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IMPACT OF NUTRITIONAL STATUS ON THE EVOLUTION OF ALZHEIMER'S DISEASE AND ON RESPONSE TO ACETYLCHOLINESTERASE INHIBITOR TREATMENT

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Abstract: Background: Weight loss is frequently observed in patients with Alzheimer's disease (AD), as observed in clinical practice and reported in the literature. However, information on the evolution of nutritional status and its impact on the prognosis of AD is still scarce. Objective: Our aim was to determine the impact of nutritional status on the evolution of AD and on the response to treatment with acetylcholinesterase inhibitors (AChEI) by prospective one-year follow-up of AD patients living at home. Methods: We studied a cohort of 523 patients with Alzheimer's disease referred from 1994 to 2002 to an Alzheimer centre. After diagnosis, they were followed for one year in a prospective observational study in clinical practice. At entry and every 6 months, patients underwent standardised neurocognitive and geriatric evaluation (MMSE, ADAS-cog, IADL, MNA, caregiver burden). These evaluations were accompanied by complete clinical examination, standard paraclinical investigations and recording of treatment received. Results: Of our patients, 25.8% presented at inclusion a risk of undernutrition with an MNA score of 23.5 or less. During follow-up, the number of patients with rapid loss on the MMSE (3 points or more in one year) was higher in subjects who presented a risk of undernutrition at inclusion (53.6%) than in well-nourished subjects (43.2%) (P = 0.07). Similarly, increased dependence at one year was more frequent in subjects at risk of undernutrition at inclusion (57.7% versus 44.4%, P = 0.0219). The beneficial effect of AChEI treatment on cognitive function was not influenced by initial nutritional status; on the contrary, among the subjects at risk of undernutrition at inclusion, the risk of rapid loss on the MMSE in one year was decreased in subjects treated during follow-up compared with untreated subjects (43.9% versus 73.1% ; OR = 0.29; 95% CI = 0.10-0.83; P = 0.0219). This relationship was not found in subjects whose initial MNA score was greater than 23.5. Conclusion: Our work indicates that AD patients living at home with a caregiver are frequently at risk of undernutrition. Undernourished patients seem to present more rapid aggravation of the disease, but paradoxically, these patients appear to be those who best respond to AChEI treatment.

Key words: Alzheimer's disease, Mini Nutritional Assessment (MNA), acetylcholinesterase inhibitors, undernutrition.

Introduction

The natural history of Alzheimer's disease (AD) is now increasingly well known, thanks to recently published longitudinal studies (1-4). The evolution of nutritional status and its impact on the prognosis of the disease are however less well documented. Ths is an important issue as weight loss is frequently observed (5,6) in clinical practice in AD patients. Weight loss may increase the likelihood of intercurrent diseases, cognitive decline, frailty of the patient and progression to dependence (7). Moreover, it is related to the characteristics of the principal informal caregiver, who if also elderly is at high risk of undernutrition (8-11). It is in addition a risk factor for admission to a retirement home (12). Identification of nutritional problems is all the more important now that we have the means of evaluating, preventing or correcting malnutrition in Alzheimer patients. We have recently demonstrated the efficacy of nutritional management in subjects at risk of malnutrition, who have a Mini Nutritional Assessment (MNA) score less than 23.5 (13).

The study of factors associated with weight loss is today all the more topical as weight loss is one of the main side effects of specific treatment of the disease. It is difficult at the present time to define the profile of those treated patients who are at risk of altered nutritional status and to estimate reliably the impact of these treatments on nutritional status because there are few prospective studies which include precise, objective evaluation of this factor.

Our aim in this work was to determine the impact of nutritional status on the evolution of AD and on response to AchEI treatment by prospective one-year follow-up of a cohort of AD patients living in their own home.

Methods

Recruitment

We collected data on 585 patients with dementia of Alzheimer type, followed prospectively in the Alzheimer

Centre of the Department of Internal Medicine and Clinical Gerontology, Purpan University Hospital, Toulouse. This dynamic follow-up of the cohort included 6-monthly evaluation of patients and of caregiver burden using a standardised protocol. These patients initially presented dementia of Alzheimer type according to DSM-IV and NINCDS-ADRDA criteria (14,15). They had mild to moderate dementia with a Mini-Mental State examination (MMSE) score (16) between 10 and 26, corresponding to stages 3, 4 and 5 of the Global Deterioration Scale (GDS) (17). All patients were mobile, lived at home and had a clearly identified informal caregiver. At inclusion, each patient underwent full investigation including a brain CT scan and thyroid tests, as well as neuropsychological evaluation according to ANAES recommendations (18).

Data collected

The initial evaluation, as well as the six-monthly investigations, were carried out by multidimensional and multidisciplinary methods. Patients underwent clinical, neuropsychological and biological examination. The 6-monthly investigations included:

- recording of sociodemographic data such as age, sex, educational level and living arrangements,
- duration of the problems and time since diagnosis of dementia as declared by the caregiver (initial evaluation only),
- cognitive evaluation by a neuropsychologist using Folstein's MMSE (16),
- the patients' physical disability, evaluated by interview with the family, was quantified on the ADL (19) and IADL scales (20). The ADL scale examines the basic activities of daily living by means of 6 items: continence, feeding, personal hygiene, toileting, dressing and mobility. The IADL scale examines instrumental activities of daily living by means of 8 items: phone use, transportation, shopping, meal preparation, ordinary housework, laundry, managing medication and managing finance.
- the nutritional status of the patients was assessed by anthropometric measurements (weight, height, skinfold thickness, body mass index) and by biological parameters (albumin, prealbumin, CRP). Quantitative assessment of nutritional status was carried out with the Mini Nutritional Assessment or MNA (21). The MNA is at the present time the instrument most widely used for nutritional evaluation in studies in elderly subjects, including those with dementia (13). It is closely correlated with anthropometric and biological nutritional markers and with dietary intake (21).

These evaluations were accompanied by full clinical examination of patients and standard paraclinical investigations. Treatments were carefully recorded at each evaluation, in particular any specific treatment with acetylcholinesterase inhibitors (AChEIs); this was either tacrine for patients included as early as 1994, or donepezil, rivastigmine or galantamine for patients included since 1997. Lastly, the social and familial dimension of the disease was also taken into account by administration to caregivers of the Zarit scale (22).

During follow-up, events which had occurred during the previous 6 months were recorded, in particular hospital admissions (frequency, reasons, duration, circumstances), admissions to institutions (sheltered housing, retirement home, long-stay hospital unit, respite family), use of new support services (day hospitals, day centres, other facilities for temporary accommodation of dependent persons), as well as changes occurring among the patient's relatives (life events, widowhood, departure of the caregiver, moving house...). Withdrawals from the study (deaths, loss to follow-up, wishes of the family or the patient) with the date and reason were also recorded by questionnaire.

We analysed the data concerning the 523 patients who underwent full evaluation of their nutritional status at inclusion.

Statistical analysis

We first compared baseline parameters between well-nourished AD patients (MNA score >23.5, n = 388) and AD patients at risk of malnutrition (MNA score $\leq$ 23.5, n = 135). This analysis uses classic methods (chi-2 test for qualitative variables, analysis of variance for quantitative variables). For each of the modalities of the qualitative variables, the number and frequency are given; for continuous variables, the mean and standard deviation are given (the median and the interquartile space, if relevant). Bivariate analysis was then done to describe the changes at one year in cognitive and non-cognitive parameters according to baseline MNA score. Wilcoxon's non-parametric test was used for quantitative variables and the McNemar test for qualitative variables in each MNA group (well-nourished group and group at risk of undernutrition). The Kruskall-Wallis test was used to compare changes in the parameters between the two groups.

In order to study the potential effect of AChEIs, we took into consideration treatment at 6 months and defined the treatment variable as follows: " 0 exposure = not treated ", " 1 exposure = treated at one timepoint during follow-up ", " 2 exposures = treated at 2 timepoints during follow-up ", " 3 exposures = treated at 3 consecutive timepoints (during the whole year of follow-up) ".

Results

Table 1 shows patient characteristics at inclusion according to nutritional status. The subjects at greater risk of undernutrition (MNA score $\leq$ 23.5) were older and thinner than those with satisfactory nutritional status. Concerning cognitive function, the MMSE score was globally equivalent in the two groups. We also found an increased risk of undernutrition according to 1/ patient gender: 14% of men had a MNA score

<= 23.5 compared with 31.5% of women (p<0.0001), and 2/ caregiver status: the frequency of patients with an MNA <= 23.5 was significantly higher in patients living with an adult child (30.4%) than in those living with their spouse (19.8%) (P = 0.0107). Lastly, we observed higher mean scores on the Zarit scale, at the limit of significance, in caregivers of patients at risk of undernutrition compared with those of well-nourished subjects (25.3 ± 16.7 versus 28.7 ± 15.9, P = 0.0529).

Table 1
Comparison of Patient Characteristics at Inclusion according to Nutritional Status (n = 523)

Baseline parameters	MNA score at baseline		
	> 23.5 mean ± SD	≤23.5 mean ± SD	P Student
Age (years)	75.46 ± 6.60 n = 388	77.15 ± 5.96 n = 134	0.0091
Body weight (Kg)	64.55 ± 11.12 n = 388	53.47 ± 12.07 n = 134	<0.0001
BMI (Kg/m2)	25.56 ± 3.48 n = 388	22.03 ± 4.07 n = 133	<0.0001
MMS score	19.21 ± 5.45 n = 387	19.14 ± 4.75 n = 134	0.8908
ADL score	5.51 ± 0.79 n = 388	5.48 ± 0.86 n = 135	0.6596
IADL self-maintenance (dependence)	4.60 ± 1.66 n = 385	4.31 ± 1.71 n = 134	0.0373
IADL score	4.61 ± 2.16 n = 258	4.46 ± 2.05 n = 109	0.4834
Zarit score	25.32 ± 16.70 n = 326	28.68 ± 15.94 n = 111	0.0529

Four hundred and two patients were reevaluated at one year. Analysis of evolution of cognitive and non-cognitive function at one year showed that cognitive decline, assessed by the MMSE, was significantly greater in subjects who presented at inclusion an MNA score of 23.5 or less compared with those whose score was greater than 23.5 (D MMSE: -3.19 ± 3.56 versus –2.07 ± 3.79; P = 0.0104) (Table 2). We also observed in these patients more marked deterioration of their ability to perform the activities of daily living (D ADL: -0.78 ± 1.19 versus –0.55 ± 1.00; P = 0.0523). Subjects at risk of undernutrition were more likely to present a rapid decline on the MMSE (53.6%) than well-nourished subjects (43.2%) (P = 0.07). Similarly, increased dependence at one year was more frequently observed in subjects at risk of undernutrition at inclusion (57.7% versus 44.4%, P = 0.0219). Lastly, admission to a retirement home at one year also tended to be higher in subjects at risk of undernutrition at inclusion, but this result was not statistically significant (12.6% versus 7%; OR = 1.93, 95% CI: 0.91-4.08; P = 0.082).

Table 3 shows the cognitive evolution at one year of patients treated with AChEI during the year and of untreated patients, according to their initial MNA score. Among the untreated subjects at risk of undernutrition at inclusion (n = 19), 73.1% lost 3 points or more on the MMSE in one year compared with 48.8% of untreated subjects whose MNA was greater than 23.5 at inclusion (n = 52). Among the subjects with an MNA score of 23.5 or less at inclusion, the risk of rapid loss on the MMSE was significantly decreased in those treated throughout the duration of follow-up compared with those who were not (OR = 0.29; 95% CI: 0.10-0.83; P = 0.0219). This relationship was not found in treated subjects with an MNA score above 23.5 at inclusion. The beneficial effect of AChEI treatment on cognitive function does not therefore seem to be affected by the patient's nutritional status at inclusion. Subjects at risk of undernutrition appeared to respond better to AChEI treatment than well-nourished subjects. In order to confirm the impact of nutritional status on response to AChEI treatment, we also studied the evolution of cognitive function at one year according to plasma albumin levels at inclusion and the number of exposures to treatment during follow-up (Table 4). Similarly, we found a decreased risk of rapid loss on the MMSE in one year in subjects treated for one year who were at risk of

Table 2
Evolution of Patient Characteristics at One Year according to Nutritional Status (MNA Score) at Inclusion (n = 402)

Baseline MNA score	Parameters studied	n	Difference between baseline and one year	P Wilcoxon	P Kruskal - Wallis
> 23.5: well-nourished	MMS score	303	-2.07 ± 3.79	<0.0001	0.0104
≤ 23.5: risk of undernutrition		97	-3.19 ± 3.56	<0.0001	
> 23.5: well-nourished	Body weight (kg)	305	-0.22 ± 6.76	0.3301	0.1161
≤ 23.5: risk of undernutrition		97	1.85 ± 9.08	0.2709	
> 23.5: well-nourished	BMI (kg/m2)	305	-0.07 ± 1.81	0.3642	0.2181
≤ 23.5: risk of undernutrition		97	0.26 ± 1.82	0.4409	
> 23.5: well-nourished	ADL score	302	-0.55 ± 1.00	<0.0001	0.0523
≤ 23.5: risk of undernutrition		97	-0.78 ± 1.19	<0.0001	
> 23.5: well-nourished	IADL score	160	-1.08 ± 1.45	<0.0001	0.1464
≤ 23.5: risk of undernutrition		61	-1.41 ± 1.78	<0.0001	
> 23.5: well-nourished	Zarit score	193	4.65 ± 14.68	<0.0001	0.5873
≤ 23.5: risk of undernutrition		58	3.43 ± 13.00	0.0374	
> 23.5: well-nourished	MNA score	255	-1.15 ± 2.28	<0.0001	<0.0001
≤ 23.5: risk of undernutrition		78	1.43 ± 3.02	<0.0001	

Table 3
Response to AChEI Treatment according to Nutritional Status measured by the MNA

Baseline MNA score **MNA ≤ 23.5 = risk of undernutrition**	**Loss of 3 or more MMSE points in one year**			
	yes n (%)	P (χ^2)	OR	95% CI
Number of exposures to AChEI treatment, n = 93		0.1246		
0 exposure, n = 26	19 (73.08)	-	1	-
1 exposure, n = 6	3 (50.00)	0.2822	0.37	0.06-2.27
2 exposures, n = 20	10 (50.00)	0.1123	0.37	0.11-1.26
3 exposures, n = 41	18 (43.90)	0.0219	0.29	0.10-0.83
MNA score at baseline **MNA > 23.5 = well nourished**	**Loss of 3 or more MMSE points in one year**			
	yes n (%)	P (χ^2)	OR	95% CI
Number of exposures to AChEI treatment, n= 296		0.4738		
0 exposure, n = 52	25 (48.08)	-	1	-
1 exposure, n = 28	14 (50.00)	0.8696	1.08	0.43-2.71
2 exposures, n = 68	31 (45.59)	0.7866	0.90	0.44-1.87
3 exposures, n = 148	57 (38.51)	0.2290	0.68	0.36-1.28

Table 4
Response to AChEI Treatment according to Plasma Albumin Level at Inclusion

Baseline: **Albumin <44 g/l**	**Loss of 3 or more MMSE points in one year**			
	yes **n (%)**	**P (χ^2)**	**OR**	**95% CI**
Number of exposures to AChEI treatment, n = 138		0.0738		
0 exposure, n = 50	33 (66.00)	-	1	-
1 exposure, n = 15	9 (60.00)	0.6704	0.77	0.24-2.53
2 exposures, n = 39	19 (48.72)	0.1024	0.49	0.21-1.15
3 exposures, n = 34	13 (38.24)	0.0134	0.32	0.13-0.79
Baseline: **Albumin ≥ 44 g/l**	**Loss of 3 or more MMSE points in one year**			
	yes **n (%)**	**P (χ^2)**	**OR**	**95% CI**
Number of exposures to AChEI treatment, n = 139		0.8430		
0 exposure, n = 59	31 (52.54)	-	1	-
1 exposure, n = 20	10 (50.00)	0.8441	0.90	0.33-2.49
2 exposures, n = 43	20 (46.51)	0.5477	0.78	0.36-1.73
3 exposures, n = 17	10 (58.82)	0.6475	1.29	0.43-3.85

undernutrition at inclusion and had albumin levels below 44 g/l (P = 0.0134; OR = 0.32; 95% CI: 0.13-0.79). This relationship was not found in treated subjects with an albumin level of 44 g/l or higher at inclusion.

Lastly, we found no increased risk of weight loss at one year in subjects at risk of undernutrition at inclusion and treated with AChEI during follow-up compared with well-nourished subjects (23.8% versus 19.6%, P = 0.55). The at-risk subjects tended rather to gain weight (+ 1.73 ± 8.96%) during follow-up.

Discussion

This study clearly shows in a large cohort the frequency, importance and consequences of poor nutritional status in

patients with Alzheimer's disease. The fact that nutritional status was not taken into account could be at the origin of the divergent results found in certain studies (23-26).

In our study, at inclusion 25% of patients presented a risk of undernutrition. This risk was increased in older female patients whose informal caregiver was a person other than their spouse. On the other hand, the risk of undernutrition did not seem to be related to cognitive impairment as measured by the MMSE. These findings suggest that it is mainly the capacities of those close to the patient and the quality of management that enable the maintenance or otherwise of patients' nutritional status during the course of the disease. Deterioration of nutritional status is accompanied by lower dietary intake, and in particular by altered vitamin and mineral status which, as is suggested by the data in the literature, play an important role in neurocognitive function (27, 28). Earlier works have also shown that the MNA score was correlated not only with dietary intake, but also with biological and protein markers (13).

At the present time, it is of even greater concern to identify nutritional problems as we now have the means to prevent or even to correct malnutrition in Alzheimer's patients, such as in particular the use of home helps and meal delivery services or the prescription of nutritional supplements, whose efficacy has recently been demonstrated (13). As our possibilities of intervention in the other aspects of AD are still limited, the value of nutritional management should not be neglected. This is particularly important as we observed in our study greater cognitive decline in patients initially at risk of undernutrition, as well as increased risk of admission to an institution. Paradoxically however, these subjects appear to respond better to AChEI treatment. Compared with untreated subjects at risk of undernutrition, about 30% fewer treated at-risk subjects presented rapid loss of cognitive function (loss of 3 or more points on the MMSE in one year). This result is clinically significant. One explanation could be that as natural decline is more marked in the group of undernourished patients, the impact of treatment is more evident than in a group of patients who would naturally show less deterioration. Another explanation could be that the treatment is more effective in patients with low albumin levels, as we have seen, since a greater amount of AChEI may not be bound to the carrier albumin and may therefore be more active.

In conclusion, our study demonstrates that the risk of undernutrition is frequent in patients with Alzheimer's disease living in their own home with a caregiver. Undernourished patients appear to deteriorate more rapidly, but, paradoxically, they also seem to respond better to AChEI treatment.

Like those who are not at risk, Alzheimer patients at risk of undernutrition should therefore receive AchEI treatment, especially as we did not observe increased weight loss in these patients, but rather a tendency to gain weight (26). In the light of these findings, identification and both therapeutic and nutritional management of these patients are shown to be warranted. This opportunity to improve their prognosis should not be missed.

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