result from a questionnaire directed for memory complaints and other based on spontaneous self reported complaints. Other possible explanations is that some subjects are more able to perceive subtle memory changes before they become detected by neuropsychological testing, what can be true especially in higher educated individuals [12]. Another explanation, proposed recently, is that some patients have no memory deficit in conventional tests (so not fulfilling criteria for MCI) but only in forgetting, reflecting deficit in long-term consolidation [43]. It is also possible other non-memory cognitive domains deficits can be erroneously be perceived as a memory deficit, instead of, for instance attention or processing speed difficulties. To make this issue more complicated, in patients with diagnosis of cognitive impairment (dementia or MCI), the positive predictive value of memory complaint for the diagnosis of cognitive impairment is poor [44], and it was recently questioned the value of complaining from memory among subjects with MCI [19]. A recent systematic review approaching subjective memory complaints in MCI patients found strong evidence for the variability in the level of awareness among individuals with MCI, and the difficulty found due to the lack of comparability between studies due to methodological issues [45].

Age-related cerebral white matter changes are associated with cognitive decline and dementia, mainly of the vascular type. In our baseline analysis, we found that self perceived memory complaints in elderly subjects with WMC living independently, were associated with worse performance on the memory domain [46]. On the longitudinal approach we controlled our analysis to cognitive status at baseline. Our study has some limitations and may not be generalized for a community sample, mostly due to the sample selection, which does not represent the community: participants were selected due to the presence of WMC and could have minor complaints. Our sample probably represent the first moment when non-disabled elderly with cerebral WMC seek medical attention. Other limitation was related with the duration of the follow-up, as 3 years was probably shorter to have a higher conversion into dementia. However, we had unequivocally positive results concerning the influence of self perceived memory complaints and dementia of the Alzheimer type after 3 years of follow-up in elderly subjects with small vessel disease that lived independently. We could hypothesize that memory complaints in this sample of independent elderly with a marker of vascular disease would represent an executive syndrome and would not be associated with progression for AD. From our best knowledge this is the first study that approach implications of memory complaints in independent elderly with WMC. Prediction of AD among elderly subjects with evidence of small vessel disease and self perceived memory complaints was surprisingly high, and we think this fact remarkable and it reinforces the power of memory complaints in the elderly.

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