Journal of the Neurological Sciences 288 (2010) 112–116

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Effects of insulinic therapy on cognitive impairment in patients with Alzheimer disease and Diabetes Mellitus type-2

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ARTICLE INFO

Article history:
Received 8 July 2009
Received in revised form 23 September 2009
Accepted 23 September 2009

Keywords:
Alzheimer disease
Dementia and Diabetes Mellitus
Insulin therapy
Risk of dementia
Antidiabetic oral medications

ABSTRACT

Background: Type-2 Diabetes Mellitus (DM-2) is an important risk factor for Alzheimer disease (AD) and vascular dementia (VD). The role of insulinic therapy on cognitive decline is controversial.
Objective: To evaluate cognitive impairment in patients with AD and DM-2 treated with either oral antidiabetic drugs or combination of insulin with other diabetes medications.
Methods: 104 patients with mild-to-moderate AD and DM-2 were divided into two groups, according to antidiabetic pharmacotherapy: group A, patients treated with oral antidiabetic drugs and group B, patients treated with insulin combined with other oral antidiabetic medications. Cognitive functions were assessed by the Mini Mental State Examination (MMSE) and the Clinician's Global Impression (CGI), with a follow-up of 12 months.
Results: At the end of the study, the MMSE scores showed a significant worsening in 56.5% patients of group A and in 23.2% patients of group B, compared to baseline MMSE scores ($P=.001$). Also CGI-C scores showed a significant worsening for all domains after 12 months in group A vs group B ($P=.001$). The two groups were matched for body mass index, serum lipids, triglycerides, Apo ε4 allele and smoke habit. Conversely, ischemic heart disease and hypertension were significantly higher in group B ($P=.002$). After adjustment for this risk variables, our results remained significant ($P=.001$).
Conclusions: Our study suggests that insulinic therapy could be effective in slowing cognitive decline in patients with AD.

1. Introduction

Population-based longitudinal studies have shown that the risk of vascular dementia (VD) and Alzheimer disease (AD) is increased in patients with Diabetes Mellitus (DM) [1–3]. Both dementia and diabetes are complex disorders related to age and lifestyle. Epidemiological and clinical studies report that environmental factors, such as birth weight and childhood socioeconomic level, can play a role in the development of diabetes as well as dementia [4]. Moreover, most diabetic patients have insulin resistance (IR) that is associated with compensatory hyperinsulinemia, one of the mechanisms suggested to explain the increased AD risk in diabetic patients [5]. In addition metabolic syndrome, a clustering of interrelated metabolic risk factor such as diabetes, obesity, and hypertension, has been linked to cognitive decline [6]. Evidence from genetic and epidemiological studies indicate that genetic and environmental factors may interact to affect the association between diabetes and dementia during life course [7]. A recent study suggests that the combination of insulin with other antidiabetic medications is associated to a substantially lower neuritic plaque density in several areas of AD brains [8]. To our knowledge, data about the role of antidiabetic therapies on cognitive decline in AD are lacking.

In our study we evaluate the effect of antidiabetic therapy on cognitive impairment in patients with type 2 DM (DM-2) and AD.

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doi:10.1016/j.jns.2009.09.022

2. Methods

2.1. Patients and ethical committee approval

After a complete description of the study all patients gave their informed consent, in accordance with the official standards of the 1964 declaration of Helsinki, local laws and regulations. The study was approved by the Ethical Committee of "S. Giovanni di Dio" Hospital, Crotone, Italy. Between May 2004 and February 2008 we recruited prospectively 104 patients (57 women and 47 men), with mild-to-moderate AD associated with DM-2, according to the current DSM-IV criteria [9]. Differential diagnoses were made according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's disease and Related Disorders Association International pour la Recherché et l'Enseignement en Neurosciences criteria for vascular dementia [10]. We defined DM as the documented use of insulin or an oral hypoglycemic drug or a casual (nonfasting) plasma glucose level greater than or equal to 200 mg/dl (11.1 mmol/l), recorded at the 16th biennial examination or at an earlier examination [11]. We excluded subjects with documented evidence of known cause of dementia, such as: *a.* history of psychiatric disease and/or behaviour disorders; *b.* tumour and/or vascular disease; *c.* toxic or pharmacological exposure, alcohol overuse, coexisting medical conditions associated with cognitive impairment (e.g. disthyroidism, human immunodeficiency virus and/or other active infections); *d.* abnormal results on blood tests including electrolytes, renal and hepatic function, B12 and folic levels, serum protein electrophoresis with serum immunofixation, autoimmune and infective screening; *e.* hydrocephalus; *f.* extrapyramidal disease. Enrolled patients were divided into two groups, according to their current therapies:

- *Group A*; mild-to-moderate AD with DM, treated with oral antidiabetic medication (49 patients);
- *Group B*; mild-to-moderate AD with DM, treated at the same time with insulin and oral antidiabetic medications (55 patients).

2.2. Clinical evaluation

After a first-level check-up carried out by a neurologist, or a geriatrician or a psychiatrist, patients underwent the following tests: neuroimaging studies (CT scans or MRI) and neuropsychological assessment. History of DM-2 was ascertained by patient self-reports or by antidiabetic medication use at baseline and during follow-up visits. Recorded medical data included demographic information (age, sex), educational level, health and behaviour status, common disease and body mass index (BMI). Heart disease and smoking habit were defined by self-reports. Heart disease included a history of ischemic heart disease and hypertension. To rule out potentially reversible causes of cognitive impairment, laboratory tests were performed, including: thyroid function, complete blood count, blood chemistry, folic acid and vitamin B12 level, blood lipid profile, and syphilis tests (Table 1). APO E allelic status was determined at baseline, following a standard procedure [12], using genomic DNA prepared from peripheral blood samples. A pattern comprising one, or predominantly two, ε4 alleles has been suggested to be associated with AD. In this study, the variable APO E was dichotomous, as the presence or absence of ε4 allele.

2.3. Neuropsychological assessment

Cognitive function was evaluated using the Folstein Mini Mental State Examination (MMSE) [13]. This was administered at baseline, at 6 and 12 months (end of the study). A global measure included a comprehensive assessment at each visit. A variety of domains of cognition, functioning and behaviour were evaluated using an abbreviated version of the Clinician's Global Impression (CGI) of severity scale [14]. Physicians were asked to rate the patients on a standard scale, ranging from one (not impaired/not present) to seven (very severe impairment). The cognitive domains were orientation, memory, language, and judgment; functioning domains were planning, social interactions, daily activities, and self-care; the behaviour domains were false ideas, hallucination, mood agitation, sleep patterns, and apathy. After 6 and 12 months, the physicians evaluated patients on the same domains and they were asked to provide their impression of changing on a standard scale ranging from one (markedly improved) to seven (markedly worse) [abbreviated version of the CGI of Change (CGI-C)].

Table 1
Clinical features of 104 patients with mild-to-moderate Alzheimer disease and Diabetes Mellitus type-2 who were recruited into two different groups, according to the current treatment: *Group A*; 49 patients treated with only oral antidiabetic medication; *Group B*; 55 patients treated at the same time with insulin and oral antidiabetic medications (55 patients).

	Group A	Group B	*P* value
Number of patients	49	55	//
Age; years	73.7 (10.2)	>81.7 (8.2)	.005.
Sex (m/f)	23/26	26/29	3.4
Disease duration; (years)			
a. Alzheimer disease	4.3 (1.1)	3.9 (1.5)	1.3
b. Diabetes Mellitus	6.9 (1.9)	7.7 (2.1)	.005
Educational level (years)	11.5 (4.3)	12.4 (5.9)	3.3
MMSE baseline score	20.4 (4.1)	21.9 (5.1)	1.3
Drugs anti-Alzheimer disease			
a. Donepezil	23 (47%)	26 (47.2%)	1.43
b. Rivastigmina	19 (39%)	21 (38%)	2.12
c. Galantamina	8 (16.3)	6 (10.9)	1.91
d. Memantina		2 (3.6)	
Fasting glycaemia (mg/dl)	126 (26.2)	149 (36.8)	.001
Fasting insulinemia (UI/ml)	10.6 (3.8)	13.4 (2.9)	2.2
BMI	23.8 (3.1)	21.7 (3.4)	2.3
Triglycerides (mg/dl)	161 (32.6)	155 (29.1)	1.4
Serum lipid (mg/dl)	132 (23.6)	141 (30.1)	2.79
Smokers (no.)	12 (24.4)	15 (27)	1.43
Ischemic heart disease (no.)	7 (14.2)	14 (25.5)	.002
Hypertension (no.)	18 (36.7)	26 (47.2)	.002
APO E ε4 (no.)	10 (20.4)	12 (21.8)	3.7

2.4. Study design

This is a prospective, open label, observational study performed from May 2004 to February 2008, it was carried out in the outpatients dementia in a southern Italy town (Crotone, Calabria). Study duration was 12 months and consisted of three consecutive periods. At study entry (Visit 1), informed consensus was obtained, and each patient underwent neurological and neuropsychological evaluation. Clinical and neuropsychological assessments were also performed at months 6 (Visit 2) and 12, the end of the study (Visit 3). For the entire duration of the study the treatment for dementia [cholinesterase inhibitors (ChE) (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine] were kept fixed.

2.5. Data analysis

Data were expressed as mean ± SD. No confirmatory statistical testing was performed. Results were summarized using descriptive statistics. Baseline and demographic characteristics were summarized for all enrolled patients. For categorical variables, this was performed by comparing distributions using χ^2 tests and for calculated variables by comparing means using *t tests* with correct test of the normal assumption required. Where these were not satisfied due to skewed data distributions, logarithmic trans-formations were used. Finally, to assess and allow for discrepancies among the clinical characteristics in the group comparisons and to assess the relative significance of potential aetiological variables, logistic regression was used. MMSE

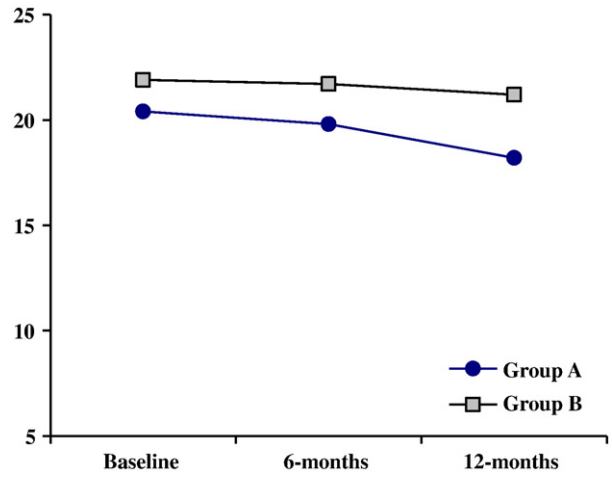

Fig. 1. The MMSE scores for group A (oral antidiabetic medication) and group B (insulin and oral antidiabetic medication) at baseline, at 6 and 12 months.

scores were summarized using means for patients' scores at baseline, months 6 and 12. CGI-C scores were assessed in terms of proportions of patients showing improvement, worsening, or no change from previous visit. In all cases, a *P* value of .05 was considered to be statistically significant. All statistical analysis was performed with SPSS 12.0.

3. Results

3.1. Demographic features

During a period of four years (2004→2008), we recruited prospectively 104 patients (55 women and 49 man; mean ± Standard Deviation (SD), age 76.2 ± 16.4 years), with mild-to-moderate AD and DM-2. Patients were successively divided into two groups, according to current treatments: group A, treated with oral antidiabetic drugs (26 women and 23 men) and group B, treated with combination of insulin and oral antidiabetic drugs (29 women and 26 men). The mean age of group B was significantly higher than of group A (group A vs group B: 73.7 ± 10.2 vs 81.7 ± 8.2; $P = .005$). Consequently, any statistical comparison of the two groups took age into account. The mean duration of DM was respectively 6.9 ± 1.9 years vs 7.7 ± 2.1 years for group A and group B. The mean duration of AD was 4.3 ± 1.1 years in group A and 3.9 ± 1.5 years in group B. Education level was respectively 11.5 ± 4.3 years in group A and 12.4 ± 5.9 years in group B. At the time of our study all patients received drugs for dementia following outline: *Group A* 23 donepezil, 19 rivastigmine and 8 galantamine; *Group B* 26 donepezil, 21 rivastigmine, 6 galantamine and 2 memantine (Table 1).

3.2. Clinical features

The mean fasting glucose level was 126 ± 26.2 mg/dl in group A and 149 ± 36.8 mg/dl in group B respectively ($P = .001$), while the mean fasting insulin was similar in both groups (10.6 ± 3.8 UI/ml vs 13.4 ± 2.9 UI/ml; $P = 2.2$). At presentation the mean BMI between the two groups was similar ($P = 2.3$). After similar adjustment for age, the mean values for serum lipid and triglycerides were not significantly different in the two groups. The smoking use in our population was similar between the two groups (group A vs group B: 12/49; 24.4% vs 15/55; 27.2%), with no statistical difference ($P = 1.43$). At the time of our study 7 (14.2%) patients of group A and 14 (25.5%) patients of group B were affected by ischemic heart disease, after adjusting for age this difference was significant ($P = .002$). Hypertension was present in 18 (36.7%) patients of group A and in 26 (47.2%) patients of group B, after similar adjustment this difference was significant ($P = .002$).

3.3. Genetic features

The prevalence of the APOE ε4 allele was: group A vs group B; 10/49, 20.4% vs 12/55, 21.8%. This difference, after adjustment for age was not statistically significant ($P = 3.79$).

3.4. Neuropsychological assessment

The overall average MMSE score at baseline for group A was lower than the baseline mean in group B (20.4 ± 4.1 vs 21.9 ± 5.1). This difference, after age adjustment, was not $P = 1.9$. At 6 months, the mean MMSE score showed a small but not significant reduction in both groups vs baseline value (baseline vs 6 months: group A, 20.4 ± 4.1 vs 19.8 ± 5.1; $P = 2.12$; group B, 21.9 ± 5.1 vs 21.7 ± 4.1; $P = 1.1$), after similar adjustment. At 12 months the average MMSE decreased significantly in group A patients (20.4 ± 4.1 vs 18.2 ± 3.6; $P = .001$), while MMSE remained above baseline in group B (21.9 ± 5.1 vs 21.2 ± 3.9; $P = 1.03$). At 12-month follow-up, patients with unchanged MMSE score were, 43.5% in group A and 76.8% in group B ($P = .001$). A further 56.5% and 23.2% respectively showed significant worsening from baseline ($P = .001$) (Fig. 1). The CGI-C scores for all the domains of cognition, functioning, and behaviour showed significant worsening from baseline at 6 and 12 months in group A vs group B. Among group A patients, for each of the 12 domains, there were more subjects who reported worsening vs patients of group B, both at 6 and 12 months. The percentages of improved, stable or worsened patients on each domain are shown in Table 2 for both groups. In the domain of mood the overall percentage unchanged was 55.9% in group A and 74.5% in group B at 12 months ($P = .001$). In group A, the percentage of patients with improvement was 3.5%, and the percentage for worsening was 40.6%. In group B, the percentage of the patients with improvement was 11.7%, while the percentage for worsening was 13.8%. These differences were statistically significant (Table 2). After additional adjustment for cardiovascular risk factors (ischemic heart disease and hypertension), the MMSE and CGI-C scores after 12 months remained significant.

4. Discussion

In this prospective study, we evaluated the effects of antidiabetic therapy on cognitive function and memory ability in 104 patients with mild-to-moderate AD and DM-2. The result of this study in a real-life, naturalist clinical setting indicates that a large percentage of AD patients could benefit from insulinic therapy; in fact we documented a significant slowing in cognitive decline, both at 6 and 12 months of follow-up in the group of patients treated with combination of insulin and oral antidiabetic medications (group B) vs group with only oral diabetes medications (group A). Among group B patients, more than 76.8% were found to be stabilized over 12 months on MMSE scores; moreover, the CGI-C domains of cognition, functioning and behaviour showed a significant worsening in a great part of patients of group A vs group B. Besides, in the present study, overall the 62.8% and 71.4% of patients of groups A and B respectively, remained unchanged on the daily living items after 12 months. The role of insulin therapy or insulin combination with other diabetes medications on cognitive decline is controversial [15,16]. Prospective population-based cohort studies recognized that DM increases the risk of dementia, principally in patients treated with insulin [17]. The Honolulu–Asia Aging Study demonstrated that the effect of high levels of insulin on the risk of dementia was independent of diabetes and blood glucose level [18]. Conversely, some studies supported that intranasal insulin improves memory and cognitive abilities in patients with early AD [19]. Beeri et al, in a recent study showed that the combination of insulin with other diabetes medication in 124 patients with AD and DM with AD and diabetes, was associated with substantially lower neuritic plaque density (NPs) in several neocortical regions and in the hippocampus, entorhinal cortex, and amygdale [8]. We hypothesized that insulin

Table 2
The percentages of patients who improved, remained stable, or worsened on each domain of Clinician's Global Impression (CGI) severity scale at baseline, at 6 and 12 months in groups A and B.

Domain	Group A (%)	Group B (%)	*P*	Group A (%)	Group B (%)	*P*	Group A (%)	Group B (%)	*P*
	Improved (6 months)			Unchanged (6 months)			Worsened (6 months)		
Orientation	15.5	21.5	.005	54.4	60.4	.001	32.1	18.1	.001
Memory	16.5	22.1	.005	48.9	57.9	.001	34.6	20.6	.001
Language	15.9	14.9	3.40	64.7	71.7	.001	19.4	13.4	.005
Judgment	5.2	12.2	.005	66.1	70.1	1.28	28.7	17.7	.005
Planning	8.7	14.2	.005	63.0	70.0	.005	28.3	15.8	.005
Social interactions	19.9	17.3	2.21	57.2	64.2	.001	22.9	18.5	3.21
Daily activities	6.4	23.9	.001	63.8	60.8	.001	29.8	5.3	.001
Self-care	10.2	19.0	.001	67.4	70.4	2.43	22.4	10.6	.001
False ideas	14.2	18.2	1.10	71.1	62.1	1.22	14.7	9.7	.001
Hallucinations	14.6	18.2	1.21	73.4	78.4	1.98	12.0	10.9	2.12
Mood	3.5	8.6	2.32	69.9	77.9	.005	26.6	13.5	.001
Agitation	13.6	19.1	.001	67.2	70.2	3.34	19.2	10.7	.001
Sleep patterns	17.6	20.6	2.34	66.6	69.6	2.34	15.8	9.8	.005
Apathy	21.8	18.8	1.32	61.0	72.0	.001	17.2	9.2	.005
	Improved (12 months)			Unchanged (12 months)			Worsened (12 months)		
Orientation	13.5	18.5	4.14	49.4	62.4	.001	37.1	19.1	.001
Memory	9.5	15.5	.005	50.9	61.9	.001	39.6	22.6	.001
Language	11.9	16.3	2.14	67.7	70.7	4.04	20.4	13.0	.001
Judgment	0.2	14.2	.001	61.1	67.1	0.05	38.7	18.7	.005
Planning	2.1	8.4	.005	68.0	76.0	.005	29.9	15.6	.005
Social interactions	13.9	17.9	2.15	60.2	63.1	2.23	25.9	19.0	.001
Daily activities	4.4	23.4	.001	62.8	71.4	.001	32.8	5.2	.001
Self-care	8.8	15.4	.001	67.8	74.2	.005	23.4	10.4	.001
False ideas	13.5	18.9	1.34	70.8	71.6	1.30	15.7	9.5	.005
Hallucinations	16.5	12.0	1.15	70.5	75.1	1.12	13.0	12.9	1.21
Mood	3.5	11.7	.001	55.9	74.5	.001	40.6	13.8	.001
Agitation	15.6	22.6	.005	64.2	65.0	3.22	20.2	12.4	.005
Sleep patterns	15.6	19.0	1.33	69.6	71.6	2.34	14.8	9.4	.005
Apathy	16.8	15.9	5.32	64.0	73.0	.001	19.2	11.1	.005

therapy plays an important role in cognitive functioning and could slow dementia process in AD patients. In healthy older adults and in adults with AD, increasing plasma insulin levels by insulin intravenous infusion, while maintaining euglycaemia, facilitates recall of verbal declarative memory and enhances selective attention [20]. In our population the mean duration of DM and AD, educational level and anti-dementia drugs were similar in both groups. After adjusting for age there was no difference in BMI, serum lipids, triglyceridemia and smoking among both groups. Also the prevalence of the APOE ε4 allele between two groups was similar. Ischemic heart disease and blood pressure, after adjustment for age, was significantly higher in group with combining therapy ($P=.002$). Hypertension has also been reported to modify the association of diabetes with dementia [21]. However, in our study after additional adjustment for cardiovascular risk factors (ischemic heart disease and hypertension), the correlation between cognitive decline and insulinic treatment was slightly attenuated, but remained significant ($P=.001$). Therefore, we supposed that insulinic therapy could have an independent effect on cognitive performance. This association could be explained through several mechanisms: *molecular mechanisms*, notably, insulin promotes cell membrane expression of NMDA receptors, which increases neuronal Ca^{2+} influx [22]. Ca^{2+} influx presumably activates Ca^{2+}-dependent enzymes, including α-dependent enzymes and strengthens neuronal synaptic association [23]. Besides, a recent study identified a molecular mechanism that protects CNS neurons against beta-amyloid derived diffusible ligands (ADDL), responsible for synaptic deterioration underlying AD memory failure. The authors have found that ADDL binding to particular synaptic sites and the resulting oxidative stress and synapse loss are markedly decreased by the presence of insulin. The protection mechanism does not involve simple competition between ADDLs and insulin, but rather is a signaling-dependent down regulation of ADDL binding sites [24]; *glucose metabolism*, low concentrations of exogenous insulin may increase cerebral glucose metabolism and then modulate selective brain functions such as memory [25]; *neurotransmitter modulation*, notably, low doses of insulin can reverse the amnestic effects of cholinergic blockade [26]; moreover, in humans, rising plasma insulin levels increases CSF norepinephrine [27].

Our study could be criticized because the diagnosis of AD was performed by only clinical criteria, nevertheless the clinical evaluation was accurate and complete [28]. Besides, the use of concomitant psychoactive therapies was not quantified in this study. Similarly, the study assessment did not include quantification of concomitant illnesses or site of care. The impact of these variables on the outcomes measured in this study is therefore unknown.

Finally, our data reinforce a causal link between insulin metabolism and the pathogenesis of AD. Besides, it is important to point out that this study is observational, that it is in conflict with other studies showing an association of insulinic therapy with cognitive decline, and that definitive conclusions about the value of insulinic treatment in the course of AD cannot be made at this time. Further studies, on a large sample of patients, are required before that definite effect of insulinic therapy on brain function can be fully accepted.

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