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RESEARCH

BIOMARKERS OF ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA SIMULTANEOUSLY SAMPLED FROM SERUM AND CEREBROSPINAL FLUID

- Ömer KARADAŞ[1]
- Güray KOÇ[2]
- Akçay Övünç ÖZÖN[3]
- Bilgin ÖZTÜRK[4]
- Dildar KONUKOĞLU[5]

Abstract

Introduction: Alzheimer's disease, which is a progressive disease accompanied by behavioral problems and decreased activities of daily living with early cognitive decline, and vascular dementia, which is related to cerebrovascular lesions with gradual, progressive cognitive decline, are common in the elderly. Currently, pathological examination is the gold standard in both Alzheimer's disease and vascular dementia and studies to elucidate the role of cytokines in their pathophysiology using cerebrospinal fluid and serum biological markers have been intensified. In this study, cerebrospinal fluid and serum biomarker levels from both Alzheimer's disease and vascular dementia patients were examined.

Materials and Method: Thirty patients diagnosed with Alzheimer's disease (Group 1) and vascular dementia (Group 2) were enrolled in this study. Serum interleukin-1β, tumor necrosis factor--α, and interleukin-6 levels as well as serum and cerebrospinal fluid protein carbonyl, glutathione and β-amyloid levels from Groups 1 and 2 (N=15 each) patients were compared.

Results: Serum interleukin-1β, tumor necrosis factor-α, and β-amyloid levels as well as serum and cerebrospinal fluid protein carbonyl and glutathione levels were not statistically different ($p>0.05$) between Group 1 and Group 2. Serum interlukin-6 levels and cerebrospinal fluid β-amyloid levels were significantly higher and lower, respectively, in Group 2 than in Group 1 ($p<0.05$).

Conclusion: In this study, serum interleukin-6 levels were higher, whereas cerebrospinal fluid β-amyloid levels were lower, in vascular dementia patients than in Alzheimer's disease patients.

Key Words: Alzheimer's disease; Dementia, Vascular; Cytokines; Biochemical markers

ARAŞTIRMA

ALZHEİMER HASTALIĞI VE VASKÜLER DEMANSTA EŞ ZAMANLI ALINAN SERUM VE BEYİN OMURİLİK SIVISINDA BİYOLOJİK BELİRTEÇLER

Öz

Giriş: Kognitif bozulmanın ön planda olduğu, davranışsal sorunların ve günlük yaşam aktivitelerindeki bozulmanın eşlik ettiği, ilerleyici bir hastalık olan Alzheimer hastalığı ve serebrovasküler faktörler ile ilişkili, basamaklı kognitif gerileme ile seyreden vasküler demans sıklıkla ileri yaş hastalığıdır. Günümüzde hem Alzheimer hastalığı hem de vasküler demans tanısında patolojik inceleme altın standart olmakla birlikte, beyin omurilik sıvısı ve serumdaki biyolojik belirteçler ile sitokinlerin patofizyolojideki rollerini ortaya çıkarmak için çalışmalar hız kazanmıştır. Bu çalışmada Alzheimer hastalığı ve vasküler demans hastalarının eş zamanlı alınan beyin omurilik sıvısı ve serumlarındaki biyolojik belirteç seviyeleri değerlendirilmiştir.

Gereç ve Yöntem: Çalışmaya Alzheimer hastalığı (Grup 1) ve vasküler demans (Grup 2) tanısı konulan 30 hasta alındı. Grup 1 (n=15) ve grup 2 (n=15) hastalarından eş zamanlı olarak serum ve beyin omurilik sıvısı alınarak serum interlökin-1β, tümör nekroz faktör-α, interlökin-6, serum ve beyin omurilik sıvısı protein karbonil, glutatyon, β-amiloid düzeyleri ölçülüp karşılaştırıldı.

Bulgular: Gruplar karşılaştırıldığında, serum interlökin-1β, tümör nekrozis faktör-α, β-amiloid, serum ve beyin omurilik sıvısı protein karbonil, glutatyon düzeyleri istatistiksel olarak farklı değildi ($p>0.05$). Birinci gruba kıyasla ikinci grupta serum interlökin-6 düzeylerindeki yükseklik ile beyin omurilik sıvısı β-amiloid düzeylerindeki düşüklük istatistiksel olarak anlamlıydı ($p<0.05$).

Sonuç: Bu çalışmada, Alzheimer ve vasküler demans hastalarından eş zamanlı alınan BOS ve serumlarındaki sitokinler değerlendirildiğinde vasküler demans hastalarında Alzheimer hastalarına göre serum interlökin-6 seviyelerinin daha yüksek olduğu ancak beyin omurilik sıvısı amiloid düzeylerinin ise daha düşük seviyede olduğu saptandı.

Anahtar Sözcükler: Alzheimer hastalığı; Vasküler demans; Sitokinler; Biyokimyasal belirteçler

Correspondance

Güray KOÇ
Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Neurology,
ANKARA

Phone: 0312 291 19 22
Fax: 0312 291 19 22
e-mail: gurayerhan@gmail.com

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[1] Gulhane Training and Research Hospital, Neurology, ANKARA
[2] Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Neurology, ANKARA
[3] Liv Hospital , Neurology ANKARA
[4] Haydarpasa Sultan Abdulhamit Training and Research Hospital, Neurology ISTANBUL
[5] Istanbul University Cerrahpasa Medical Faculty, Biochemistry, ISTANBUL

INTRODUCTION

Various types of dementia are characterized by impaired cognitive ability that adversely affects activities of daily living. Dementia prevalence increases with age, and the care and treatment of affected individuals are quite expensive. The most frequently observed type of this syndrome is Alzheimer's disease (AD). In AD, cerebral parenchymal lesions are observed apart from the loss of neurons and synapses. Molecular studies have shown that amyloid beta-associated amyloid plaques are important in AD pathogenesis (1,2). Patients experience organizational problems when learning information, and distortion in the semantic and episodic memory is evident (2).

Cerebrovascular factors play roles in vascular dementia (VaD), and VaD usually manifests at a much older age. Vascular lesions in the brain are known cause to VaD; however, the role of these lesions in the pathophysiology of VaD has not been fully elucidated. The size and number of lesions in the brain as well as whether subcortical white matter is affected or not is important in VaD pathogenesis. Changes in the cognitive profile occur at different rates in VaD patients, with slow mentation and deteriorations in goal setting and organizing being at the forefront. Memory performance and hint-assisted remembering is better in VaD than in AD, and there is less frequent forgetting in VaD. Previous studies have reported that neuropsychological assessments in both these dementia types are similar (2,3).

Pathological examination is the most definite method to accurately diagnose both AD and VaD dementia. Research on specific and efficacious treatment methods for dementia types is ongoing because treatment methods differ among common dementia types. The primary aim of treatment in dementia is early initiation so as to slow down the disease process and to make the treatment more effective. In addition to biochemical neurophysiological and cognitive tests, several approaches such as combinations of specific imaging and genetic profiling have been attempted. Moreover, new methods are currently being developed. Biomarkers in various body fluids may be related to the clinical manifestation and the pathology of dementia. Biomarkers that are not affected by comorbid factors and do not show any individual differences are expected to play important roles in prognosis assessments as well as early diagnosis and treatment planning (3,4).

Recent postmortem studies have focused on biomarkers for effective diagnoses, and studies on the pathophysiological mechanisms associated with these biomarkers have begun. These mechanisms offer promise in distinguishing AD and VaD, assessing prognosis, and developing effective treatment and prophylactic strategies. Amyloid gene syntehesizes amyloid precursor protein (AβPP) from a fragment of 40 to 42 aminoacids which are the major neuropathological hallmarks of AD and was choosen as neurological marker. The clinical studies have showed that oxygen and nitrogen free radicals induced protein, lipid and DNA oxidation which were leading to the cytotoxic effect. Impaired permeability of the blood-brain barrier and endothelial damage in small vessels in AD patients were reported implying that the presence of oxidative radicals or free radical increase in systemic circulation might affect the brain in AD. Protein carbonyl (PCO) and glutathion (GSH) was choosen as oxidative stress markers (2,5,6,7).

Inflammatory mechanisms have been strongly linked to the pathogenesis of both AD and VaD. Cytokines such as interleukin 1β (IL-1β), tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6), which have been involved in the inflammatory process located close to amiloid plaques might be cytotoxic when chronically produced and might stimulate the production of β-amyloid peptides. Increased levels of TNF-a and IL-6 have been reported in the cerebrospinal fluid of patients with VaD which suggests a possible involvement of inflammatory mechanisms in the pathogenesis of cognitive impairment in patients with cerebrovascular disease (8). IL-1β, TNF-α and IL-6 were choosen as inflammatory markers.

The primary aim of this study was to compare biomarker levels measured in serum and cerebrospinal fluid (CSF) samples obtained simultaneously from patients with AD and VaD. The secondary aim was to define correlations within the groups.

MATERIALS AND METHOD

This prospective comparative clinical trial complies with the Declaration of Helsinki and was

approved by the Local Ethics Committee (August 2010, 984), and informed consent was obtained from all participants. A total of 30 patients diagnosed with AD and VaD were included in the study. Fifteen patients with Global Deterioration Scale (GDS) scores of 4–6 who were diagnosed with AD according to the diagnostic criteria of Communicative Disorders and Stroke and the Alzheimer's Disease and related Disorders Association (NINCDS-ADRDA) were included in the AD group (Group 1) (9). Fifteen patients with GDS scores of 4–6 and diagnosed with VaD according to the diagnostic criteria of Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN) were included in the VaD group (Group 2) (10).

Clinical and demographic data of all patients was collected. General physical and neurological examinations were performed for each patient. Clinical evaluation and biochemical analyses were performed to exclude other pathologies. Brain magnetic resonance and brain computed tomography images of all patients were evaluated to exclude other pathologies and to support the diagnosis. Patients with a history of malignancies; those with inflammatory disease, uncontrolled hypertension (HT), uncontrolled diabetes mellitus (DM), chronic liver failure, chronic renal failure, congestive heart failure, hypophyseal and hypothalamic dysfunction, major psychiatric disorders; or those who took steroids, antibiotics, and nonsteroidal anti-inflammatory drugs in the last 10 days were excluded from the study.

The diagnosis of HT was based on antihypertensive drug use and three or more blood pressure measurements above 140/90 mmHg. The diagnosis of DM was based on the fact that at least two measurements of fasting glycemia were>126 mg/dl and that blood glycemia was>200 mg/dl 120 min after the oral glucose challenge test. Smokers were defined as those who smoked 10 cigarettes/day.

According to the inclusion and exclusion criteria, 15 men and 15 women were included in the study. Blood and CSF samples were obtained simulteanously from the patients between 8–10 a.m. after they were maintained on fasting since 10 p.m.. CSF was collected in 2.5 samples in the lateral decubitus position from the L4–L5 intervertebral disc space. Blood and CSF samples were then poured into regular biochemistry tubes and were centrifuged for 10 min at 1000 rpm before being placed in deep freezers (−80°C) after removing the precipitates from the bottom. All patients in the AD group were taking acetylcholinesterase inhibitor (AChEI), whereas none of the patients in the VaD group were taking AChEI or N-Methyl-D-aspartic acid (NMDA) receptor antagonist.

Serum levels of IL-1β, IL-6, and TNF-α were measured using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits (AssayPro LCC, St. Charles, MO, USA). Results are provided in pg/mL. According to the manufacturer's guidelines, the coefficient of variation was 10.2%, 9.7%, and 10.5% for the assessments of IL-1β, IL-6, and TNF-α, respectively. Serum and CSF $A\beta_{1\text{-}40}$ levels were measured by ELISA (Invitrogen Corporation, CA, USA), as were serum and CSF protein carbonyl (PCO) levels (Northwest Life Science Specialties, LLC, WA, USA). Serum and CSF glutathione (GSH) assays were analyzed with the Modified Tietze method using the NWLSS Glutathione Assay kit (Northwest Life Science Specialties, LLC, WA, USA).

Statistical analysis was performed using SPSS software (version 15). The normal distribution of variables was examined with visual (histogram) and analytical (Kolmogorov–Smirnov) methods. Descriptive analyses for non-normally distributed variables are shown as median, minimum, and maximum levels. Serum and CSF GSH, PCO, and β-Amyloid, as well as serum TNF-α, IL-1β, and IL-6 levels were non-normally distributed; these parameters were compared between groups using the

Mann–Whitney U test. Differences were considered statistically significant when P values were<0.05. Correlation coefficients and statistical significance for intervariable correlations that were non-normally distributed were calculated using the Spearman's rank correlation coefficient. The type-1 error level of 5% was considered statistically significant.

RESULTS

Fifteen (8 males, 7 females) AD and 15 (7 males, 8 females) VaD patients were included in the study. No significant difference was detected between the groups in terms of age and gender. There was no significantly significant difference in comorbidities between the prevalence of DM and coronary heart disease (CHD) between the groups. HT was statistically higher in Group 2 (p<0.05). There was no significant difference between the groups in terms of smoking habits (Table 1).

There was no statistically significant difference between the groups regarding serum and CSF GSH median levels (p>0.05) or PCO levels (p>0.05). Although there were no differences in serum β-amyloid levels between the groups, CSF β-amyloid levels were lower in Group 2 (p<0.05). Although there were no significant differences in serum TNF-α and IL-1β levels between the groups (p>0.05), serum IL-6 levels were higher in Group 2 (p<0.05; Table 2).

DISCUSSION

According to the findings obtained in this study, serum IL-1β, TNF-α, and β-amyloid levels as well as serum and CSF PCO and GSH levels were not statistically different between the AD and VaD groups. Compared to the AD group, VaD group had significantly higher serum IL-6 levels and significantly lower CSF β-amyloid levels. HT was statistically higher in the VaD group. These statistical significant findings are important because they show a pathological association when evaluated in terms of sensitivity and specificity.

Clinically apparent impairment in memory functions in AD indicates severe loss of neurons in the entorhinal cortex. Hence, attempts to detect these pathophysiological changes early to develop treatments to prevent this progressive process are underway. Studies have shown that many biomarkers, such as IL-1β, IL-6, IL-10, TNF-α, Aβ1-42 and Aβ1-40 are related to pathological processes (5,6). In recent studies, the search for specific biomarkers associated with pathological processes in dementia patients has been accelerated. Whether these markers are the cause or the consequence of disease is crucial in understanding the pathophysiology and in developing new treatment strategies. Some of the biomarkers identified show an association with the dementia type rather than with etiologies. Therefore, these biomarkers may be important indicators of sensitivity and specificity in support of diagnosis and treatment planning.

Table 1. General characteristic of Alzheimer's Disease (Group 1) and vascular dementia (Group 2) patients

Parameter	Group 1	Group 2	p
n (Women/Men)	15 (7/8)	15 (8/7)	0.71
Age	70.20±6.25	71.26±6.45	0.72
HT (n)	6	12	0.025[a]
DM (n)	2	6	0.099
Smoking (n)	6	7	0.71
CHD (n)	3	5	0.40

[a]p<0.05 N,Number; HT, Hypertension; DM, Diabetes Mellitus; CHD, Coronary Heart Disease

Table 2. Biomarker levels for Alzheimer's Disease (Group 1) and vascular dementia (Group 2) patients

		Group 1	Group 2	[a]p
Serum GSH level (μmol/L)	**Mean±sd**	15.99±6.00	15.68±5.75	0.7089
	Min-Max	5.25–26.25	5.25–28.60	
	Median	18.20	15.00	
	95% CI	12.67–19.31	12.50–18.86	
CSF GSH level (μmol/L)	**Mean±sd**	12.23±7.47	12.67±7.16	0.6936
	Min-Max	4.59-36.75	5.25–34.12	
	Median	10.46	10.50	
	95% CI	8.09–16.37	8.70–16.63	
Serum PCO level (nmol/mg)	**Mean±sd**	2.29±0.82	1.80±0.81	0.0969
	Min-Max	0.68–3.64	0.45–3.18	
	Median	2.18	1.59	
	95% CI	1.83–2.75	1.35–2.25	
CSF PCO level (nmol/mg)	**Mean±sd**	9.13±4.09	7.78±2.72	0.4124
	Min-Max	2.15–15.90	3.32–10.50	
	Median	8.75	8.89	
	95% CI	6.86–11.40	6.28–9.29	
Serum Amyloid level (pg/ml)	**Mean±sd**	3.98±2.72	5.30±3.85	0.4427
	Min-Max	0.50–10.64	0.57–11.93	
	Median	3.78	3.57	
	95% CI	2.47–5.48	3.16–7.43	
CSF Amyloid level (pg/ml)	**Mean±sd**	391.23±56.45	334.27±43.85	0.0062
	Min-Max	295.0–475.0	239.0–399.0	
	Median	395.0	340.0	
	95% CI	360.0–422.5	310.0–358.6	
Serum TNF-α level (pg/ml)	**Mean±sd**	32.17±11.52	27.50±11.78	0.1607
	Min-Max	8.62–54.40	12.63–57.62	
	Median	30.45	26.90	
	95% CI	25.79–38.55	20.97–34.02	
Serum IL-1β level (pg/ml)	**Mean±sd**	15.05±5.24	11.84±4.65	0.0975
	Min-Max	5.89–25.96	6.67–21.33	
	Median	15.40	10.96	
	95% CI	12.15–17.95	9.26–14.42	
Serum IL-6 level (pg/ml)	**Mean±sd**	28.48±9.11	38.96±9.19	0.0153
	Min-Max	13.90–43.00	25.60–57.56	
	Median	27.90	35.90	
	95% CI	23.43–33.52	33.87–44.05	

[a]Mann–Whitney U Test; GSH, Glutathione; PCO, Protein carbonyl; CSF, Cerebrospinal fluid

With high lipid content and oxygen capacity brain is more prone to oxidative stress. Serum and CSF PCO and GSH levels as oxidative stress markers were found similar both in AD and VaD. According to our results these oxidative stress markers are not crucial for differentation of both diseases. Serum TNF-α and IL-1β as inflammatory mediators, produced in both brain and systemic, were found similar in AD and VaD groups. Therefore these mediators have no an important role in the pathophysiology of AD and VaD.

Zuliani et al. measured plasma levels of IL-6, TNF-α, IL-1β, and IL-10 in four groups of patients: a late-onset Alzheimer's disease group (LOAD, 60 subjects), a vascular dementia group (VaD, 80 subjects), a cerebrovascular disease without dementia group (CDND, 40 subjects), and a control group (C, 42 subjects). Compared to the C group, the LOAD, VaD, and CDND groups had high IL-1β levels. TNF-α levels were higher in the VaD and LOAD groups than in the C group; furthermore, TNF-α and IL-6 levels were higher in the VaD group than in the LOAD group. Logistic regression analysis indicated that higher IL-6 levels increased VaD risk compared to LOAD risk (8). In our study, serum IL-6 levels were higher in the VaD group.

Angelopoulos et al. found elevated serum IL-1β, IL-6, and IL-10 levels in dementia patients. There was no statistically significant correlation between interleukin levels in AD and VaD patients. However, there was a significant correlation between IL-6 and TNF-α levels and age. IL-1β and IL-6 showed a positive correlation with HT (11). In our study, HT prevalence was higher in the VaD group than in the AD group, and IL-6 levels were similarly high. Yasutake et al. examined serum BDNF, TNF-α, and IL-1β levels in 60 AD, 60 VaD, and 33 healthy control participants. Serum BDNF levels were found to be significantly lower in the AD group than in the VaD and control groups. There was no correlation between TNF-α and IL-1β levels or BDNF levels in the dementia groups, and there were no differences in TNF-α and IL-1β levels between the groups (12). In our study, there was no difference between the AD and VaD groups in terms of TNF-α and IL-1β levels.

Vascular infarcts and presence of neuroinflammation associated with increased IL-6 levels in different types of dementia was well known (13). Helmy et al. evaluated IL-6 levels, C-reactive protein levels, and serum protein electrophoresis results in 10 AD, 10 VaD, and 20 non-demented control participants. Serum IL-6 and C-reactive protein levels were significantly higher in both the dementia groups than in the control group. There was no statistically significant difference between the AD and VaD groups in terms of IL-6 levels. The serum IL-6 cutoff level at which statistical significance was observed was 14.25 pg/mL. It has been concluded that serum IL-6 levels may be used to differentiate dementia from the normal aging-related changes (14). In our study, serum IL-6 levels were higher in the VaD group. These differences may be because of differences in the number of patients, their treatment status, and the presence of comorbidities, such as HT, DM, and CHD.

In the study by Janelidze et al., different types of dementia biomarkers in CSF were studied. When CSF β-amyloid levels were examined in the AD and VaD groups, levels in the VaD group were lower than those in the AD group (15), consistent with the findings of the present study. Acetylcholinesterase inhibitor usage in the AD group, no AChEI or NMDA receptor antagonist usage in the VaD group, and many possible confounding factors, such as accompanying HT, DM, or CHD, may have influenced this result. In many studies, β-amyloid levels were lower in the AD groups than in the control groups, whereas IL-6 levels were higher in the VaD groups than the control groups. Therefore, the lack of a control group is the most important limitation of the present study. The second limitation is the limited number of patients.

In conclusion, serum IL-6 and CSF β-amyloid levels showed significant differences between VaD and AD patients, suggesting that this distinction may be important in the pathophysiological process. There is a need for randomized, double-blind, placebo-controlled, and long-term follow-up studies in which patients are assessed for comorbid factors to accurately demonstrate the efficacy and potency of these biomarkers in determining AD and VaD.

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