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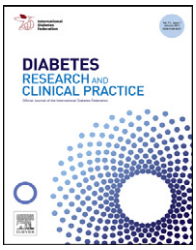

Type 2 diabetes and/or its treatment leads to less cognitive impairment in Alzheimer's disease patients

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ABSTRACT

Aim: To evaluate the cognitive performance of a homogeneous population of Alzheimer's disease (AD), non-demented Type 2 Diabetes Mellitus (DIAB), demented with concomitant diseases (AD+DIAB) and healthy control subjects. AD is a progressive dementia disorder characterized clinically by impairment of memory, cognition and behavior. Recently, a major research interest in AD has been placed on early evaluation. Diabetes is one of the clinical conditions that represent the greatest risk of developing oxidative stress and dementia. Glucose overload, leading to the development of impaired-induced insulin secretion in DIAB and has been suggested to slow or deter AD pathogenesis.

Methods: The degree of cognitive impairment was determined on the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) and the Folstein's Mini Mental State Examination (MMSE); the severity of dementia was quantified applying the Clinical Dementia Rating (CDR) test; the Hamilton test was employed to evaluate depressive conditions; the final population studied was 101 subjects.

Results: The cognitive deterioration is statistically significantly lower ($p < 0.05$) in AD+DIAB patients as compared with AD patients.

Conclusions: In this longitudinal study the superimposed diabetic condition was associated with a lower rate of cognitive decline, while diabetic non-demented patients and controls present normal scores.

1. Introduction

Alzheimer's disease (AD) is the most common dementing disorder of late life characterized by progressive loss of cholinergic neurons and a devastating cognitive decline [1]. Currently there are no drugs that significantly improve the deteriorated cognitive conditions and/or stop the progression of the disease.

Diabetes Mellitus Type 2 (DIAB) is common in the elderly and in Alzheimer's patients as a concomitant pathology. DIAB is recognized as a risk factor for the development of probable AD [2–4]. Both entities share metabolic disorders associated with different pathological developments.

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The study of peripheral markers in probable AD patients and AD with concomitant DIAB (AD+DIAB) has shown significant differences in biochemical variables: (i) reduced changes in the oxidative metabolism related with the damage stress and oxidative stress in AD+DIAB patients; (ii) similar reduction in the variables related with the methionine cycle (homocysteine, folic acid and vitamin B12), and; (iii) opposite signs in the correlation of insulin/glucose and insulin/glycated hemoglobin. Paradoxically, patients with both diseases – dementia plus diabetes – present significantly lower or attenuated metabolic disorders than the pure forms of dementia, e.g. Alzheimer's and vascular [5–8].

Some recent works report that the presence of DIAB in conjunction with the AD, results in a better cognitive performance of patients suffering of both diseases [9–11].

Accordingly with these relatively new findings the presence of DIAB tends to decrease the alterations observed in biochemical variables when it is superimposed with the AD. However, current knowledge does not allow concluding that cognitive performance, as quantified by the tests applied with *consensum scholarum*, also could be improved in AD+DIAB patients.

The purpose of the present pilot study was to assess cognitive performance in a sample of a homogeneous population of probable AD with and without superimposed DIAB, non demented DIAB patients and a control group of healthy subjects. Cognitive and functional performances were assessed with the Alzheimer's Disease Assessment Scale (ADAS-Cog) [12,13], the Folstein's Mini Mental State Examination (MMSE) [14], and the Clinical Dementia Rating (CDR) [15].

Two hypotheses were tested in this pilot study: (i) whether the degree of cognitive deterioration in AD+DIAB patients is lower than the decline observed in non-diabetic AD patients; (ii) whether there exists differences in the cognitive status of DIAB patients and healthy controls.

2. Subjects

2.1. Patients and controls

The total population of one hundred and ten subjects consisted of non-demented Type 2 Diabetes Mellitus patients (DIAB), demented patients of the probable Alzheimer's disease with and without concomitant diabetes (AD+DIAB and AD, respectively) and healthy controls (C); all subjects were from Caucasian origin. This sample was studied at the Neurological Service of the Sirio-Libanés Hospital, in Buenos Aires. Control subjects were selected by age and sex to reflect the general gender and age distribution of the diseased groups and they were non-relatives of AD and DIAB patients. Outpatients and controls were recruited at the Neurology and Geriatric Services of the Hospital Sirio-Libanés.

Patients and controls were included in the study accordingly with accepted neurological criteria for each group: probable AD patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease Association and Related Disorders criteria for a clinical diagnosis of probable AD [16]; DIAB patients using the criteria revised by the expert group of the American Association of Diabetes (ADA) and the World Health Organization (WHO) [17]; non-demented control subjects were defined using the American Psychiatric Association DSM IV criteria [18].

Exclusion criteria comprised, inter alia, systemic or other neurological disorders causing cognitive impairment. Volunteer controls were selected from Geriatrics Service of the Hospital, provided they have not a history of chronic diseases, neurological and/or psychiatric disorders. Patients suffering from systemic or other neurological disorders making diagnostics uncertain were excluded, i.e. head trauma, seizures, uncontrolled hypertension, mental retardation, psychosis or depression, etc. All subjects underwent neurological, psychiatric, physical examination and a comprehensive set of neurological tests, and were recruited provided that they had not a history of smoking or alcoholism in the last five years.

3. Materials and methods

Cognitive evaluation of the one hundred and ten subjects was studied with the Folstein's MMSE and the ADAS-Cog scale. Functional assessment of all patients and control subjects was conducted using the CDR. Depression was measured in all population with the Hamilton test [19].

All subjects had brain images with a 64-channel MDCT scanner GE Healthcare, Milwaukee (CT), or MR imaging of the brain at field strengths of 1.5 T, Signa, GE Medical Systems (MRI). The interpretation of the results was centralized and blinded to clinical characteristics.

Along the study period (one year) all subjects were monitored five times applying the cognitive and functional tests; the mean of the five observations was used. A total of nine subjects were excluded because of various reasons (tumors, sudden death, heart failure, renal failure, cerebrovascular disease, blood dyscrasia, severe depression and chronic hepatitis). After the selection process, four groups were formed:

AD group: Twenty-six patients fulfilling the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease Association and Related Disorders criteria for a clinical diagnosis of probable AD (NINCDS-ADRDA) [16]. All patients in this group were in CDR stages 1 or 2. None of them presented vascular lesions on CT (18%) or MRI (82%).

DIAB group: Twenty-five non-demented patients according to the revised criteria of the Expert Group of the American Association of Diabetes (ADA) and the World Health Organization (WHO) [17]. No subject presented lesions on CT (14%) or MRI (86%).

AD+DIAB group: Twenty-six patients fulfilling both NINCDS-ADRDA [16] and ADA/WHO [17] criteria. All patients in this group were in CDR stages 1 or 2. None of them presented vascular lesions on CT (20%) or MRI (80%).

C group: Twenty-four subjects meeting the American Psychiatric Association DSM IV [18] criteria, without neurological symptoms and normal activities of daily living. No subject presented lesions on CT (22%) or MRI (78%).

The onset of dementia is established as the time when the functionality of everyday life reaches the CDR 1 stage. It was

determined retrospectively when the patient and/or their household family members (spouses, children, brothers and sisters or friendly neighbors) observed deficits in memory, and in two or more tasks of daily living, compared with performance in the previous year, involving the need for third-party support due to these changes. Probable AD patients were included only if they had CDR 1 or 2; ranged from 3 to 7 years of evolution with state of mild and moderate dementia. The proximity of the appearance of AD provided greater certainty about the age of the clinical onset of cognitive manifestations.

In the AD group 57.6% of patients were at CDR stage 1 and 53.8% in the AD+DIAB group. The age of onset of Type II DIAB is established when the patient had two blood glucose tests with results above 120 mg%, and after they installed a diabetic diet accompanied by oral hypoglycemic agents.

Within the DIAB population ($n = 51$), 22 patients (43.14%) were on sulfonylurea medication (15 on glibenclamide, 2 on glimepiride, and 5 on glicazide), 26 patients (50.98%) were on metformine medication, and 3 patients (5.88%) received no medication but only diet, with a almost similar distribution of percentages in both AD+DIAB and DIAB groups.

The gold standard for arterial hypertension was the diagnostic criteria established in the Joint National Committee (JNC 7) of the United States [20].

3.1. *Cognitive tests*

The ADAS-Cog test was applied to quantify the degree of cognitive impairment, in AD and AD+DIAB patients; it is a widespread numerical test based on responses to questionnaires and exercises. The Folstein's MMSE test was used to quantify the severity of the dementia through a short and quick screening, evaluating several cognitive domains. The CDR test was also employed to quantify the stage of the dementia trough functional impairment; the results are ordered numerically and based on conversations and colloquial evaluation aimed to explore various cognitive domains related with daily activities; as the MMSE is also related with cortical and subcortical areas. The Hamilton test is also ordered numerically and was used to quantify depressive conditions, which in severe forms are similar to dementia; none of the subjects in this study should have high Hamilton values (>22).

3.2. *Blood sampling*

Small volumes of venous blood were obtained with written informed consent from healthy volunteers and patients. Each subject of healthy controls, DIAB patients, and demented patients of the AD with and without associated DIAB, contributed one sample of glucose and glycohemoglobin, to check the groups with and without diabetes, which was heparinised and processed; all the laboratory determinations were run in duplicate and the mean was used. As in previous studies, the analysis of the differences of the duplicates indicated that this source of variability is non-significant.

3.3. *Statistical analysis*

The homogeneity of the groups was tested with the usual χ^2 (Chi square) and Student's "t" test for the variables age, sex, years of formal education, age at the onset of dementia, age at the onset of diabetes. Since the assumptions of the usual Student's statistic are not fulfilled by the present dataset, the results of the cognitive tests (Folstein's and ADAS-Cog) and the measure of depression (Hamilton) were compared applying the standardized bootstrap technique [21].

4. Results

Table 1 summarizes the demographical and experimental data of the one hundred and one subjects studied in this protocol.

Arterial controlled hypertension was almost similar between groups: seven patients in the AD group (27%), six patients in the AD+DIAB group (23%), seven patients in the DIAB group (28%) and eight subjects in the C group (33%). The MRI shows that all patients and controls present a state of unspecific cerebral atrophy in accordance with their age.

The groups resulted homogenous with regard to the relevant demographic variables and time of onset of dementia (Table 1).

The null hypothesis of no differences between AD patients with and without superimposed Diabetes (AD vs. AD+DIAB) yielded statistically significant results ($p < 0.05$) for the Folstein's and ADAS-Cog tests (Table 1). As expected, the statistic differences in the comparisons AD+DIAB vs. DIAB and AD vs. C resulted extremely significant (in the range of 10^{-17} to 10^{-24}).

No differences were found in the Hamilton test across the groups; depression was similar in the four experimental groups ($p > 0.1$) (Table 1).

Cognitive deterioration as reflected in the results of these tests is statistically significantly lower in the AD+DIAB group as compared with pure demented AD patients (Figs. 1 and 2).

The concentration of glycated hemoglobin (GHb) is expressed in percentage and increased among groups as: C < AD < AD+DIAB < DIAB, being significant in the DIAB and AD+DIAB groups.

Correlation coefficients between variables in the groups are presented in Table 2. These included those found between glycated hemoglobin (GHb) and age, ADAS Cog and Folstein; age against ADAS Cog and Folstein; years of dementia against ADAS Cog and Folstein; and years of diabetes against ADAS Cog and Folstein. The correlation coefficients resulted significant only in the demented groups (AD and AD+DIAB) for the cognitive tests against years of dementia.

5. Discussion

Little is known about the effect of DIAB on the rate of cognitive decline in established probable AD [9]. This prospective and longitudinal study by Sanz et al. presented the usual problems in the following up of elderly populations. Starting with six hundred AD patients, sixty of them with concomitant DIAB, by death or other reasons less than half of them were included in the study.

Forgetfulness, distractibility and impaired executive function are manifestations of the normal aging process in both

Table 1 – Summary statistics of the total population and experimental groups: demographical and cognitive tests data.

Total population

Number of subjects, $n = 101$
Sex = 52 F (51.5%)/49 M (48.5%)
Age = 76.3 ± 4.9 years
Time of formal education = 12.2 ± 1.9 years
Dementia population (AD and AD+DIAB groups, $n = 52$)
  Age of the onset of dementia = 73.1 ± 3.5 years
  Time of the cognitive impairment = 4.8 ± 1.4 years
Diabetic population (DIAB and AD+DIAB groups, $n = 51$)
  Age of the onset = 64.2 ± 3.9 years
  Time of diabetes = 11.6 ± 4.0 years
Healthy control population (C group, $n = 24$)

	Groups			
	AD	AD+DIAB	DIAB	C
Age[a]	77.92 ± 3.73	78.04 ± 3.38	73.64 ± 5.61	75.46 ± 5.23
Range	71/86	71/84	65/84	65/85
n	26	26	25	24
Sex	12 M/14 F	15 M/11 F	11 M/14 F	11 M/13 F
Education time[a]	12.27 ± 1.97	12.00 ± 1.79	12.16 ± 2.07	12.17 ± 2.09
Range	8/17	8/17	8/17	8/18
Onset time[a]	73.23 ± 3.85	73.04 ± 3.14	69.44 ± 4.41	
Range	3/7	3/7	4/15	
ADAS-Cog test[b]	18.42 ± 1.12*	15.46 ± 0.95*	0.44 ± 0.18	0.42 ± 0.19
Folstein's MMSE[c]	19.42 ± 0.46*	21.27 ± 0.58*	29.28 ± 0.22	29.50 ± 0.18
Hamilton test[d]	14.61 ± 0.64	15.35 ± 0.55	14.72 ± 0.64	13.71 ± 0.68
GHb Values[e]	5.76 ± 0.18	6.54 ± 0.35*	7.15 ± 0.30*	5.92 ± 0.14

Numerical values of the demographical variables were expressed as mean ± standard deviation; numerical values of the cognitive tests were expressed as mean ± standard error; n is the total number of subjects in each group; M: males; F: females. The units and variables were: [a] years; [b,c,d,e] numerical values of the cognitive tests and GHb.
* Statistically differences at $p < 0.05$ level.

humans and monkeys, and can be observed as early as in middle age [22]. In aged mice and in the plasma and cerebrospinal fluid of healthy aging human's recent data indicate that the decline in neurogenesis and cognitive impairments observed during aging can be in part attributed to changes in blood-borne factors [23].

Although there might be various different triggering events in the early stages of the AD, they seem to converge on a few characteristic final pathways in the late stages, characterized by inflammation, neurodegeneration and microcirculation failure. Oxidative stress and advanced glycation end-products initiate a positive feedback loop, where normal age-related changes develop into a pathophysiological cascade [24–26].

In our pilot protocol, patients with dementia had a slow and progressive cognitive impairment, Alzheimer's type, being affected mainly the function of memory. Other cognitive functions also had a poor performance. Patients suffering

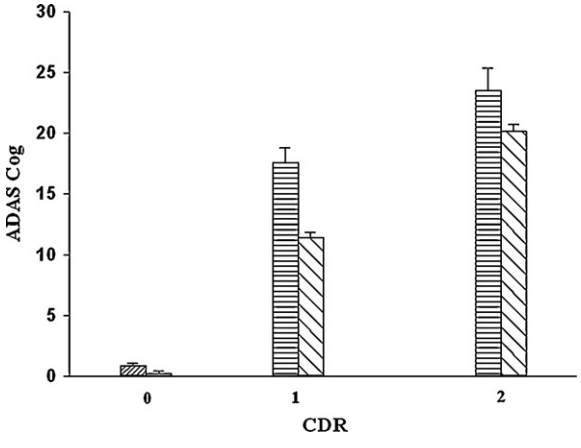

Fig. 1 – Mean values and standard errors of the ADAS Cog test results in the CDR stages. Numerical data are from Table 1. CDR 0: DIAB and C groups; CDR 1 and 2: AD and AD+DIAB groups.

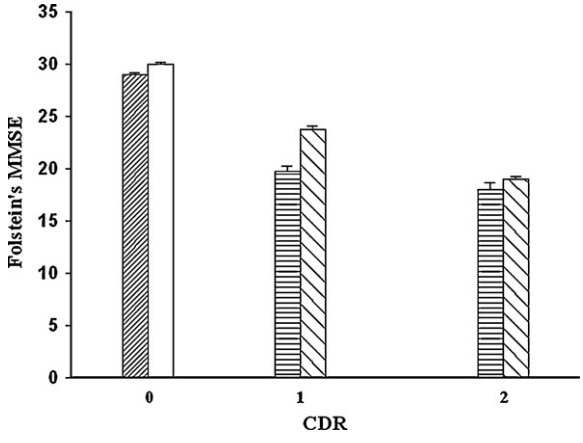

Fig. 2 – Mean values and standard errors of the Folstein MMSE test results in the CDR stages. Numerical data are from Table 1. Groups and CDR stages as in Fig. 1.

Table 2 – Correlation coefficients between variables within groups.

	GHb vs. ADAS Cog	GHb vs. Folstein	Age vs. GHb	Age vs. ADAS Cog	Age vs. Folstein
C	−0.160	−0.235	0.283	0.135	−0.289
DIAB	0.366	0.028	−0.414	0.293	−0.393
AD	0.255	−0.267	−0.418	0.146	−0.063
AD+DIAB	0.442	−0.359	0.567	0.225	−0.202
	Years of dementia vs. ADAS Cog	Years of dementia vs. Folstein		Years of diabetes vs. ADAS Cog	Years of diabetes vs. Folstein
C	Not applicable	Not applicable		Not applicable	Not applicable
DIAB	Not applicable	Not applicable		0.249	−0.294
AD	0.638	−0.695		Not applicable	Not applicable
AD+DIAB	0.851	−0.849		0.395	−0.387

from systemic or other neurological disorders making diagnostics uncertain were excluded, i.e., head trauma, seizures, uncontrolled hypertension, and history of stroke, mental retardation, vitamin deficiency, hypothyroidism, psychosis or depression. All patients and subjects had CT and MRI without visible vascular lesions by this methodology. According to the clinical features and neuroimaging, patients with dementia had a probable Alzheimer's disease. Only pathological studies could verify microinfarcts associated with DIAB.

There is considerable evidence that a chronic inflammatory response is ongoing in and actually precedes DIAB and neurodegenerative disorders, in relation with an impairment of mitochondrial function [27]. Hyperglycemia decreases the activity of mitochondrial complex I by the insulin resistance that is associated with DIAB [28]. Inhibition of complex I create an environment of oxidative stress that ultimately leads to the aggregation of β-proteins with the consequent neuronal death. Complex I dysfunction, also called ''complex I syndrome'' results in complex I inactivation, reduced oxygen (O_2) uptake and ATP formation, increased O_2^- formation, oxidative stress and lipid peroxidation, events that lead to neuronal depolarization and contribute to excitotoxic neuronal injury [29,30].

Oxidative stress is an important pathophysiological mediator of the diabetes and neurodegeneration development and progression along with associated inflammatory processes, wherein monocyte/macrophage activation in adipose tissue contributes to maintaining a proinflammatory response [31]. Polymorph nuclear leukocytes of diabetic patients present reactive oxygen species generation, mitochondrial dysfunction and redox imbalance. Oxidative stress is one of the risk factors, which can initiate and/or promote neurodegeneration and correlates with the severity of the disease [32,33]. Neurons are particularly vulnerable to oxidative damage, not only as a consequence of mitochondrial dysfunction [34]. Oxidative damage to lipids and protein of neuronal membrane affects activities of membrane-bound enzymes, ion channels and receptors. Glial cells contribute to the inflammatory response by transforming themselves into activated microglia, and also release matrix metalloproteinase's, oxidants, prostaglandin E2, and proinflammatory cytokines such as TNF-α and IL-γ [35].

Levels of insulin and insulin resistance were associated with a higher risk of AD within 3 years of baseline; from there the risk was no longer increased. These findings suggest that insulin metabolism influences the clinical manifestation of AD [4]; the authors hypothesize a possible pathophysiologic mechanism by glucose toxicity and a direct effect of insulin on amyloid metabolism.

The paradoxical ''protective'' effect of diabetes on dementias was also mentioned in our previous report [8]. Perhaps, the most surprising ''protective action'' of diabetes was described in association with metastasis in patients with malignant tumors, such as in lung and prostate cancer [36–38].

However, until now, the most plausible explanation of this paradox is the basic communication by De Felice et al. [39], conducted in mature cultures of hippocampal neurons. They demonstrate a protective action of insulin against oxidative stress and synapses protection, among other effects related with specific damage in AD disease. Synapse deterioration underlying severe memory loss in early AD is thought to be caused by soluble amyloid beta (Aβ) oligomers. Soluble Aβ oligomers act as highly specific pathogenic ligands, binding to sites localized at particular synapses. This binding triggers oxidative stress, loss of synaptic spines, and ectopic redistribution of receptors critical to plasticity and memory. The loss of surface plasma membrane insulin receptors, and Aβ-derived diffusible ligands induced oxidative stress and synaptic spine deterioration, could be completely prevented by insulin. At submaximal insulin doses, protection was potentiated by rosiglitazone, an insulin-sensitizing drug used to treat type II diabetes.

According to the findings presented here and as shown in Figs. 1 and 2, a higher cognitive performance exists in probable AD+DIAB patients as compared with the pure probable AD patients. Currently there is widening recognition that AD is closely associated with impaired insulin signaling and glucose metabolism in brain. With regard with the usual treatments with hypoglycemic drugs, metformin sensitized the impaired insulin actions and also prevented appearance of molecular and pathological characteristics observed in AD. Administration of antidiabetic drugs, glibenclamide and pioglitazone, resulted in significant improvement in spatial cognition and in learning and memory performance, as well as significant decrease in hippocampal hyperphosphorylated tau protein and hippocampal galanin [40–42]. In the present probable AD+DIAB patients group, 84.6% of them were under treatment with metformin and glibenclamide perhaps producing the improvements reported.

The results presented here suggest an order relationship between the functional impairment – from the CDR scale – and the cognitive deterioration – quantified by the tests applied – with an apparent trend to reduce the differences between

demented groups along CDR increases, at least to reach the moderate stage (i.e., CDR 2). In other words, these results can be described as a *pari passu* process between functional impairment and cognitive performance.

Additionally, the non existence of differences in the depression results – measured trough Hamilton's test – of the pure probable AD and probable AD+DIAB patients are well in line with the recent report by Emery [43].

Regarding the tested hypothesis of this pilot study it can be concluded that: (i) the degree of cognitive deterioration in patients with probable AD+DIAB resulted statistically significantly lower as compared with pure probable AD patients; (ii) no significant differences exist in the cognitive status between the DIAB patients and the healthy controls; the current evidence is insufficient to draw firm conclusions on the association of AD+DIAB, but recent years and actual data suggest a potentially beneficial role of glucose lowering drugs. More extensive experimental and clinical studies are needed, with larger samples, long-term follow-up from 4 to 6 years and an extended cognitive assessment battery. Unfortunately, these kinds of studies are not easy in elderly populations.

Conflict of interest

The authors declare that they have no conflict of interest.

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