Neurophysiological study of Alzheimer's Disease and Diabetes Mellitus type 2 patients. Is there a common link?

ABSTRACT

Introduction: Recent **s**tudies have shown that insulin resistance and deficiency, a marker of Diabetes mellitus type 2 (DM), interact with beta amyloid and tau protein phosphorylation, which are the basic neuropathological hallmarks of Alzheimer's Disease (AD). Based on these results, it was recently proposed that AD might be considered as 'Diabetes type 3'. Aim of the current study is to assess the cognitive function of DM patients and Mild cognitive impairment (MCI) patients with neurophysiological and neuropsychological measures and seek possible correlations.

Methods The study participants were divided into two groups: group 1 and group 2. Group 1 consisted of 24 DM patients (7 men, 17 women; age 70.6±6.5 (mean ± SD) years; age range 55-86 years. Group 2 consisted of 16 MCI patients age 72.61±7.42 (mean ± SD)years; age range 58-89 years) age-matched (t-value=1.06, p=0.30) and gender matched (χ^2=0.084, p=0.772) with group 1 patients. All patients were assessed with auditory event-related potentials (AERPs) and neuropsychological tests, which include MMSE, MOCA, IADL, and HAMILTON depression scale. Latencies and amplitudes of the major AERP waves (N200, P300 and Slow Wave) were determined,

Results No statistically significant difference was observed in the AERP characteristics and the performance of the patients in the neuropsychological tests between the two groups (p>0.05).

Conclusions From the results of the current study, it appears that the higher cognitive functions of DM patients as assessed with ERPs and neuropsychological tests are affected in a similar way with that of MCI patients; a finding which supports the existence of common pathophysiological mechanisms between the two diseases.

Keywords: [Keywords: Alzheimer's disease, insulin, type 3 diabetes; Event Related Potentials

1. INTRODUCTION

Event-related potentials (ERPs) have been widely used as an accurate neurophysiological marker in the study of cognitive disorders including mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1,2]. Of the major waves observed in the ERPs (N200, P300 and Slow Wave), P300 component is the most studied wave and corresponds to mental processes such as recognition, categorization of stimuli, or short-term memory, while there are many regions in the brain, especially in the temporal lobe, the parietal lobe and the hippocampus which are thought to responsible for P300 generation. ERPs have been used in other disorders that may affect cognitive functions such as diabetes mellitus [3,4]. In particular, P300 has been found to be more accurate in the detection of cognitive deficits in Diabetes mellitus type 2 (DM2) than neuropsychometric tests [5]

Recent evidence from pathophysiological human and animal studies has indicated a close pathophysiological relationship between AD and DM2. This includes several factors such as: oxidative stress, neuroinflammation, insulin, insulin resistance and IGF [6,7]. Hyperinsulinemia and insulin resistance, two of the main characteristics of DM2, have been shown to be important risk factors for cognitive decline and AD in the elderly [8] In particular, lower serum levels of IGF-1 are associated with an increased risk of developing AD [9]. Insulin resistance is associated with elevated levels of proinflammatory cytokines such as C-reactive protein, tumor necrosis factor- (TNF-) α, interleukin- (IL-) 1, and IL-6 [10]. Moreover, T2DM and AD patients have similar amyloid beta deposits both in pancreas as in the brain [11]. As a result, several researchers have proposed AD to be a Type 3 DM [12,13]. The aim of the current study is the neurophysiological and neuropsychological assessment of the cognitive function of DM2 and MCI patients and the study of possible correlations between neurophysiological and neuropsychological parameters as well as differences between the two groups

2. MATERIAL AND METHODS

2.1 PARTICIPANTS

The patients were recruited from the Memory and Dementia Outpatient Clinic of the Third Department of Neurology in "G. Papanikolaou" Hospital as well as “Aretaios” private diabetes clinic. They underwent detailed history and neurological examination as part of their diagnostic work up. Informed consent was obtained by all patients and the study was conducted according to the declaration of Helsinki [14]. All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journaL

The study participants were divided into two groups: group 1 and group 2

Group 1 consisted of 24 DM patients (7 men, 17 women; age 70.6±6.5 (mean±SD) years; age range 55-86 years; years of education 15.7±2.8).

Group 2 consisted of 16 MCI patients (4 men, 12 women; age 72.6±7.4 (mean±SD) years; age range 58-89 years; years of education 16.1±2.4) age- ($t=1.06$, $p=0.30$) and gender matched ($\chi^2=0.084$, $p=0.772$) with group 1 patients. Both groups were also matched for education ($t=1.93$, $p=0.45$). All patients were assessed with auditory event-related potentials (AERPs) and neuropsychological tests, which include MMSE [15,16], MOCA [17], IADL [18,19] and HAMILTON scale for depression [20].

MMSE is a widely used test for assessment of global cognitive function. Items address orientation, memory, recall, attention, naming objects, following verbal and written commands, writing a sentence, and copying a figure. MoCA is a more sensitive tool for detecting MCI which addresses: orientation, drawing figures, processing speed, naming objects, memory, recall, attention, vigilance, repetition, verbal fluency, and abstraction.

Independent Activities of Daily living (IADL) is an instrument that is most useful for identifying a person's functionality at the present time and for identifying improvement or deterioration over time. There are 8 domains of functionality in complex activities of daily living, measured with the Lawton IADL scale.

All neuropsychological tests applied were validated in the Greek Population.

Latencies and amplitudes of the major AERP waves (N200, P300 wave, Slow wave latency) were determined and correlations between them and the neuropsychological test results were sought.

2.2 Event related potentials stimuli and procedures

Auditory event-related potentials were elicited using the "oddball" paradigm. Event-related potentials use two different tones, an inter-stimulus interval of several seconds, with the target oddball stimulus presented less frequently than the non-target or standard stimulus that is a series of binaural tones at 70 dB sound pressure level (SPL) with a 10 ms rise/fall and a 100 ms, plateau time was presented to all study participants The auditory stimuli were presented in a random sequence with target tones of 2000 Hz occurring 20% of the time and standard tones of 1000 Hz occurring 80% of the time at a rate of 0.5 Hz [1]. Each subject was asked to count only the target tones and report the total number at the end of the test

EEG activity was recorded (filter bandpass:0.1–50 Hz, analysis time:1 sec) from scalp AgCl electrodes at Cz and Pz sites according to the 10/20 system referred to linked earlobe electrodes, with ground placed at the right hand. Artifacts caused by ocular movements ± 50 μV were automatically rejected. Each patient was tested twice to ensure that waveform components are reproducible. The peak of the ERP components was measured as follows: if the waveform was smooth, the maximal amplitude point was taken as a peak. Otherwise, the leading and trailing slopes of the waveform were extended, and the intersection point was determined

In order to reduce electrode impedance, we used a special type of paste (Elefix Nihon-Kohden, EEG paste Z-401 CE), while the auditory event-related potentials were elicited and analyzed by means of Neuropack 4 (Nihon-Kohden, Tokyo) equipment.

2.3 Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software (version 23, SPSS, Inc, Chicago, IL, USA). Continuous variables were displayed as means ± standard deviation (SD). The student's *t*-test was used to assess the differences between means in variables that follow normal distribution, whereas Mann-Whitney U test was used when one of the variables was not normally distributed. In our study, N200 amplitude, P300 amplitude and IADL scores in both groups did not follow normal distribution. Differences between categorical variables were analyzed by chi-square test. *P* values <0.05 were considered to be statistically significant.

3. RESULTS AND DISCUSSION

Event related potentials

ERP characteristics (N200, P300 wave latency and amplitude, SW latency) of groups 1 and 2 are depicted in Table 1 No statistically significant difference was observed between the two groups (p>0.05).

	Mild Cognitive impairment (N=16) (Mean±SD or Median±IQR)	**Diabetes Mellitus (N=24) (Mean±SD or Median±IQR)**	**p**
N200 wave latency (msec)	282±40.94	269±37.91	0.288
P300 wave latency (msec)	386±43.29	367±42.7	0.181
Slow wave latency (msec)	482±56.29	451±63.36	0.124
N200 amplitude (μV)	Median 4.93±4.35	4.09±2.91	0.318 (M-W test)
P300 amplitude (μV)	Median 8.59±8.66	7.36±3.3	0.222 (M-W test)

Table 1. ERP characteristics of Groups 1 and 2

Neuropsychological evaluation

There was no statistically significant difference in all of the five neuropsychological test scores between the two groups (p>0.05). Results are shown in Table 2. Moreover no significant difference was observed when testing MoCA subtests separately

	Mild Cognitive Impairment (N=16)	Diabetes Mellitus N=24	p
MMSE	27.12±2.06	26.62±2.6	0.523
MoCA	24.68±3.89	23.08±3.83	0.205
IADL	Median±IQR 8±0.8	Median±IQR 8±1	0.165 (M-W test)
Hamilton	Median±IQR 6±6	7.87±5.27	0.288 (M-W test)

Table 2. Values of neuropsychological tests in Groups 1 and 2

Discussion

There are many pathophysiological mechanisms that have been implicated in the association between DM2 and cognitive dysfunction in AD. In a recent review de la Monte et al [12], mentioned that: (i) impaired insulin signaling; (ii) insulin resistance, (iii) advanced protein glycation, oxidative stress and (iv) inflammation; are potential mechanisms linking the two disorders. Type 2 DM has been associated with impairment in working memory, verbal fluency, attention and executive functions [21,22]. To our knowledge, our study is the first that addresses the higher cognitive functions of DM2 and MCI

patients with accurate neurophysiological such as event related potentials and neuropsychological markers. From the study results, there is evidence that the cognitive functions are affected in a similar way; a finding that supports the existence of common pathophysiological mechanisms between the two diseases. Similar results were found by Winkler et al.,[23]. Roberts et al., [24] who observed that DM2 is associated with MCI and MCI subtypes middle aged and elderly patients. It is well recognized that patients with DM2 have a two-fold increased risk for developing dementia compared to non-diabetic subjects [25,26] Moreover, DM2 may serve as a concomitant factor in accelerating the conversion of MCI to AD [27].

4. CONCLUSION

Our study provides fair evidence that, when assessed with neuropsychological and neurophysiological measures, there is similar degree of cognitive impairment in DM and MCI patients, which comes into agreement with the above mentioned studies.

A limitation of the current study was the small sample size and the loss of follow-up, therefore further and larger studies are warranted in order to confirm these results.

CONSENT

Obtained from the patients for publication of this research article. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. THE PRODUCTS USED FOR THIS RESEARCH ARE COMMONLY AND PREDOMINANTLY USE PRODUCTS IN OUR AREA OF RESEARCH AND COUNTRY. THERE IS ABSOLUTELY NO CONFLICT OF INTEREST BETWEEN THE AUTHORS AND PRODUCERS OF THE PRODUCTS BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

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