Original Research Article

Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

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Abstract
Background: Longitudinal reports on the clinical features of patients with Alzheimer's disease (AD) and concomitant cerebrovascular disease are scarce. **Methods:** We elaborated a working definition of AD with vascular component (ADVC), and this definition was retrospectively investigated in a cohort of patients with cognitive deterioration who were prescribed a cholinesterase inhibitor during usual practice. **Results:** A total of 137 patients with probable AD and 66 patients with ADVC were studied during a mean follow-up period of 2.8 years. Univariate analyses demonstrated worse functional evolution and anticipation of psychotic symptoms and agitation in the ADVC group. **Conclusions:** The present results are consistent with an additive model of predominantly frontal-subcortical vascular damage in AD.

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Introduction

Evidence from clinicopathological studies demonstrated that multiple brain pathologies usually coexist in old people with dementia, and that was particularly the case for the combination of Alzheimer's disease (AD) and cerebrovascular lesions [1–3]. Persons with mul-

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Dement Geriatr Cogn Disord Extra 2012;2:400–410

DOI: 10.1159/000342346
Published online: September 22, 2012

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401

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

tiple pathologies were also more likely to exhibit dementia during life, compared with persons with a single diagnosis [4]. Regarding the combination of AD and cerebrovascular lesions, dementia was more prevalent and more severe when, for a given level of AD pathology, brain infarcts were present [5, 6].

It is still unclear whether AD and cerebrovascular pathology are two age-dependent processes that merely coexist or whether there are some synergistic mechanisms shared by the two conditions [7–9]. Some studies suggested that AD and cerebrovascular pathology contributed to cognitive performance independent from each other [8, 10]. However, synergistic mechanisms could be hypothesized when considering that small amounts of cerebrovascular pathology may significantly worsen the cognitive impact of mild AD pathology [5, 6]. Recently, a model of both additive and synergistic mechanisms was proposed, depending on the magnitude of vascular and neurodegenerative pathology and also on the stage of evolution of the disease process [11].

On either additive or synergistic model, the combination of AD and cerebrovascular disease should be accompanied by some distinct clinical characteristics when compared with pure AD. A more rapid decline could be hypothesized in those patients with AD and concomitant cerebrovascular disease. In addition, given the predominance of frontal-subcortical ischemic damage in old age [12], clinical features of parkinsonism and executive dysfunction should be more frequently observed in the patients with combined disease.

We elaborated a working definition of AD with potentially significant cerebrovascular disease and compared the clinical characteristics of so-called 'Alzheimer's disease with vascular component' (ADVC) patients with the characteristics of patients with pure AD. The present investigation was conducted in the context of a cohort of patients with cognitive deterioration who were prescribed a cholinesterase inhibitor (ChEI) during usual practice. The existence of a distinct clinical profile in patients with AD and concomitant cerebrovascular disease would help to identify those patients, to understand the pathological underpinnings, and to improve treatments and care.

Methods

Setting and Study Process

The ChEI Study was designed and launched in two neurology clinics to assess the effects and tolerance of 3 marketed ChEI (i.e. donepezil, rivastigmine, and galantamine) during usual practice. The two study clinics served two low-middle class areas in the southern suburbs of the city of Madrid, Spain. Most patients were referred by their family physicians. Patients were systematically and prospectively recruited from January 1, 2002, to May 31, 2006, by the authors, two senior neurologists with special dedication to dementia, according to the following inclusion criteria: (i) patient attended the clinic accompanied by a reliable caregiver; (ii) cognitive impairment of any aetiology was diagnosed; (iii) a ChEI was prescribed for the first time to that patient by the study neurologist, and (iv) a 1-year follow-up visit was performed.

All the included patients received a complete medical history that was comprised of anamnesis, physical and neurological exam, Mini-Mental State Examination (MMSE) [13], and Clinical Dementia Rating (CDR) scale [14]. That visit was considered the baseline visit for the ChEI Study. When not available, blood determinations, including blood count, glucose, creatinine, transaminases, calcium, thyroid-stimulating hormone, B12, and folate, and structural brain imaging study [i.e. computerized tomography (CT) scan or magnetic resonance imaging (MRI)] were ordered [15]. ChEI was prescribed at baseline visit or, in case that tests were ordered, 1–3 months later. Since the inclusion day was the day of ChEI prescrip-

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Dementia
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Cognitive Disorders

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402

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

tion and a 1-year follow-up visit was required for inclusion, baseline data were retrospectively collected.

ChEI were prescribed according to patient and caregiver characteristics. Due to commodity of use, donepezil was chosen when there were not many assurances that the patient and the caregiver would comply with the prescribed medication. Rivastigmine was preferred in case of parkinsonism, liver disease, or high risk of drug interactions. Impaired sleep-wake rhythm and mixed dementia were reasons to choose galantamine [16]. In case of tolerance and good health, the maximum dose of the respective ChEI was tried, usually within a period of time longer than the period recommended by the manufacturers. Yearly follow-up visits were scheduled during 5 years, plus additional visits as the clinical situation indicated. Dementia diagnosis and aetiology were established at baseline visit, and those diagnoses were reconsidered at every annual visit. For the present investigation, baseline and 3-year follow-up results were analyzed. Only those patients for whom there was a final diagnosis of probable AD [17] or ADVC (see below for inclusion criteria) were included and analyzed.

Study Groups

The ADVC study was designed once the database of the ChEI Study was completed and closed. All selected patients presented with progressive and predominantly amnesic cognitive deterioration. Patients displaying clinical features suggestive of non-AD degenerative dementia (e.g. Lewy body dementia [18] or frontal lobar degeneration [19]) or presenting medical, psychiatric, or neurological processes (other than cerebrovascular disease) that could produce cognitive deterioration (e.g. major depression, normal pressure hydrocephalus) were excluded. On that basis, the following two study groups were further defined.

Probable AD (PAD) group: the traditional criteria of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) were observed for this group [17]. Of particular interest for the present investigation, subjects with a history of symptomatic cerebrovascular disease or with significant cerebrovascular disease in the structural imaging study were excluded from this group.

ADVC group: apart from dementia otherwise suggestive of AD, these patients had a clinical history of cerebrovascular disease (i.e. transient ischemic attack or stroke) or significant data of cerebrovascular disease on neuroimaging study (i.e. brain infarct or moderate to severe leukoaraiosis as indicated by a score of 2 or 3 in the Wahlund scale [20]).

Outcome Variables

The following scales, conducted at baseline and annually by the study neurologists during usual practice, were utilized as outcome variables.

MMSE [13]: the MMSE is a brief and widely used test of general cognition. The score of the MMSE ranges from 0 (worse cognitive state) to 30 (best cognitive state). Although originally conceived as a screening instrument, this test was chosen because it was feasible in the context of usual practice and also because it provides an easily interpretable and comparable score.

Functional Assessment Staging Scale (FAST) [21]: the FAST depicts the predictable functional losses of a typical AD patient. The possible score ranges from 1 (lack of functional symptoms) to 16 (vegetative state). Both the MMSE and the FAST were able to detect differences in clinical course in a previous study of AD and vascular risk factors [22].

Behavioral and psychological symptoms of dementia (BPSD) and anosognosia: during visits, the neurologist elicited information from both the patient and caregiver regarding the following potential BPSD: delusions, hallucinations, aggressive behaviour, dysphoria, anxiety, apathy, irritability, aberrant motor behaviour, appetite and eating disorders, euphoria,

KARGER

403

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

and disinhibition. These BPSD categories and their corresponding definitions were taken from the Neuropsychiatric Inventory [23], although this instrument was not formally administered. The BPSD were codified as present or absent. Symptoms were present if they appeared any time from the beginning of cognitive symptoms (baseline visit) or from the last visit (annual follow-up visits). Those BPSD that were completely controlled with medication were codified as absent. Both the total number of BPSD and the frequency of the different BPSD were analyzed. Anosognosia was codified as present if, during the visit, the patient did not have cognitive complaints (either spontaneously or at physician's request).

Statistical Analyses

Descriptive statistics were used to depict the clinical characteristics of the two study groups. Baseline characteristics were compared using Student's t test and χ^2 test. The MMSE, the FAST, and the number of BPSD were considered as primary outcome measures. Analysis of the primary outcome variables was performed using a repeated-measures analysis of variance model that included aetiology (i.e. AD vs. ADVC) as the factor of interest. To account for all the observations, separate models were elaborated for 1-, 2-, and 3-year follow-up results. A complementary analysis with a last observation carried forward approach was also conducted to deal with missing data. In addition, the prevalence of the individual BPSD and of anosognosia were compared using χ^2 test. All the statistical tests were two sided and p values <0.05 were considered significant. Given the lack of previous longitudinal studies comparing ADVC and PAD, the present study was considered exploratory in nature, and multiple comparison adjustment was not conducted [24]. Statistical analyses were performed using SPSS version 16.0 software (SPSS, Chicago, Ill., USA).

Results

The ChEI Study cohort was comprised of 270 patients, of whom 203 (75%) met the inclusion criteria for the present investigation (PAD n = 138, ADVC n = 65). All the included patients lived in the community. Reasons for exclusion were: alcohol abuse (n = 2), clinically atypical AD (n = 4), degenerative aetiology different from AD (n = 34), non-degenerative aetiology (n = 6), and cognitive impairment of uncertain aetiology (n = 21).

The mean age was 77.0 years (SD 6.3, range 51–89), and 67% of the patients were female. The educational achievement of the whole sample was as follows: illiterate (16%), incomplete primary studies (46%), primary studies (35%), and superior studies (3%). Most patients were in the initial stages of dementia according to the CDR (20% CDR 0.5, 71% CDR 1, 8% CDR 2, and 1% CDR 3). Caregivers were mostly female (69%) and the majority of them (69%) lived with the patient. The family link of the caregivers was as follows: daughter or son (48%), spouse (43%), sister or brother (4%), and other link (5%).

The diagnosis of ADVC was performed on the basis of previous cerebrovascular episode (n = 5, 7.6%), presence of brain infarct on neuroimaging study (n = 14, 21.2%), moderate to severe leukoaraiosis (n = 18, 27.3%), and a combination of the former (n = 29, 43.9%). The clinical and paraclinical characteristics of the patients, according to study group, are presented in table 1. Statistically significant differences between the two study groups (p < 0.05) were observed for medical history of hypertension, diabetes, and loss of consciousness; total number of medications; use of antiaggregant and antihypertensive agents; presence of parkinsonism in the neurological exam, and presence of atrophy on neuroimaging study, which were higher or more frequently recorded in the ADVC group. Parkinsonism was not associated with functional performance at baseline (Spearman's r = 0.04).

404

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

Table 1. Characteristics of the two study groups at baseline

	PAD (n = 137)	ADVC (n = 66)	p
Age	76.5 (6.7)	78.2 (5.1)	0.060
Females	70.1	59.1	0.120
Education			0.376
Illiterate	14.7	20.0	
None/incomplete	50.0	38.5	
Primary	32.4	40.0	
Superior	2.9	1.5	
Comorbidities (past or present)			
Hypertension	46.7	72.7	0.000
Diabetes	18.2	31.8	0.031
Dyslipidaemia	56.9	59.1	0.771
Ischemic cardiopathy	7.3	7.6	1.000
Cerebrovascular episodes	0*	34.8	0.000
Peripheral arteriopathy	1.5	3.0	0.451
Loss of consciousness (last year)	0	7.6	0.001
Fall (last year)	4.4	3.0	1.000
Emergency room visit (last year)	7.3	15.2	0.079
Tobacco use			0.292
Never	75.0	68.2	
Past	21.3	30.3	
Present	3.7	1.5	
Number of medications	2.7 (2.0)	3.4 (2.1)	0.018
Antiaggregant agents	19.0	50.0	0.000
Anticoagulant agents	5.1	7.6	0.533
Antihypertensive agents	40.4	63.6	0.002
Oral antidiabetic agents	10.3	13.6	0.483
Insulin	3.7	6.1	0.478
Hypolipemiant agents	16.2	27.3	0.063
Antidepressants	22.6	19.7	0.635
Neuroleptics	5.1	3.0	0.721
Anxiolytic/hypnotic agents	19.1	15.2	0.490
Other medications for BPSD	2.9	0	0.306
Disease duration, years	2.5 (1.9)	2.6 (2.4)	0.681
Parkinsonism	0	9.1	0.001
CDR score			0.055
0.5	24.1	12.1	
1	70.1	72.7	
2	5.1	13.6	
3	0.7	1.5	
Neuroimaging study (CT or MRI)			
Leukoaraiosis			0.000
No	96.3	33.3	
Mild	3.7	6.1	
Moderate	0*	54.5	
Severe	0*	6.1	
Vascular lesion (location)			0.000
No lesion	100	47.0	
Subcortical	0*	40.9	
Cortical	0*	3.0	
Cortical and subcortical	0*	6.1	
Posterior fossa	0*	3.0	
Atrophy	72.6	87.9	0.015
Family history of dementia	43.5	41.9	0.836
Prescribed ChEI			0.163
Donepezil	56.6	48.5	
Rivastigmine	16.9	12.1	
Galantamine	26.5	39.4	

Data are expressed as mean (SD) or percentage. * As per predefined inclusion criteria.

405

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

Table 2. Outcome variables by study group

	Baseline visit	1 year	2 years	3 years	LOCF
Cognition (MMSE)					
PAD	17.1 (4.6)	15.4 (5.2)	14.2 (6.0)	12.1 (6.4)	12.6 (5.9)
n	137	123	108	87	137
ADVC	17.2 (5.4)	15.3 (5.4)	13.0 (5.3)	10.9 (5.6)	11.5 (5.8)
n	66	61	60	47	66
p*	NA	0.763	0.227	0.219	0.121
Function (FAST)					
PAD	3.9 (0.8)	4.4 (1.1)	5.0 (1.7)	5.8 (2.1)	5.7 (2.0)
n	137	137	130	115	137
ADVC	4.2 (0.8)	5.0 (1.6)	6.1 (2.3)	6.8 (2.4)	6.8 (2.3)
n	66	66	64	54	66
p*	NA	0.015	0.002	0.020	0.008
Behaviour (number of BPSD)					
PAD	1.5 (1.4)	1.4 (1.4)	1.6 (1.4)	1.9 (1.6)	1.8 (1.5)
n	137	137	130	111	137
ADVC	1.7 (1.5)	2.1 (1.8)	1.7 (1.7)	1.4 (1.1)	1.6 (1.3)
n	66	66	65	50	66
p*	NA	0.017	0.773	0.036	0.065

Data are expressed as mean (SD). * Within-group analysis of variance (baseline score as reference). LOCF = Last observation carried forward; NA = not applicable.

All included patients were evaluated with at least two primary outcome measures (FAST and BPSD) at the 1-year follow-up visit [the MMSE could not be conducted for 19 patients (9.4%) at that visit]. Six patients died between the 1- and 3-year follow-up visits (2.6% in the PAD group, 5.2% in the ADVC group; p = 0.399), and 28 additional patients were lost to follow-up. Hence, 169 patients (83.3%) could be evaluated with at least one primary outcome measure (FAST) at the 3-year follow-up visit, and 134 patients (66.0%) could be evaluated with all three primary outcome measures at that visit. Cerebrovascular episodes occurred in 6 patients of the ADVC group during follow-up (5 patients had 1 episode, 1 patient had 2 episodes).

At study inclusion, patients from the ADVC group displayed a trend of more functional dependence compared to PAD patients (p < 0.1), and this difference was clearly enlarged during follow-up, reaching statistical significance in all subsequent visits (p < 0.05, table 2). Cognitive performance was similar in the two study groups at baseline, and some worse cognitive evolution was observed in the ADVC group during follow-up, but statistical significance was not achieved (table 2; fig. 1).

Psychotic symptoms, particularly delusions, were more frequent in the ADVC group at baseline and 1-year follow-up visits, but the reverse pattern was observed at the end of the study period (table 3). In addition, higher frequencies of agitation and disinhibition were recorded in the ADVC group at the 1-year follow-up visit. Those behavioural results contributed to the appearance of a peak of BPSD in the ADVC group at the 1-year follow-up visit. In addition, motor hyperactivity was more frequent at the 2-year follow-up visit in the ADVC group, and a trend of less awareness of deficit appeared at the end of the study period in that group. As for the PAD group, the total number of BPSD (anosognosia not considered) was highest at the end of follow-up (table 2).

406

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?
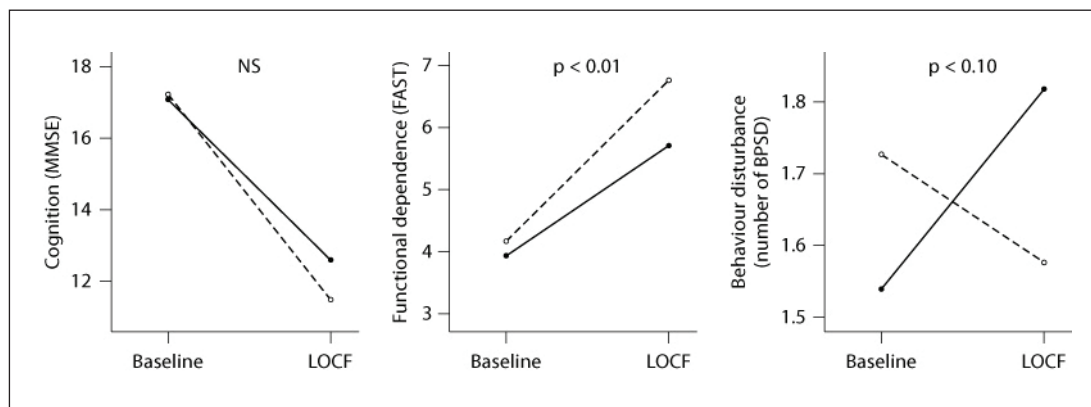
Fig. 1. Three-year results of probable AD (continuous line) and ADVC (dotted line) patients in the primary outcome measures. LOCF = Last observation carried forward; NS = statistically not significant ($p > 0.10$) (two-factor repeated measures analysis of variance).

To better understand the evolution of BPSD in the two study groups, a post hoc analysis of medications for BPSD was conducted. Consistently with findings of more frequent delusions, hallucinations, and agitation, neuroleptics were more frequently prescribed to ADVC patients at 1- and 2-year follow-up visits (1-year follow-up visit, 4.4% PAD vs. 15.2% ADVC, $p = 0.008$; 2-year follow-up visit, 9.3% PAD vs. 20.0% ADVC, $p = 0.036$; 3-year follow-up visit, 17.5% PAD vs. 13.2% ADVC, $p = 0.479$; rest of data on medication use at follow-up visits is not shown).

Discussion

A working definition of AD with concomitant cerebrovascular disease was elaborated on the basis of clinical and neuroimaging data, and the cognitive, functional, and behavioural evolution of those patients (i.e. ADVC group) was compared with the evolution of typical AD patients who did not have cerebrovascular disease (i.e. PAD group). This was a naturalistic study conducted in two neurology clinics where patients were referred by their family physicians and, in all cases, a ChEI was initiated by the attending neurologist. In that context, which seems quite representative of incident AD, one third of the patients (32.5%) qualified for the ADVC group. Autopsy-proven studies demonstrated a range of prevalence of cerebrovascular lesions in AD from 39 to 68% [1–4, 7] and that variability mostly depended on differences in the kind of studied vascular lesions (macroscopic infarcts, microscopic infarcts, etc.). Our patients displayed an inferior prevalence of cerebrovascular disease possibly due to the low sensitivity of ADVC working definition or, in the autopsy-proven studies, due to accumulation of cerebrovascular pathology near death.

Worse functional evolution and anticipation of some BPSD, which were observed in the ADVC group, were the most salient findings of the present investigation (table 2). These findings could be explained on the basis of frontal-subcortical brain damage of vascular origin that would impinge on executive functions, motor functions, and behaviour control of AD patients. Conditioned by the ADVC definition, patients from the ADVC group presented a high prevalence of leukoaraiosis (66.7%) and subcortical infarcts (47.0%), while only a minority of patients (9.1%) presented cortical lesions (table 1). Frontal-subcortical damage was

Dement Geriatr Cogn Disord Extra 2012;2:400–410

DOI: 10.1159/000342346
Published online: September 22, 2012

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407

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

Table 3. Evolution of the different BPSD and of anosognosia in the two study groups

		Baseline visit	1 year	2 years	3 years
Delusions	PAD	9.5	9.5	16.9	23.5
	ADVC	24.2	28.8	18.5	5.7
	p	0.005	0.000	0.790	0.005
Hallucinations	PAD	1.5	1.5	4.6	11.3
	ADVC	7.6	7.6	7.7	5.7
	p	0.038	0.038	0.511	0.396
Agitation	PAD	16.1	16.1	20.8	28.7
	ADVC	24.2	30.3	21.5	24.5
	p	0.161	0.019	0.901	0.573
Dysphoria	PAD	38.0	26.3	26.9	23.4
	ADVC	37.9	28.8	12.3	14.0
	p	0.992	0.706	0.020	0.171
Anxiety	PAD	23.4	17.5	20.0	21.6
	ADVC	22.7	27.3	16.9	12.0
	p	0.921	0.108	0.605	0.147
Euphoria	PAD	0	0	0	1.7
	ADVC	0	1.5	0	1.9
	p	NA	0.325	NA	1.000
Apathy	PAD	14.6	10.2	12.3	13.0
	ADVC	10.6	12.1	13.8	15.1
	p	0.433	0.683	0.762	0.719
Disinhibition	PAD	3.6	2.9	4.6	7.0
	ADVC	4.5	9.1	9.2	7.5
	p	0.717	0.081	0.219	1.000
Irritability	PAD	27.0	29.2	28.5	28.7
	ADVC	28.8	36.4	30.8	34.0
	p	0.790	0.303	0.738	0.490
Motor hyperactivity	PAD	2.9	6.6	5.4	7.8
	ADVC	4.5	7.6	13.8	5.7
	p	0.684	0.774	0.042	0.755
Night-time behaviour	PAD	13.1	16.1	16.9	20.0
	ADVC	7.6	13.6	21.5	15.1
	p	0.241	0.653	0.434	0.446
Appetite and eating	PAD	4.4	2.2	2.3	0
	ADVC	0	1.5	1.5	1.9
	p	0.180	1.000	1.000	0.315
Anosognosia	PAD	25.5	37.2	46.2	59.1
	ADVC	34.8	48.5	55.4	73.1
	p	0.169	0.126	0.224	0.083

Data are expressed as percentage of patients displaying the abnormal behaviour.

further supported by the observations of less awareness of deficit and more frequent parkinsonism in the ADVC group.

The low sensibility of the MMSE to detecting frontal-subcortical cognitive dysfunction could have contributed to the lack of statistically significant differences regarding cognitive evolution in the two study groups [25]. Alternatively, a selective impairment of function could have appeared as the consequence of motor disability due to cerebrovascular disease in the ADVC group. We did not observe a correlation between parkinsonism and function-

408

al performance at baseline; however, since motor measurements were not conducted during follow-up, some influence of motor performance on the functional evolution of the ADVC group cannot be definitely ruled out.

Former investigations are consistent with an additive model of frontal-subcortical damage in ADVC. In a small autopsy-proven series, cases of mixed dementia more frequently presented executive dysfunction than pure AD cases, although statistical significance was not achieved [26]. In an analysis of the AD Research Database, higher executive dysfunction was found in those AD patients who had a clinical history of stroke, radiological infarct, or both [27]. In another study of patients with dementia, white matter hyperintensities were associated with failure in recognition memory [28]. In a recent series of 1,257 patients admitted to a tertiary centre with a diagnosis of stroke, small vessel cerebrovascular disease was associated with executive dysfunction and gait disturbance [29]. Contributions from the present investigation were the long-term longitudinal data and the global perspective of clinical assessment, which, apart from general cognition, included the study of function, behaviour problems, and anosognosia.

Also as a new contribution, we described the longitudinal profile of BPSD in ADVC patients and compared it with the profile of patients with PAD. A 2-year anticipation of psychotic symptoms and agitation was observed in ADVC patients, again consistently with a model of frontal and limbic damage of vascular origin [30]. In addition, functional deterioration, perhaps through psychological and environmental mechanisms, could have contributed to the anticipation of BPSD observed in the ADVC patients [30, 31]. More research is necessary to confirm the longitudinal profile of BPSD in ADVC and to better understand the involved mechanisms.

We also need more understanding of the mechanisms that underlie the cognitive and functional manifestations of ADVC. In a recent study, more rapid cognitive and functional deterioration was associated with the presence of vascular risk factors in PAD patients who did not have clinical nor MRI data of cerebrovascular disease, either at study entry or during follow-up [22]. A more rapid cognitive decline was also reported in AD patients who lacked evidence of cerebrovascular disease when vascular risk factors were not treated [32]. Hence, suboptimal control of, or some other mechanisms linked to, vascular risk factors could contribute to a more rapid cognitive and functional decline in AD, independent of the existence of cerebrovascular lesions. Our patients received frequent medical care, which included the adequate control of vascular risk factors. However, only 57.6% of the patients in our ADVC group were on antiaggregant or anticoagulant medications (table 1). Other explanations, such as microscopic (i.e. not detected by conventional neuroimaging studies) ischemic brain damage, for the more rapid decline of ADVC would also deserve investigation [33].

The present study has several limitations. It was only partially prospective, not blinded, and not pathologically verified. In addition, the two study groups were not perfectly balanced at baseline, ChEI treatment was initiated and maintained during the study, and frontal-subcortical functions were not specifically evaluated. Most of these limitations were derived from a naturalistic research context. It should be said though that the study was designed 2 years after the ChEI Study database was closed, thus reducing the possibility of data collection bias. Treatment with ChEI should have not influenced results either, since benefits of ChEI in patients with AD associated with cerebrovascular disease were similar to benefits observed in PAD patients across the domains of cognition, function, and behaviour [34]. Nevertheless, the presented results should be confirmed and extended in the future, particularly with respect to frontal function assessment and validation of ADVC definition against brain necropsy. As the result of future research, the definition of ADVC could experience some modification or refinement (e.g. use of MRI rather than CT scan for the detection of brain cerebrovascular lesions).

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409

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

In conclusion, a distinct clinical profile was observed in patients with AD who, by study definition, were suspected of having concomitant and clinically relevant cerebrovascular disease. More rapid functional decline and anticipation of psychotic symptoms and agitation were observed, which are all features consistent with an additive model of predominantly frontal-subcortical damage of vascular origin in AD. Further research is warranted to confirm these results, to better delineate the clinical profile, and to understand the involved physiopathological mechanisms. In a scenario of increasing aging and combined disease, early and accurate diagnosis of ADVC should become a matter of outmost importance, with specific implications for treatments and care.

Disclosure Statement

The authors declare no potential conflict of interests.

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410

Olazarán et al.: Alzheimer's Disease with Vascular Component: A Distinct Clinical Entity?

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