Review Article

Vascular Risk Factors which Influence the Prognosis of Prodromal Alzheimer Disease

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Abstract

Objective: To analyze the demographic, clinical and biomarker factors that may influence the prognosis and survival in prodromal Alzheimer´s Disease (AD) in Spanish patients.

Study population and methods: Between 2008 to 2011, 170 mild cognitively impaired patients who were reviewed clinically at 6 monthly intervals were included in the study. During the follow-up, assessment of the progression to AD was performed according to NIA-AA (2011) criteria and patients were then classified following the Global Deterioration Scale (GDS).

Results: After a follow-up period of 5.5 ± 1.2 years, 95 patients developed AD. In May 2016, 11 were GDS 4 and 62 GDS 5 or greater and 21 were deceased. Diabetics and non hypercholesterolemic patients died in a larger proportion than non-diabetics patients (p<0.03) and hypercholesterolemic patients treated with statins (p<0.02). Patients with hypertension reached faster GDS 5 than non-hypertensive patients (p<0.02) as well as the patients treated only with anticholinesterasic drugs (p<0.03).

Conclusion: Diabetes was associated with a worse determinant prognosis in prodromal Alzheimer´s disease in Spanish patients.

Keywords: Alzheimer´s disease; Determinant prognosis; Diabetes; Hypertension; Hypercholesterolemia; Anticholinesterasic drugs

Introduction

Alzheimer´s Disease (AD) is currently considered a leading social-health problem. Therefore, knowing the functional and vital prognosis of these patients in the different aspects such as personal, familial and social factors is important, along with in the investigation for future treatments.

We know that the life expectancy of AD patients is lower than in the cognitively normal of the same age [1]. However, studies in this area can be problematic when there is diversity in the severity of the disease at inclusion [2]. We have not found published works in which all included patients were in the prodromal phase of the disease. In addition, opinions differ in the literature about the influence of vascular risk factors on the vital and functional prognosis of patients with AD [1-7], especially diabetes, hypertension and hypercholesterolemia. As far as we know, no works have been published on Spanish patient populations.

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Our objective was to analyze the clinical and analytical factors which may influence the functional evolution and the vital prognosis in Spanish patients with prodromal AD.

Materials and Methods

Study design

Longitudinal study.

Patients

Between 2008 and 2011, 170 patients diagnosed with Mild Cognitive Impairment (MCI) according to the criteria of Petersen et al. [8] were included. The majority of the patients were recruited from the department of Cognitive Impairment of the Hospital General University of Alicante, 25 from the Hospital of Denia and 21 from the Hospital Baix Vinalopó of Elche. Patients underwent physical and neurological examinations, neuropsychological testing, blood tests, brain Magnetic Resonance Imaging (MRI) and lumbar puncture. Patients were reviewed every six months, assessing the progression to AD according to the NIA-AA criteria and classifying patients according to the Reisberg GDS [9] [10].

Inclusion criteria

Patients with MCI over 55 years of age, with a score lower than 27 in the Mini Mental State Examination (MMSE) [11] and lower than 78 in the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [12]. Inclusion in the study and performance of the lumbar puncture required that an informed consent was signed by all patients.

Exclusion criteria

Presence of dementia or other neurological or internistic disease which could lead to cognitive deterioration, anticoagulant treatment, absence of informed consent or a score higher than 5 in the Yesavage Geriatric Depression Scale [13].

Procedure

The responsible neurologist provided a diagnosis of pure amnesic MCI or multi domain, according to the criteria of Petersen 2006 [8]. The neuropsychological tests performed were the MMSE, Rey Auditory-Verbal Learning Test (RAVLT) [14], Trail Making Test (TMT), Yesavage test and IQCODE. It was valued memory, language, executive functions, attention, visuoconstructive skills, functionality and depressive symptomatology. The alteration of a function was defined as a Z-value resulting in -1.5 or less, which means at least 1.5 standard deviations below the average of the control, in at least one of the tests used to study the function. The criteria to consider the conversion from MCI to AD were those of NIA- AA 2011 for the diagnosis of this disease [9], McKeith et al. [15] criteria for the diagnosis of dementia with Lewy bodies [16], NINDS-AIREN criteria for the diagnosis of vascular dementia [17], the Lund-Manchester Consortium criteria for the diagnosis of frontotemporal dementia [18] and the Zerr et al. [19] for the diagnosis of Creutzfeldt-Jakob disease criteria.

A cerebral MRI, General Electric's 1.5 Tesla, was performed, using the criteria of Korf et al. [20] to assess Medial Temporal Atrophy (MTA) and to exclude brain lesions responsible for neurological symptoms, especially those of vascular origin.

Finally, a lumbar puncture was performed to assess the AD biomarkers in Cerebrospinal Fluid biomarkers (CSF): Aβ1-42, T-tau and fosto-tau proteins. To analyze these samples, INNOTEST reagents (Innogenetics-Ghent, Belgium) were used. All samples were analyzed blindly with respect to clinical data.

Statistical analysis

The Kolmogorov-Smirnov test was used for analysis of the distribution type of each variable. Parametric variables were compared with Student's t-test, nonparametric variables with Mann-Whitney U test and qualitative variables with Chi square test. Survival curves were obtained for the different qualitative variables. Analyses were performed using the statistical package SPSS version 19.0 and P values of <.05 was considered statistically significant.

Ethical criteria

All patients gave informed consent to have the lumbar puncture performed and for inclusion in the study which was approved by the Ethics Committee of the General University Hospital of Alicante.

Results

Of the 170 subjects included in the study between 2008 to 2011, 15 died in the first two years of the study, so they were excluded from the analysis. Of the 155 remaining in May 2016, 44 (26%) remained as stable MCI, 15 (9%) developed other dementias (10 dementia with Lewy bodies, 2 dementia of vascular origin, 2 frontotemporal dementias and one Creutzfeldt-Jakob disease). Finally, 96 patients (56%) developed AD according to NIA-AA 2011 criteria. 21 patients of this group died during follow-up and 73 remained alive, of which 62 were in GDS 5 or higher and 11 were in GDS 4.

Analysis of vital prognosis

When comparing the group of deceased patients (n=21) during the follow-up with the live group (n=73) in May 2016 we found that among the former there were more diabetics (p<0.03) and less hyperlipidemic (p<0.02) patients. The survival curves confirmed this data (Figures 1 and 2). Otherwise, the deceased were slightly older than the alive patients, but without statistical difference. No significant differences were found in the rest of the clinical, demographic, analytical characteristics in CSF and radiology (Table 1).
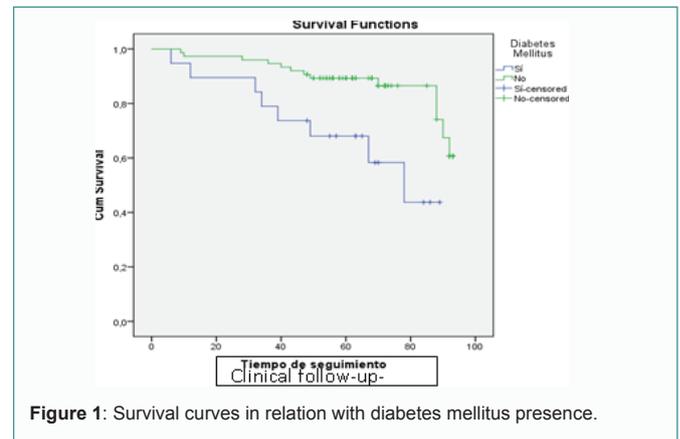

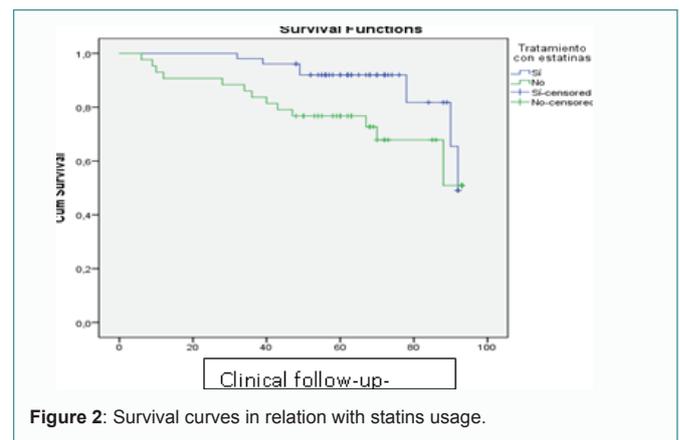**Figure 1**: Survival curves in relation with diabetes mellitus presence.

Figure 2: Survival curves in relation with statins usage.

Analysis of the functional prognosis

When comparing the group of patients in GDS 5 or higher (n=62) with those in GDS 4 (n=11) we observed that in the first group there was a greater proportion of hypertensive patients (p<0.02) (Table 2); however, when comparing the survival curves we found that they declined in a similar way6 (Figure 3). On the other hand, patients who received the dual treatment (Anticholinesterase Plus Memantine) took longer to reach the GDS 5 stage than those treated with anticholinesterase alone (p<0.03) (Table 3). No significant differences were found in the rest of the clinical, demographic, analytical variables in CSF or radiological studies.

Discussion

Analysis of vital prognosis

The life expectancy of patients with AD is lower than in cognitively normal patients of the same age. A multitude of factors have been proposed that can influence this vital prognosis: age, severity of the disease, presence of extrapyramidal signs, sex, race, diabetes mellitus, hypertension, or biomarker levels of AD in CSF [1-7].

Table 1: Comparison of the demographic, clinic and biomarkers characteristics in prodromal AD patients

	Alive	Deceased	Signification level (p<0.05)
Number of cases	73	21	….
Men (%)	25 (34)	11 (54)	0.2
Age-years-(mean ± SD)	71.9 ± 6.6	74.9 ± 6.3	0.06
Antecedents (%)			
Diabetes	11 (15)	8 (38)	0.03
Hypertension	30 (41)	13 (62)	0.09
Hypercholesterol	44 (60)	7 (33)	0.02
Depression	20 (27)	4 (19)	0.4
Familial dementia	12(16)	1 (5)	0.06
Years smoking	10.2 ± 5.2	11.2± 3.7	0.07
Body mass index	26.1 ± 4.3	26.9 ± 3.8	0.08
Atrial fibrillation	4.4	5.4	0.09
Schooling-years-median (p25-p75)	3.8 (3.1-4.6)	3.0 (1.7-4.3)	0.2
Start of the symptoms-months-median (p25-p75)	20.7 (18.0-23.3)	19.4 (15.3-23.5)	0.9
MMSE Folstein median (p25-p75)	24.6 (24.2-25.1)	23.6 (22.2-24.9)	0.1
IQCODE median (p25-p75)	65.6 (63.8-67.4)	66.4 (60.8-7 [2.0])	0.3
DCL amnésico (%)	100	100	……..
Clinical follow-up post LP-years-(mean ± SD)	5.5 ± 2.5	6.1 ± 2.1	0.1
Aβ 1-42 (pg/ml)Median (p25-p75)	542.6 (487.3-597.9)	543 (445.0-641.0)	0.8
T-tau (pg/ml) Median (p25-p75)	700.2 (598.4-802.1)	604.1 (468.9-739.3)	0.7
P-tau (pg/ml) Median (p25-p75)	91.7 (78.2-105.1)	98.8 (57.0-140.6)	0.8
T-tau/Aβ 1-42 Median (p25-p75)	1.46 (1.23-1.69)	1.3 (0.91-1.67)	0.5
P-tau/Aβ 1-42 Median(p25-p75)	0.18 (0.15-0.21)	0.24 (0.06-0.42)	0.9

Table 2: Comparison of the demographic, clinic and AD biomarkers in prodromal AD patients.

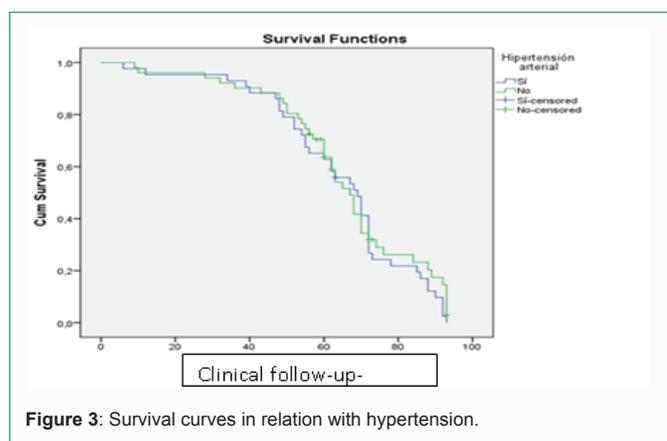|	GDS 4	GDS ≥ 5	Signification level (p<0.05)
Number of cases	11	62	….
Men %	45	32.3	0.5
Age -years-(mean ± SD)	72.3 ± 6.1	71.8 ± 6.7	0.3
Antecedents (%)			
Diabetes	1 (9)	10(16)	0.9
Hypertension	1 (9)	29 (46.8)	0.02
Hyperlipidemia	4 (36.4)	40 (64.5)	0.1
Depression	3 (27.3)	17(27.4)	0.9
Familial dementia	3 (27.3)	9 (14.5)	0.3
Years smoking	10.0 ± 14.6	9.3 ± 12.7	0.09
Body mass index	28.0 ± 5.0	27.4 5.3	0.08
Atrial fibrillation	7.7	8.6	0.09
Schooling -years- (mean ± SD)	4.55 ± 1.2	3.76 ± 1.4	0.4
Start of the symptoms–months-(mean ±SD)	16.7 ± 5.4	21.4 ± 6.7	0.3
MMSE Folstein (mean ± SD)	25.1 ± 2.3	24.6 ± 3.2	0.3
IQCODE (mean ± SD)	63.6	66	0.2
DCL amnésico (%)	100	100	1
Clinical follow-up post-LP-years-(mean ± SD)	5.0 ± 1.1	5.6 ± 1.3	0.07
Aβ 1-42 (pg/ml) Median (p25-p75)	491 (444.0-537.9)	551.8 (487.1-616.4)	0.7
T-tau (pg/ml) Median (p25-p75)	767 (421.1-1113.0)	688.4 (580.5-796.3)	0.6
P-tau (pg/ml) Median (p25-p75)	119.7 (52.3-187.0)	86.7 (75.0-98.4)	0.5
T-tau/Aβ 1-42 Median (p25-p75)	1.57 (0.94-2.2)	1.44 (1.18-1.69)	0.5
P-tau/Aβ 1-42 Median (p25-p75)	0.24 (0.10-0.37)	0.17 (0.14-0.2)	0.5

Figure 3: Survival curves in relation with hypertension.

Table 3: Comparison of time until GDS 5 depending on mono or dual therapy.

	Anticholinesterase (n=13)	Anticholinesterase + memantine (n=45)	Signification level (p<0.05)
Months from LP until GDS=5 mean (SD)	41.3 (21.3)	45.9 (13.3)	0.03

In our experience, Hispanic patients with prodromal AD have a worse vital prognosis if they are diabetics and when they are not receiving statin therapy. The influence of diabetes on the vital prognosis of these patients has been demonstrated in three publications only: in multi-ethnic population [6], in Korean population and in Polish population [21,22]. However, other authors did not find this association in the North American population [2,23]. Taking into account that diabetes mellitus also reduces the life expectancy of patients [24], it seems reasonable to think that the sum

of AD and diabetes shorten life more than each of them in isolation, as we observed in our study.

Alternatively, we observed that hypercholesterolemic patients treated with statins have a better vital prognosis than non-hypercholesterolemic patients. Some publications have shown the beneficial effect of statins on AD [25,26]. This effect has been attributed to a reduction in the inflammation in the endothelial microvascular cells [26]. However, as far as we know, the fact of increased survival of AD patients had not been previously documented in the literature.

It is evident that the age and severity of the disease can influence the life expectancy of these patients. To obtain more specific data, in our study we ruled out the influence of these two factors, as there were no differences in these variables between the group of deceased and that of survivors. Nor did we find differences by sex, education level, and depressive symptomatology, scores in the MMSE and IQCODE or biomarker levels of AD in CSF at baseline.

There is an important discussion with regards to the influence of arterial hypertension on the survival of patients with AD, being clearly supported by some authors [2,23], but not by others [1,21]. In our study, we did not find this influence, although we observed that these patients deteriorate functionally more quickly than normotensive patients, as discussed below.

Other factors that have been implicated in the survival of AD patients, such as gender, the development of functional disability or the rapid decline in cognition have been disputed by other authors [1,23], which is also the case in our experience Finally, race has also been implicated by Helzner et al. [2] as well as by Mehta et al. [5]. According to the former, Hispanic patients had a greater post-diagnosis survival than African-Americans and non-Hispanic whites; while according to the latter, African-Americans and Latinos survive longer than white Americans after diagnosis, without finding neuropathological differences that explain it. As far as we know, this is the first study which provides information on these characteristics in Spanish patients.

Analysis of functional prognosis

Normotensive patients and those receiving dual treatment of the disease seem to worsen more slowly than hypertensive patients or those who receive only anticholinesterase therapy in this cohort.

Hypertension has been associated with a greater degree of cognitive worsening in patients with AD [27-30]. However, other authors do not find this relationship [23,31] or even hypertension was associated with a smaller decrease in cognitive scores [32]. Despite obtaining this significant difference, the small number of cases with GDS 4 and hypertension does not allow us to be conclusive, especially when observing the similarity in the evolution of the survival curves.

The use of current treatments for AD has shown a positive influence on the evolution of the disease, but with disparate results between mono and combined therapy [32,33]. In our experience, the use of dual therapy significantly delays functional deterioration of patients. However, the number of monotherapy patients is reduced, so we cannot draw firm conclusions either.

The influence of diabetes mellitus on the progression of AD is not clear either, since there are publications in favor and against [2,26,34-37]. In the present study we did not find significant differences between both groups.

Other vascular risk factors, such as atria fibrillation, a history of ischemic heart disease, hypercholesterolemia or smoking, have been associated with faster progression to AD [2,26,29]. However, other authors do not recognize the influence of that vascular risk factors on the progression of AD [25,38].

Biomarkers in CSF have also been reported as possible predictors of fastest cognitive worsening [7,39,40]. However, we have not found differences that allow us to differentiate based on the results of these biomarkers.

Finally, other factors such as low educational level or lower MMSE 17 have also been associated with faster worsening, but we have not corroborated this in our patients, as there were no differences in these variables between the subgroups studied [23].

Among the limitations of this study, we have a small GDS 4 group, due to the long clinical follow-up period, which prevents us from obtaining more conclusive results of the factors that influence the functional prognosis of the patients.

Conclusion

On one hand, Spanish patients with prodromal AD have worse vital prognosis when they are diabetic and when they are not receiving statin therapy. On the other hand, normotensive patients and those receiving dual disease treatments seem to worsen more slowly than hypertensive patients or those who receive only anticholinesterase therapy. We believe that these results should be considered when making a functional and vital prognosis of patients with prodromal AD, as well as when including them in clinical trials.

Acknowledgement

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