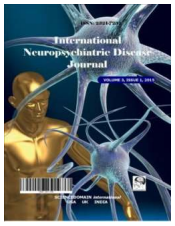

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Brain-Derived Neurotrophic Factor, Copper, Zinc and High Density Lipoprotein (HDL) in Patients with Dementia

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Authors' contributions

This work was carried out in collaboration between all authors. Authors PM and KFMV designed the study, wrote the protocol and the first draft of the manuscript. Author ARC performed the analytical determinations. Authors LZZ and VAN managed the literature search and performed statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

The levels of BDNF, copper, zinc and common blood tests of two different groups of patients were considered: those with dementia syndrome and healthy older people. It would be premature to conclude that these indicators, with the exception of high density lipoprotein (HDL), are directly associated with clinical manifestations of this disorder. The HDL levels were significantly lower in dementia patients, compared to healthy control group, so it is possible to suggest that HDL can perform a protective function.

Keywords: BDNF; dementia; HDL; MMSE; trace elements.

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1. INTRODUCTION

The term dementia comprises several symptoms, for example, a progressive loss of memory and behavioral changes, which together interfere with independent performance of tasks of daily life [1]. A number of dementia definitions have been proposed thus far. The progress and concerns in this field are discussed in a recent review [2].The lack of presymptomatic detection with reliable biomarkers is a major limitation for developing and implementing successful treatments for dementia, including Alzheimer disease (AD). Established biomarkers comprise tau (total and phosphorylated at threonine 181 and 231) and 42-amino acid β-amyloid (Aβ). Decreased Aβ42 levels and increased T and p-tau levels in the cerebrospinal fluid are reproducibly shown at different stages of this brain disorder [3]. As for blood components, no specific biomarkers were confirmed to be associated with dementia, although brain-derived neurotrophic factor (BDNF) is believed to impact neuronal survival and function as well as improve synaptic plasticity and long-term memory [4]. This bioactive compound is stored in platelets and circulates in plasma [5]. The BDNF levels increase with physical activity and caloric restriction, and may mediate some of the observed associations between lifestyle and the risk for dementia [6]. It is also generally assumed that BDNF has some relation to the pathophysiology of depression [7-10]. Nevertheless, it remains uncertain whether its plasma levels precede or follow the cognitive decline and onset of clinical manifestations. Some prior studies showed lower circulating BDNF in persons with AD or other types of dementia compared with control participants [11]. On the other hand, it was mentioned that BDNF was positively associated with cognitive performance, although, strangely, these changes were apparent only in women. No reasonable explanation to this discrepancy was given [12]. According to meta-analysis, cholesterol is known as a risk factor for dementia and cognitive decline [13]. Thus, despite extensive research, there is still an incomplete understanding of the BDNF dynamics in brain function both in Alzheimer`s disease and other forms of dementia. To the best of our knowledge this factor has never been quantified in this particular group of patients, nor were similar data published in the context of other biochemical markers referring to mineral metabolism (trace elements content and general hematological parameters).

The aim of the present study is to examine the relationships between BDNF, common electrolytes as magnesium and calcium and trace elements as copper and zinc in patients with dementia and in control group of healthy old people.

2. METHODS

Patients with dementia were from Campo Grande, Mato Grosso do Sul state, Brazil. Forty-three adults of 60–90 years old participated in the study. Subjects of two different groups were considered: those with dementia syndrome (Alzheimer disease, vascular dementia and mixed dementia) and healthy older people.

As fluticasone significantly suppress BDNF secretion [5], so it was important that patients taking corticosteroids have been completely excluded from the study. These groups were chosen because of the expected difference in the above biochemical indicators.

The diagnostic criteria were chosen in accordance to the Diagnostic and Statistical Manual of Mental Disorders, 4º edition revised text (DSM-IV-TR) published by the American Psychiatric Association. In parallel, the Mini Mental State Examination (MMSE) was applied to assess cognitive functions. Routine techniques were used to collect hematological and common biochemical data. Written informed consent was obtained from each participant or their legal representative and approved by the local Ethic Committee. The exclusion criteria were other neurological diseases, brain injury, depression and psychotic/metabolic disorders. The following electrolyte and biochemical parameters were assessed: sodium, potassium magnesium, calcium, phosphorus, vitamins B_1 and B_{12}, folate, urea, creatinine, glucose, TSH, T_4, AST and ALT. Zinc and copper concentrations were determined by Flame Atomic Absorption Spectrophotometry; BDNF levels were determined by the Promega BDNF max Immunoassay System V, according to the manufacturer`s instructions. Statistical data for BDNF, electrolytes, zinc and copper were normally distributed as proven by the Kolmogorov-Smirnov test. Correlations were calculated using Spearman coefficients. For group comparisons Mann-Whitney U-test was used. The results are expressed as x±SD, where x is the mean value and SD is the standard deviation of all variables.

3. RESULTS AND DISCUSSION

Socio demographic data along with MMSE scores are given in Table 1. There were no statistically significant differences between patients with dementia and controls in respect to age, gender and education levels. At the same time, as expected, MMSE scores were significantly different, confirming cognitive impairment in demented patients. As literature data are contradictory, our null hypothesis H_0in this study was to find a difference between experimental groups in respect to the BDNF levels and other plasma constituents. Nevertheless, the BDNF concentrations (20.34 and 20.43 ng/ml) were shown to be statistically equivalent, that is these results neither support published findings nor open the possibility of considering this factor as a viable biomarker. As for the indicators of mineral metabolism, they were statistically identical for both groups including trace elements (Table 2), despite the fact that copper and zinc had been detected in the Alzheimer´s disease-affected brain and thought to be important metabolites [14]. According to clinical criteria, the degree of dementia in both groups was comparable. However, given the advanced age of the patients, there were no reliable data as to disease duration. It is true that the type of dementia observed in this sample (Alzheimer disease, vascular dementia and mixed dementia) have differences in their pathogenesis. Nevertheless this does not seem to have been a decisive factor in BDNF expression.

As for the indicators of mineral metabolism, they were statistically identical for both groups including trace elements (Table 2), despite the fact that copper and zinc had been detected in the Alzheimer´s disease-affected brain [15]. Finally, there were no differences between the sets of general biochemical characteristics (Table 3), with the exception of HDL fraction of cholesterol which was significantly lower in patients with dementia (50.60 *vs* 39.84 mg/dL). The lack of association between BDNF levels and dementia may be explained taking into account a non-apparent lack of homogeneity in both experimental and control groups because of different life-styles, various concomitant diagnoses in old age and uncontrollable polymedication. So the resultant of these factors may be positive, negative or zero. From a statistical point of view [16] a set of such data can be considered as a badly defined system with low validity and credibility. Moreover, the lack of a common unique methodology for BDNF makes difficult the comparison and interpretation of data from different sources. It would be premature to conclude about the real correlations until the results are computed on the basis of a large meta-analysis.

In regard to the increased HDL fraction our data are consistent with the results of a recent study [17] where higher levels of HDL were shown to be associated with a decreased risk of both probable and possible AD. The models were adjusted for age, sex, education, ethnic group, and APOEe4 genotype. Additional adjustments

Table 1. Main characteristics of the sample (x ± SD, variance and Mann-Whitney statistical test)

Variable	Controls (n=16)	Patientswithdementia (n=27)	*P*
Gender	9 M; 7 F	15M; 12 F	
Age (years)	75.5±2.27 (60-90)	77.2±1.21 (67-90)	.33
Education (years)	3.63±1.4 (0-18)	2.44±0.65 (0-12)	.54
MMSE (scores)	22.25±1.08 (15-30)	10.07±1.16 (0-26)	<0.001

M –male; F – female; MMSE - Mini Mental State Examination

Table 2. Indicators of mineral metabolism (x ± SD, variance and Mann-Whitney statistical test)

Variable	Controls (n=16)	Patientswithdementia (n=27)	*P*
Sodium (mEq/L)	139.63±1.10 (135-147)	139.67±0.87 (134-152)	.93
Potassium (mEq/L)	4.46±0.13 (3.1-5.4)	4.49±0.12 (3.1-6)	.82
Calcium (mg/dL)	9.11±0.13 (8-12)	9.19±0.11 (8.1-10.2)	.78
Magnesium (mg/dL)	2.02±0.09 (1.3-2.6)	1.97±0.06 (1.3-2.5)	.60
Phosphorus (mg/dL)	3.41±0.11 (2.9-4.4)	3.72±0.17 (2.6-7.04)	.17
Copper (mg/L)	1.3±0.02 (0.18-5.6)	1.28±0.03 (1.0-1.5)	.85
Zinc (mg/L)	1.25±0.05 (0.56-1.6)	1.2±0.03 (0.46-1.4)	.48

Table 3. General hematologic parameters (x ± SD, variance and Mann-Whitney statistical test)

Variable	Controls (n=16)	Patientswithdementia (n=27)	*P*
Vitamin B1 (µg/L)	59.53±4.47 (47-100.7)	59.97±7.11 (10.9-194.9)	.37
Vitamin B12 (pg/mL)	390.84±33.35 (54.5-2000)	356.66±51.27 (145-1500)	.06
Folate (ng/mL)	10.22±1.21 (4-19.5)	9.38±1.01 (2.25-23.90)	.36
Urea (mg/dL)	42.03±5.13 (20-53)	43.06±3.79 (24-91)	.89
Creatinine (mg/dL)	0.96±0.05 (0,6-1.12)	1.04±0.07 (0.5-1.65)	.61
Glucose (mg/dL)	86.34±2.46 (68-100)	96.83±7.69 (62-257)	1.0
TSH (µU/mL)	2.94±0.48 (0.43-7.65)	4.67±0.59 (0.43-11.62)	.08
T4 (µg/mL)	4.89±1.03 (0.65-12.18)	6.81±0.85 (0.86-13.16)	.21
AST (U/L)	25.54±1.42 (14-100)	22.36±1.51 (14-40.6)	.09
ALT (U/L)	27.65±2.47 (8.3-89)	28.84±2.95 (6-55.6)	.68
Cholesterol (mg/dL)	180.50±14.57 (143-247)	175.89±8.52 (106-294)	.87
VLDL (mg/dL)	23.04±2.35 (14->400)	29.94±2.81(9-72.1)	.14
HDL (mg/dL)	50.66±4.43 (27-67.2)	39.84±1.90 (22-62)	.048
LDL (mg/dL)	111.18±13.04 (24->400)	109.64±7.24 (56-217)	.85

TSH, thyroid stimulating hormone; T4, tetraiodothyronine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; LDL, Low-density lipoprotein.

were made for vascular risk factors and lipid lowering treatment. The latter circumstance is important because frequent and incomparable statin prescriptions in old patients with atherosclerosis can interfere with the interpretation of results [14]. From the foregoing, it is also possible to suggest that HDL can perform a protective function for dementia in general.

4. CONCLUSIONS

The levels of BDNF, magnesium, calcium, copper and zinc of two different groups of patients were considered: those with dementia syndrome and healthy older people. It would be premature to conclude that these indicators, with the exception of high density lipoprotein (HDL), are directly associated with clinical manifestations of this disorder until the results are computed on the basis of a large meta-analysis. The absence of differences may be due to the lack of homogeneity of experimental and control groups because of different life-styles, concomitant diagnoses in old age and uncontrollable polymedication. The HDL levels were significantly lower in dementia patients, compared to healthy control group, so it is also possible to suggest that HDL can perform a protective function for dementia in general.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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