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Inflammatory Cytokines in a Sample of Alzheimer's Patients from Rio De Janeiro State

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Abstract

We carried out an evaluation of a sample of 45 elderly into 2 groups GA(21)=75.9+7.4 years and GC(24)=75.3+7.5 years. We evaluated CDR, MMSE, and CST, Lawton and Brody Scale and one sample of 5 ml of blood for analysis of biomarkers. The data were compared between groups. The results showed higher levels for IL-12, IL-10 and IL-1β for Alzheimer's disease. IL-10 was correlated with age, CDR and functional capacity and negative correlated with MMSE. The age was correlated with TNF-α, IL-10, IL-4. The CST was correlated with IL-4. We conclude that Alzheimer's disease changes de immune system with higher inflammatory cytokine and correlated with functional and cognitive capacity impacting the elderly health.

Keywords: Cytokine; Inflammation; Alzheimer's disease; Dementia; Cognitive decline

Introduction

Alzheimer's disease is the most common type of dementia in the world. It is a neurodegenerative disease that causes cognitive loss. The pathophysiology is characterized by the accumulation of senile plaques comprised of β-amyloid peptide and the loss of function of microtubules in the neurons caused by hyper phosphorylated tau. These pathophysiological changes lead to the activation of microglia and astrocytes, releasing inflammatory cytokines.

The presence of β-amyloid plaque sites attracts microglia and astrocytes, responsible for mediating the inflammatory response [1]. The microglia are considered to be part of the immune system in the Central Nervous System (CNS), because they are antigen presenting cells, perform phagocytosis and release cytotoxic factors [2, 3]. Studies have shown that microglia play a role in the removal of Aβ peptides in culture, and are also activated by Aβ protofibrils, triggering an inflammatory response [2,4]. Other cells responsible for the immune response in the CNS are astrocytes. Astrocytes are in greater quantity in the CNS and perform a range of functions including synaptogenesis, the formation and maintenance of the blood-brain barrier, play a role in neurotransmission, metabolic regulation and the maintenance of the ionic balance [2]. A hypertrophic astrocyte reaction is observed around senile plaques in post-mortem studies of Alzheimer's patients and activated astrocytes can perform phagocytosis and degrade amyloid peptides, which may contribute to the removal of accumulations of Aβ [1,5,6].

The evidence indicates various types of interaction between the immune system and the central nervous system in the pathogenesis of AD [1,7-10]. Both microglia and astrocytes secrete cytokines such as Interleukin 1β (IL-1β), Tumor Necrosis Factor (TNF), nitric oxide, and other molecules with cytotoxic potential to repair neuronal structural damage after exposure to Aβ [1]. From a pathophysiological perspective, neuroinflammation can be considered part of the neuropathological triad that characterizes AD (the other two being senile plaques and neurofibrillary tangles). Inflammatory markers are able to cross the blood-brain barrier and produce neuromodulatory effects [11]. However, there is still no consensus in the literature on the relationship between cytokines and Alzheimer's disease.

The objective of this study was to measure the level of cytokines in the peripheral blood of patients with Alzheimer's disease and to correlate this with the severity of the dementia, and functional and mental capacity.

Materials and Methods

Study design

The elderly were selected in the city of Rio de Janeiro, Alzheimer's disease center and other mental disorders in old age and Duque de Caxias, at the University of Rio Grande, with diagnosis of Alzheimer's disease and control.

Sample

Elderly patients aged over 60 years with Alzheimer's diagnosis, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [12], were selected for Alzheimer Group composition and without dementia diagnosis for Group Composition Control (GC). Other mental pathologies and health impairments in the last 6 months were adopted as exclusion criteria. The physical, medical-psychological

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characterization was obtained from data contained in the medical records and complemented in an interview with patient and family member, staging of the disease was measured by Clinical Dementia Rating (CDR) [13]. After data eligibility, the elderly were allocated into 2 groups: Alzheimer Group (GA) and Control Group (CG).

Assessment

For the assessment of cognitive capacity was measured by the Mini Mental State Examination (MMSE), to measure the motor variables was performed the Chair stand test in 30 seconds [14,15]. Functional capacity was evaluated by the Lawton and Brody scale [16].

Collections of blood sample

Blood samples were collected by a health professional trained for the procedure, after the Biological material collection, the sample was processed and frozen in freezer -80 ˚C for analysis in the posterior. The processing was carried out at the Immunopathology Laboratory of the State University of Rio de Janeiro (UERJ), through flow cytometry by the Cytometric Bead Assay (CBA; BD Biosciences, San Jose, California, USA) using the kits: Human Inflammatory Cytokines and Human Th1/TH2/Th7 Cytokine. Ten cytokines (IL-17, IFN-γ, IL-4, IL-2, IL-12, TNF, IL-10, IL-6, IL-1β and IL-8) were analyzed. All samples were centrifuged at 1050 g for 3 min within 30 min after phlebotomy. The resultant supernatant (serum fraction) was transferred and divided into four aliquots of 400 μL of serum. Serum samples were stored at –80 ˚C with constant temperature monitoring before cytokine assay.

The project was approved by the Research Ethics Committee (CEP) of the University of Grande Rio (UNIGRANRIO) with CAEE 57332116.7.0000.5283 numbering. All individuals signed the informed consent form.

Statistical analysis

The clinical and socio-demographic data are described in Mean and Standard Deviation (m; sd) and the Chi-square and T student test were used for comparison. The Mann-Whitney and T student tests were used for the biomarkers to analyze the parametric and non-parametric data, respectively.

A correlation of the biomarkers with the cognitive and physical-functional variables was performed using the Spearman and Pearson tests. P<0.05 was adopted for statistical significance. We used Cohen's classification for the intensity of the correlations [17].

Results

The study included 45 elderly participants, including 24 elderly controls (CG) and 21 elderly with diagnosis of AD (AG). There was a female predominance in both groups. The control group obtained, as expected, higher scores in the MMME compared to the Alzheimer group. Most of the Alzheimer's group has more than 8 years of schooling, while in the control group a large part has less than 8 years of schooling. Regarding the numbers of comorbidities in the participants, most had only one comorbidity or none. Among the comorbidities, systemic arterial hypertension was the most common, as shown in Table 1.

In physical assessments, both groups presented no significant difference in BMI and CST. However, for functional capacity at all levels, when the total, basic or instrumental functional capacity was evaluated, the control group presented a higher functional capacity as shown in Table 1.

	Alzheimer M(± DP)	**Controle M(± DP)**	**p**
N (M/F) ¥	21 (9/12)	24 (4/20)	0.06
%Female	57.10%	83.30%	-
Age*	75.9 (7.4)	75.3 (7.5)	0.7
MSSM*	17.9 (5.7)	25.4 (4.0)	<0.001
CDR	-	-	-
0	-	75%	-
0.5	-	25%	-
1	52.40%	-	-
2	42.90%	-	-
3	4.80%	-	-
Schooling			
Illiterate (%)	9.50%	8.30%	-
<8 Years (%)	28.60%	58.30%	-
>8 Years (%)	61.90%	33.30%	-
Comorbidities			
0	23.8%	33.3%	-
1	57.1%	33.3%	-
2	14.3%	29.2%	-
3+	4.8%	4.2%	-
Hypertension (%)	42.9%	33.3%	-
Diabetes (%)	9.5%	16.7%	-
BMI**	27.1 (4.7)	27.6 (5.3)	0.7
CST**	10.0 (4.3)	10.1 (4.9)	0.6
Lawton Total**	37.3 (21.9)	8.8 (11.5)	0.000
Lawton Basic**	6.0 (4.2)	0.3 (1.0)	0.000
Lawton Instrumental**	31.2 (20.0)	8.5 (10.9)	0.000

Note: M=mean; DP=Standard Deviation; CDR=Clinical Dementia Rating, MMSE= Minimental State Examination; BMI=Body Mass Index; CST=Chair Stand Test; *=teste t (for normality); **=teste de Mann-Whitney U. ¥=Chi square test.

Table 1: The demographics of AD patients and Control group.

Three cytokines were found increased in patients with DA compared to the control (IL-12; IL-10 and IL-1β), as shown in Figure 1. Other cytokines showed no significant differences. The IL-10 was the cytokine that obtained a positive correlation of moderate intensity with age, CDR, Lawton in the total score and in the score for basic life activities. A negative correlation of IL-10 with MMME was found, showing that the lower the score in the test, the greater the concentration of this cytokine.

Age was moderately correlated with three cytokines (IL-12, IL-10 and IL-6). For the CDR, a positive and moderate correlation was found for IL-10. The CST correlated negatively and moderately with TNF, showing that the higher the concentration of this cytokine the lower the individual's ability to stand up without support, as shown in Table 2.

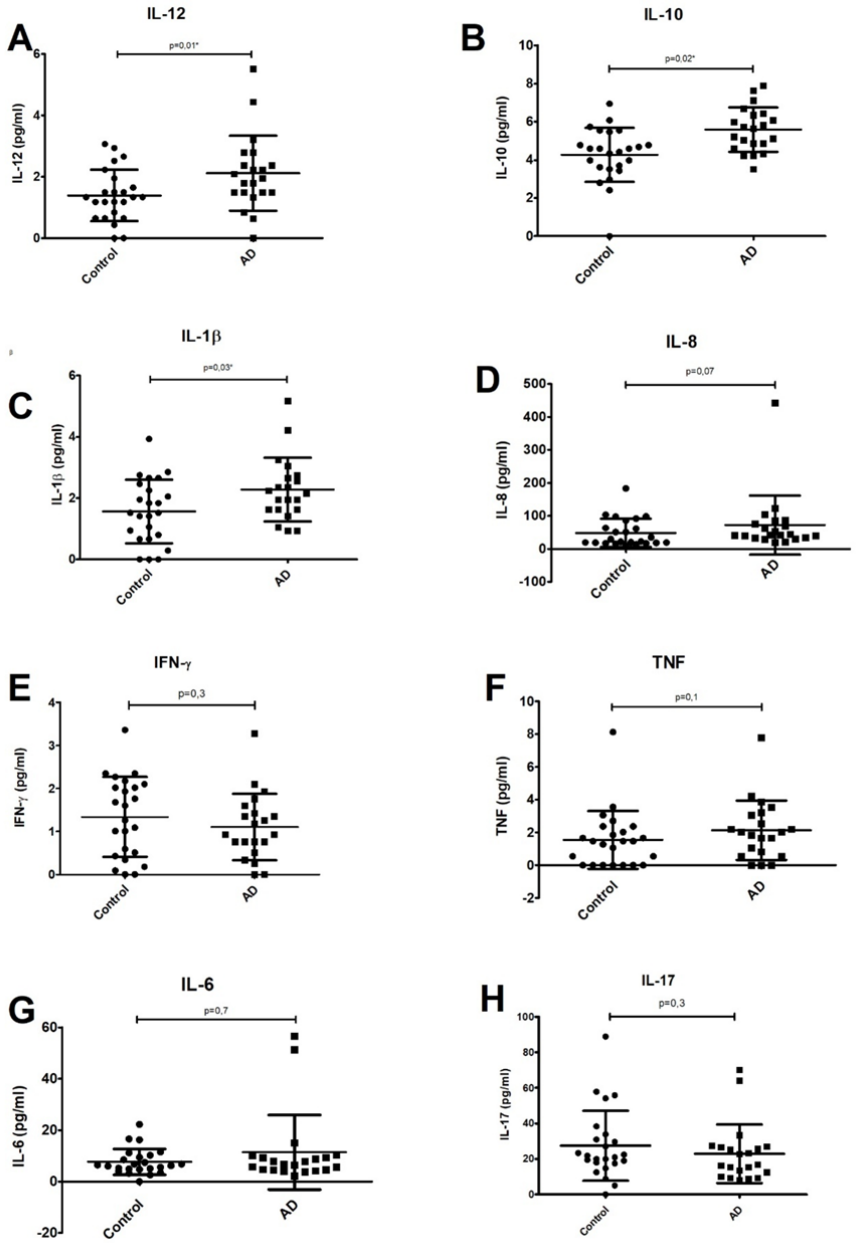

Figure 1: Serum levels of biomarkers in AD and control groups. A) Serum IL-12 levels in control group and AD patients; B) Serum IL-10 levels in control and AD group; C) Serum IL-1β levels in control and AD groups; D) Serum IL-8 levels in control and AD groups; E) Serum IFN-γ levels in control and AD group; F) Serum TNF levels in control and AD group; G) Serum Il-6 levels in control and AD group; H) Serum IL-17 levels in control and AD group. IL-8, IFN-γ, TNF and IL-17 were no significant difference.

Note: *Serum IL-12, IL-10, IL-1β levels in AD group increased compared with control.

	IL-17		IFN-γ		IL-12		TNF		IL-10		IL-6		IL-1β		IL-8	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Age	0.13	0.39	0.1	0.49	0.31	0.04*	-0.02	0.9	0.37	0.01*	0.32	0.03*	0.12	0.41	-0.15	0.31
CDR	-0.15	0.39	-0.21	0.17	0.27	0.07	0.2	0.18	0.38	0.01*	-0.01	0.97	0.26	0.09	0.16	0.28
MMSE	0.06	0.68	-0.01	0.95	-0.18	0.23	-0.2	0.19	-0.32	0.03*	-0.05	0.72	-0.03	0.82	0.03	0.85
CST	-0.17	0.25	-0.25	0.1	-0.3	0.87	-0.31	0.04*	-0.13	0.4	-0.08	0.6	0.16	0.29	-0.15	0.34
Lawton Total	0	0.98	-0.1	0.53	-0.22	0.14	0.28	0.06	0.31	0.04*	0.09	0.55	0.1	0.49	0.14	0.35
Basic	-0.11	0.46	-0.16	0.3	0.24	0.11	0.27	0.06	0.35	0.02*	0.03	0.86	0.15	0.31	0.21	0.16
Instrumental	0.01	0.93	-0.08	0.59	0.2	0.19	0.26	0.09	0.28	0.06	0.08	0.62	0.09	0.57	0.13	0.4

Note: Correlation with age, severity, cognitive and functional capacity. CDR=Clinical dementia rating; MMSE=Minimental State Examination. IL-10 was combine with age, CDR and functional capacity; and was a negativity correlation with MMSE. TNF was negativity combined with chair stand test. IL-12 and IL-6 was correlated with age.

Table 2: Biomarkers correlation with age, severity, cognitive and functional capacity.

A correlation of the MMSE cognitive test with all the physical-functional capacity tests used in this study was performed. As shown in Table 2, the MMSE was strongly correlated with the Lawnton test for instrumental activities and with very great intensity with the Lawnton tests for the basic activities and the total score of Lawnton and Brody. With the chair stand test in 30 seconds, the MMSE correlated moderately. The CST was also moderately correlated with Lawton's total score and evaluation of instrumental activities by Lawnton and Brody.

Discussion

Our results demonstrated that patients with AD presented a change in their immune system assessed by the inflammatory cytokines. We found higher levels of IL-12, IL-10 and IL-1β in the AD group compared to those in the control group. For IL-12, our results contradicted the results of other studies that demonstrated a decrease in this cytokine for patients with AD [11,18,19]. However, the study performed by Motta et al., reported that this cytokine is at very high levels in the early-stage of AD but falls as the severity of the pathology increases [18]. Our sample mainly comprised patients with mild Alzheimer's, which could explain the difference found compared to the control group.

We identified an increase of IL-10 in AD; however, other studies found no statistical difference for this marker [20,21]. Wang et al., demonstrated a difference in this cytokine in patients with cognitive decline compared with healthy individuals, but it was shown to have a low discriminating potential [22]. The authors evaluated three groups (patients with AD, patients with mild cognitive decline with amnesia and controls). The increase of this cytokine in the AD patients demonstrated the activate anti-inflammatory character of this population, as IL-10 can be considered a potent anti-inflammatory derived from T helper 2 (Th2) and T regulators (Treg) cells with role of inhibiting the production of other pro-inflammatory cytokines such as TNF, IL-1β and IL-12 released in the CNS by microglia and astrocytes [22]. Kiyota et al., demonstrated that the increase of IL-10 in response to CNS inflammation was necessary for the reduction of microgliosis and astrogliosis and important for the maintenance and cognitive ability gain in mice in an Alzheimer's model [23].

For IL-1β, we demonstrated an increase in its peripheral concentration in AD, corroborating other studies that demonstrated an increase of this cytokine in AD [8,24]. However, this is contrary to the results of some other studies, which reported that there was no significant difference in respect of this cytokine in AD in peripheral blood and in spinal fluid [20,25,26]. In one study the authors identified an increase of this cytokine in AD and negative correlation of the same cytokine with the cognitive ability, evaluated by the MMSE, as in our study in which we found a very large negative correlation between IL-1β and cognitive ability through the MMSE [8].

In our study, we found an increase in IL-10 and IL-1β in AD patients, showing the inflammatory response to Alzheimer's pathophysiology, but there was no increase in IL-6, perhaps due to the comorbidities of both groups that may have influenced the production of cytokines. The concentration of IL-6 in the blood was correlated with the levels in cerebrospinal fluid in Alzheimer's patients, demonstrating that this cytokine could be related to the pathophysiology of the disease [27]. IL-6 is a multifunctional cytokine, having both an anti and pro-inflammatory function. It is present in the early stage of inflammation, being induced by TNF or IL-1β [28,29]. It may have anti-inflammatory action when it induces the production of IL-10, which inhibits the action of TNF [30].

Our results demonstrated a correlation between TNF and functional capacity, both in the chair stand test in 30 seconds (moderate correlation), and in the Lawton and Brody scales (small correlation). TNF is considered a non-specific cytokine, but is a significant factor for the development of psychiatric diseases, including Alzheimer's [9]. It can be secreted by the activation of the microglia in response to β-amyloid accumulation sites [9]. However, Uslu et al., found no difference in the levels of this cytokine compared to a control, as in this study, but Belkhelfa et al., demonstrated a high level of TNF in Alzheimer's patients and a significant difference also when comparing TNF levels in people with mild cognitive decline and severe Alzheimer's [31,32]. Leung et al., showed an inverse correlation of TNF levels with hippocampal volume [33].

Mirhafez et al., found that arterial hypertension may increase the levels of some cytokines such as IFN-γ, TNF, IL-2 and IL-8 compared to individuals without SAH. This could explain our results, in which no difference was found between these cytokines in the control and

Alzheimer groups, as in both groups there was a high percentage of a hypertensive individual which may have increased these cytokines in the control group [34]. Another interleukin with no differences found between the groups was IL-6: however, Marsland et al., found a correlation between this cytokine and BMI and bilateral gray matter volume in the hippocampus [35]. The study showed a correlation of r=0.23 between IL-6 and BMI and a negative correlation between IL-6 and left and right hippocampal volume (r=-0.42 and r=0.24 respectively) [35]. We can infer that the high levels of IL-6 in our control group may also have been due to the presence of comorbidities, including hypertension, and may lead to the cognitive decline of these individuals in the near future, necessitating monitoring of this population to confirm this inference.

Our study evaluated another important issue for the general health of patients with Alzheimer's, their oral health. We ascertained whether the individuals went to the dentist or received any dental treatment. We discovered the important fact that in both groups only a small percentage went to the dentist or received any dental treatment. However, 9 individuals in the control group and 5 in the Alzheimer's group did not have their own teeth. In all cases this procedure had been performed at least 1 year previously and we could not identify the cause; however, this suggests that these individuals may have had some oral pathology, A study by Gaur and Agnihotri showed that chronic periodontitis may lead to increased levels of inflammatory cytokines such as IL-1, IL-6 and TNF-α and contribute to the worsening of Alzheimer's [36].

Our study found a reduced functional capacity for Alzheimer's patients. These findings agree with those of Talmelli et al., who reported lower physical capacity in older adults with Alzheimer's disease, which was more affected according to the severity of the dementia [37]. The authors found that older adults with higher CDRs had less functional capacity than those with lower CDRs. In our study, we demonstrated that individuals with Alzheimer's had lower functional capacity for both basic and instrumental life activities compared to individuals with CDRs of 0 or 0.5. The AD group had less institutionalization time and yet had less functional capacity than the other older adults.

Our study found a moderate to a very large intensity correlation of the MMSE with all the physical-functional capacity tests. Sobol et al., also found a correlation between the MMSE and the TUG test as well as with other tests of cognitive ability, such as the Stroop and verbal fluency tests, agreeing with our results that showed that the low physical capacity of Alzheimer's patients can influence the severity of the cognitive impact that this patient presents [38].

This study has some limitations that should be mentioned. First, the small size of each group may have affected the results in respect of some cytokines. Second, the fact that the data were collected from two different elderly care centers may have had an influence on the level of schooling and the level of medical care among the elderly. As the control group was comprised of individuals from the Duque de Caxias area of Rio, many of the participants were without adequate medical care, and this may have influenced the monitoring of the comorbidities found among them.

Conclusion

We conclude that Alzheimer's disease is correlated with changes in the immune system, observed by the differential concentration of peripheral inflammatory cytokines, such as IL-12, IL-10 and IL-1β. IL-10 is correlated with the severity of the disease assessed by the CDR, as well as with age and cognitive ability. In addition, levels of inflammatory cytokines may be correlated with the functional capacity of older adults, and TNF-α correlated with the ability to stand up from a chair, as well as with the ability to perform daily life activities. Age may be correlated with IL-6, IL-10 and IL-12 cytokines. However, more studies with larger sample populations and more robust analyses are necessary for a better understanding of cytokines.

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