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ORIGINAL INVESTIGATION

Effectiveness of a specific nutritional supplement on cognitive, behavioral and functional symptoms in mild cognitive impairment and Alzheimer's dementia: caregivers judgments. Results of an observational survey

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Background and aims. Caregivers play a central role in the evaluation of symptoms in mild cognitive impairment (MCI) and dementia, and in clinical practice their opinion is important in the definition of the effectiveness of pharmacological and not pharmacological intervention.
With the aim to explore the impact of a nutritional intervention by the use of a medical food on quality of life, cognitive and functional outcomes in large populations of Alzheimer's dementia (AD) and MCI subjects, we performed an observational survey (the MEMENTO study).
Methods. The study was carried out in 30 Italian outpatients clinics, based on patient and caregiver judgment.
Results. Five hundred patients (58.8% female, mean age 75.9 ± 7.1 SD) were included in the survey. The results confirmed the data from RCT about the effectiveness of dietary supplementation with a medical food on cognitive symptoms of AD and MCI and also the effectiveness on behavioral and functional deficits. In particular, the effectiveness was more evident in patients with higher MMSE score, and in MCI compared to AD. Interestingly, caregivers of MCI subjects reported better results than those of AD patients only in cognitive and functional domains but not in behavioral domain.
Conclusions. The study uses for the first time the subjective judgment of patients and caregivers as an outcome measure, by focusing on the cognitive aspects, and on functional status and behavior.

Key words: Nutritional supplement, Mild cognitive impairment, Alzheimer disease, Caregivers

INTRODUCTION

Several epidemiological and observational studies suggest that dietary habits, as well as physical and mental activity, and chronic diseases (e.g. hypertension, cardiovascular disease, diabetes mellitus and metabolic syndrome), are associated with cognitive impairment and increased risk of dementia [1 2]. Specific dietary pattern, and in particular, the so-called "Mediterranean diet", characterized by the presence of fruit and vegetable, olive oil, fish, low animal fats, high content of vitamin C and vitamin E, is associated with a lower risk of developing Alzheimer's disease (AD) and cognitive impairment [3 4], lower progression from mild cognitive impairment (MCI) to dementia [5] and better cognitive performances in the elderly [6]. These evidences are supported by epidemiological data, showing that in healthy elderly subjects, elevated plasma levels of vitamin B (B1, B2, B6, folate, B12), C, D, and E, and higher levels of fatty acids ω-3, are associated with better cognitive

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performance and less brain atrophy on cerebral magnetic resonance imaging (MRI) [7].

Although epidemiological data are broadly in agreement, the studies that evaluated the efficacy of dietary supplements (vitamins or nutritional elements) on cognitive functions reported contrasting results: supplementation with high doses of vitamin B does not slow cognitive decline in healthy subjects and AD patients [8 9]; the addition of polyunsaturated fatty acids does not slow the decline in AD, except in very mild stages [10]; vitamin E supplements in patients with cognitive impairment determines limited benefit on slowing the progression of AD [11 12] but no benefit in MCI patients [13]. Even the use of a combination of antioxidant substances did not produced positive results; a mixture of vitamin E, C, α-lipoic acid, coenzyme Q has even shown an acceleration of the cognitive decline in people with AD [14].

The reasons for these unsatisfactory results may be various: insufficient doses or short duration of treatment, the advanced stage of the disease, or the need to combine different nutrient acting synergically against the pathophysiological process of neurodegeneration.

Recent randomized controlled clinical trials demonstrate that a dietary supplementation with a specific combination of nutrients (docosaexhexaenoic acid, eicosapentaenoic acide, uridine monophosphate and choline as precursors required to enhance neuronal membrane formation and B-vitamins, vitamin C, E, selenium and phospholipids as cofactors by enhancing the bioavailability of those precursors) improves memory complaints in patients with mild AD: subjects treated with dietary supplementation had better verbal memory performance than controls after 12 weeks of treatment [15] and best global memory after 24 weeks of treatment [16]. The impact of the use of specific nutritional supplement on quality of life, and on cognitive and functional outcomes in large populations have not yet evaluated, as well as the judgment of the caregiver. These points of view are important because provide a measure of the impact of objective improvements assessed in randomized trials on the personal dimension of the disease on both patient and caregivers [17]. Caregiver judgment is rarely considered in the definition of the effectiveness of treatment for AD, although in the "real world" the opinion of caregivers is important in collecting patient's clinical history and definition of cognitive, functional and behavioral changes holding treatment, and the opinion of patients considered only as "secondary outcomes" although studies demonstrated that, in the mild moderate stages of the disease, AD patients provide a reliable judgement of their cognitive and functional status [18].

For these reasons we performed an observational survey (the MEMENTO study) with the aim to collect patient and caregiver judgment about changes in cognitive, behavioral and functional domains after a nutritional intervention.

MATERIALS AND METHODS

The MEMENTO study was conducted in 30 Italian outpatients clinics specifically devoted to the evaluation and treatment of Alzheimer's disease and other types of dementia (Alzheimer Evaluation Units) [19]. We used a medical food (containing a specific nutrient combination named Fortasyn Connect) [20] in addition to standard treatment in MCI and mild AD subjects. The diagnosis was made using standard criteria and shared protocols [21]. Subjects receiving nutritional treatment were evaluated at baseline using standard protocols and at the follow-up visit (usually after 3 or 6 months) using in addition to usual assessment instruments a structured interview to explore modification of cognitive, behavioural and functional domains in "real life" situations [22]. Data were collected anonymously.

The survey was carried out from June 2013 to March 2014.

Collection of clinical data

Patients and caregivers judgment about changes in cognitive, behavioral and functional domains at follow-up visit after the assumption of the medical food supplement were collected by means of a 14-items clinical structured interview designed for the study, administered to the patient and to the caregiver, exploring cognitive, behavioral and functional domains in "real life" situations (Tab. I). The answers of each item were standardized using a hierarchical scale (from 1, worsened, to 5, improved). A single domain score and a global score were calculated for the analysis. Each variable was scored on the basis of the clinical judgment: 1 point was given for "worsened", 2 points for "slightly worsened", 3 points for "unchanged", 4 points for "slightly improved" and 5 points for "improved".

For the caregiver variables specific indices were obtained by summing up the score of single variables: 1) "cognitive index" (sum of the score of "memory for appointments", "memory for name of people" and "orientation"; 2) "functional index" (sum of the score of "domestic activities", "outside activities" and "reading"; 3) "behavioral index" (sum of score of "apathy", "agitation", "sleep disturbances" and "feeding behavior". A "patient index" was calculated by summing the score of all patient variables ("memory", "orientation", "activities" and "mood"). A "global index" was obtained from the sum of all caregivers and patients variables.

The interview scale was fielded twice (the second after

Table I. Variables investigated in the structured interview used to explore the modification of cognitive, behavioral and functional domains in a 'real life' situation.

Domain	Caregiver interview	Patient interview
Cognition	Remember appointments/commitments/dates Identify persons/remember names Orientation in new places	Subjective memory Orientation in and out home
Behavior	Apathy/loss of interest Agitation/irritability Sleep disturbances Eating behavior	Depression complain
Function	Household activities/hobbies Outdoor activities Reading books/newspaper	Household activities/hobbies

two weeks by the same researcher) in a sample of 30 patients (60% female, mean age was 77.5 ± 7.5) and their caregivers. The internal consistency reliability (Cronbach's alpha coefficient) was good for both patient (0.86) and caregiver (0.83) report. Pearson correlation coefficient for the two-week retest was 0.78 ($p < .001$) for patients and 0.76 ($p < .001$) for caregivers.

Statistical analysis

Differences among groups (AD and MCI) were measured by means of chi-square for categorical variables and unpaired student t-test for continuous variables. The linear dependence between two variables was assessed by determining Pearson's correlation coefficient 'r' values. The level of statistical significance was defined as $p < 0.05$.

RESULTS

Five hundred patients (58.8% female, mean age 75.9 ± 7.1 SD) were included in the survey. The subjects received nutritional supplement for an average of 4 months with a range from 1 to 12 months. The majority of the subjects were suffering from AD (45.2%) or MCI (33.8%), the remaining patients had other forms of cognitive impairment (i.e.: vascular cognitive decline, Lewy body dementia, fronto temporal dementia). The mean baseline MMSE of the whole sample was 21.8 ± 4.6 SD; in 144 (28.8%) patients MMSE score was greater than 24, in 276 (55.2%) between 18 and 24 and in 80 (16%) less than 18. Only 27 subjects (5.4% of the sample) symptoms of intolerance were reported, mainly diarrhea and nausea; 112 patients (22.4%) completed the treatment period but reported difficulties related to the cost of treatment.

Concomitant medications were: acetylcholinesterase inhibitors (32%), memantine (14.4%), antidepressants (29.2%) and nootropic drugs (8.4%).

Table II shows the results of patients and caregivers interview in the whole sample. From 28.6% to 49.6% of caregivers provided a positive judgment on the effectiveness of the treatment (slightly improved/improved); apathy and memory about appointments are the variables with higher frequency of positive judgment; orientation and sleeping disturbances showed less relevant improvement. From 36.2% to 46.2% of patients provide a positive judgment (maximum for memory and mood, minimum for orientation and activities).

To explore more deeply the relationship between severity of disease and response to treatment a comparison between AD (n = 226) and MCI (n = 169) subjects was performed. The groups did not differ for mean age (MCI: 75 years ± 7.1 SD; AD: 76.2 years ± 6.9 SD); MCI subjects had a significantly higher MMSE mean score than AD patients (MCI: 24.6 ± 2.9 SD; AD: 19.9 ± 4.6 SD; $F = 23.5$, $p < 0.0001$).

The efficacy judgments were then grouped into three levels: 1 = worsened (including the judgments "slightly worsened" and "worsened"); 2 = unchanged (including the judgment "unchanged"); 3 = improved (including the judgment "slightly improved" and "improved") and the results in MCI and AD compared (see Table III). Caregivers of MCI patients reported better positive judgments of effectiveness compared to caregivers of AD patients, with statistically significant differences for the items exploring household activities ($p = 0.005$), memory for appointments ($p = 0.002$), remember person's name ($p = 0.023$) and orientation in new places ($p = 0.023$). Patients with MCI reported a better positive judgment for subjective memory ($p = 0.017$).

Table IV shows linear correlations among efficacy indices, months of treatment, age of patients, basal MMSE scores, follow-up MMSE scores and delta MMSE scores (difference between MMSE at follow-up and MMSE at baseline). All clinical indices were positively correlated with months of treatment and delta MMSE and inversely correlated with age of patients. The score of MMSE,

Table II. Distribution of the efficacy judgment of nutritional supplement treatment by caregivers and patients. Data obtained in the whole sample.

	Worsened n (%)	Slightly worsened n (%)	Unchanged n (%)	Slightly improved n (%)	Improved n (%)
Caregivers interview					
Apathy	0 (0)	31 (6.2)	221 (44.2)	202 (40.4)	46 (9.2)
Agitation	0 (0)	40 (8.0)	300 (60.0)	136 (27.2)	24 (4.8)
Sleep disturbances	0 (0)	24 (4.8)	327 (65.4)	129 (25.8)	20 (4.0)
Feeding behavior	0 (0)	22 (4.4)	310 (62.0)	146 (29.2)	22 (4.4)
Domestic activities	1 (0.2)	36 (7.2)	249 (49.8)	183 (36.6)	31 (6.2)
Outside activities	1 (0.2)	30 (6.0)	288 (57.6)	161 (32.2)	20 (4.0)
Reading	2 (0.4)	34 (6.8)	302 (60.4)	140 (28.0)	22 (4.4)
Memory for appointments	6 (1.2)	41 (8.2)	235 (47.0)	185 (37.0)	33 (6.6)
Memory for name of peole	3 (0.6)	32 (6.4)	271 (54.2)	168 (33.6)	26 (5.2)
Orientation	1 (0.2)	38 (7.6)	318 (63.6)	129 (25.8)	14 (2.8)
Patients interview					
Memory	1 (0.2)	32 (6.4)	236 (47.2)	203 (40.6)	28 (5.6)
Orientation	1 (0.2)	18 (3.6)	294 (58.8)	166 (33.2)	21 (4.2)
Activities	0 (0)	25 (5.0)	294 (58.8)	166 (33.2)	15 (3.0)
Mood	1 (0.2)	26 (5.2)	246 (49.2)	196 (39.2)	31 (6.2)

Table III. Comparison between MCI and AD group (caregivers and patients efficacy judgment).

	MCI			AD			X^2	p
	Worsened n (%)	Unchanged n (%)	Improved n (%)	Worsened n (%)	Unchanged n (%)	Improved n (%)		
Caregivers interview								
Apathy	6 (3.6)	69 (40.8)	94 (55.6)	19 (8.4)	102 (45.1)	105 (46.5)	5.628	0.060
Agitation	11 (6.5)	101 (59.8)	57 (33.7)	26 (11.5)	130 (57.5)	70 (31)	2.887	0.236
Sleep disturbances	9 (5.3)	112 (66.3)	48 (28.4)	12 (5.3)	146 (64.6)	68 (30.1)	0.135	0.935
Eating behavior	7 (4.1)	110 (65.1)	52 (30.8)	10 (4.4)	136 (60.2)	80 (35.4)	1.013	0.603
Household activities	6 (3.6)	83 (49.1)	80 (47.3)	29 (12.8)	107 (47.3)	90 (39.8)	10.732	0.005*
Outdoor activities	10 (5.9)	90 (53.3)	69 (40.8)	18 (8)	137 (60.6)	71 (31.4)	3.901	0.142
Reading	10 (5.9)	102 (60.4)	57 (33.7)	19 (8.4)	129 (57.1)	78 (34.5)	1.011	0.603
Memory for appointments	9 (5.3)	72 (42.6)	88 (52.1)	34 (15)	104 (46)	88 (38.9)	12.386	0.002*
Remember persons name	6 (3.6)	89 (52.7)	74 (43.8)	24 (10.6)	119 (52.7)	83 (36.7)	7.575	0.023*
Orientation	8 (4.7)	108 (63.9)	53 (31.4)	29 (12.8)	135 (59.7)	62 (27.4)	7.555	0.023*
Patients interview								
Memory	9 (5.3)	68 (40.2)	92 (54.4)	22 (9.7)	112 (49.6)	92 (40.7)	8.152	0.017*
Orientation	5 (3)	98 (58)	66 (39.1)	12 (5.3)	127 (56.2)	87 (38.5)	1.304	0.521
Activities	6 (3.6)	99 (58.6)	64 (37.9)	14 (6.2)	133 (58.8)	79 (35)	1.563	0.458
Mood	7 (4.1)	85 (50.3)	77 (45.6)	15 (6.6)	106 (46.9)	105 (46.5)	1.328	0.515

MCI: mild cognitive impairment; AD: Alzheimer's disease; * statistically significant difference between AD and MCI group

at follow-up visit was positively correlated with clinical indices except for caregiver behavioral index.

Among symptoms belonging to the behavioral index, we performed a sub-analysis exploring the correlation between the symptom "apathy" and MMSE follow-up scores: a correlation between the two variables was

Table IV. Correlations among efficacy indices and clinical variables in the whole group of MCI and AD patients.

	Months of treatment	Age of patient	MMSE at baseline	MMSE at follow-up	Δ MMSE (MMSE at follow-up – MMSE at baseline)
Cognitive index – caregiver	r = 0.181 p < 0.0001*	r = -0.209 p < 0.0001*	r = 0.064 p = 0.205	r = 0.226 p < 0.0001*	r = 0.371 p < 0.0001*
Functional index – caregiver	r = 0.183 p < 0.0001*	r = -0.162 p = 0.001*	r = 0.059 p = 0.240	r = 0.196 p < 0.0001*	r = 0.312 p < 0.0001*
Behavioral index - caregiver	r = 0.135 p = 0.007*	r = -0.114 p = 0.024*	r = 0.064 p = 0.205	r = 0.071 p = 0.160	r = 0.305 p = 0.0001*
Patient index	r = 0.183 p < 0.0001*	r = -0.182 p <0.0001*	r = 0.054 p = 0.282	r = 0.209 p < 0.0001*	r = 0.354 p < 0.0001*
Global index	r = 0.195 p < 0.0001*	r = -0.190 p < 0.0001*	r = 0.030 p = 0.556	r = 0.198 p < 0.0001*	r = 0.383 p < 0.0001*

R: Pearson's correlation; * statistically significant

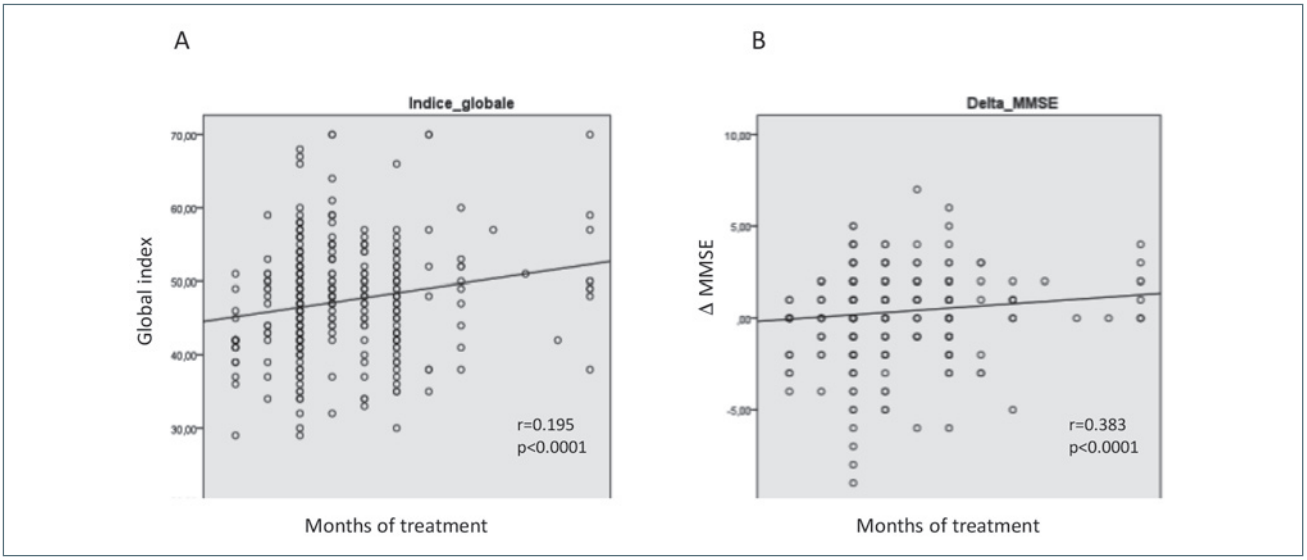

Figure 1. Relationship among global index (figure A) and delta MMSE (figure B) in MCI and AD patients.

found (r = 0.147, p = 0.003); on the contrary no correlation between MMSE baseline score and clinical indices was found.

Figure 1 shows the correlation between the duration of treatment and the response to treatment (the global index of efficacy) (r = 0.195; p < 0.0001; Figure A) and the delta MMSE score (r = 0.383; p = 0.0001; Figure B) in the whole group of MCI and AD patients.

DISCUSSION

The role of nutritional factors for the prevention and for the treatment of neurodegenerative diseases is based on biological observation, and confirmed by epidemiological and clinical data.

In recent years products containing substances with mutually reinforcing actions on mechanisms underlying cognitive impairment have been developed and evidences of efficacy in AD and MCI were demonstrated [22]. A medical nutrition containing a specific nutrient combination (Fortasyn Connect) designed to support synapse formation, demonstrated efficacy on memory deficit in mild AD subjects in RCT [23].

With the aim to evaluate the effectiveness of this medical food in clinical practice, we explored the opinion of patients and caregivers in a "real world" situation. Our survey was based on a questionnaire administered to caregivers and patients during a clinical interview with the aim of investigating those cognitive, behavioral and functional symptoms that are most prevalent in MCI and mild AD (i.e. cognitive: episodic memory and orientation; behavioral: apathy, sleep disorders and depression; functional: instrumental activities of daily living) [24-26].

Caregivers of patients with dementia have to perform many different tasks and roles as the disease

progresses and frequently experiment stress and physical and emotional burden and their involvement in the care plan of patients is fundamental in all the stages of the disease. Family caregivers are central to the assessment and care of the patient with dementia and establishing and maintaining collaboration with caregivers is critical for care of the patient [27]. For these reasons in our survey we evaluated caregivers judgment in the assessment of the modification of cognitive, behavioral symptoms of dementia and functional status after a not pharmacological intervention (supplementation of diet with a medical food).

Recent studies demonstrated that patients with dementia may evaluate properly their symptoms of cognitive decline and gathering information from both patients and caregivers may be considered an ameliorative element for the interpretation of dementia progression, since the two sources of information increase the quality of evaluation [28 29].

In our survey we analyze caregiver and subjects judgment about the evolution on cognitive, behavior and functional symptoms after a nutritional intervention and found three important clinical results: 1) both patients and caregivers provided an overall positive opinion about the effectiveness of the dietary supplementation on cognitive, behavioral and functional domains explored using "real life" situations; 2) the level of satisfaction was higher for patients with higher MMSE score and in those with MCI compared to AD, and 3) patients with higher duration of treatment reported higher benefit from the treatment.

Our survey also demonstrated that the medical food is well tolerated in clinical practice (only 6.5% of patients discontinued) confirming data from RCT.

Our results confirmed the data from RCT about the effectiveness of this nutraceutical product on cognitive symptoms of AD and MCI and also the effectiveness on behavioral and functional deficits. In particular, the effectiveness was more evident in patients with higher MMSE score, and in MCI compared to AD, as demonstrated in clinical trials. Interestingly, caregivers of MCI subjects reported better results than those of AD patients only in cognitive and functional domains but not in behavioral domain. Among symptoms included in behavioral domain, we analyzed the symptom "apathy" alone due to its higher prevalence in MCI and mild AD patients and the role as risk factor for conversion from MCI to dementia [30 31]. As we expected, differently from other behavioral symptoms, apathy improvement was strictly correlated with MMSE score, with better results in subject with higher MMSE scores.

An important aspect is represented by the fact that the supplementation was significantly more effective if administered in the earliest stages of the disease (MMSE greater) and for a longer duration of treatment (number of months).

The study uses for the first time the subjective judgment of patients and caregivers as an outcome measure, by focusing not only on the cognitive aspects, but also on functional status and behavior. It is interesting to observe that apathy, together with memory, is the neuropsychiatric symptoms that most improves in our investigation.

One possible explanation for results reported in this study is that in Alzheimer's disease the synaptic damage is the pathogenic element mostly correlated with the extent of cognitive decline [32]. In the course of a neurodegenerative disease, characterized by a progressive extent and spread of the synaptic damage, a product able to increase the synthesis of synaptic membrane precursors has a greater likelihood of effectiveness and consequently clinical evidence when administered in the earliest stages of the disease.

The study has limitations due to the observational design and to the lack of a control group. The strength of the study is that the results have been obtained in the real world; they should be read together with those derived from randomized trials to confirm the therapeutic role of a medical food in subjects affected by MCI or AD.

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Conflict of Interest

The authors declare no conflicts of interest.

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