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VCAM-1 as an Endothelial Factor for Diagnosis of Dementia in Parkinson's Disease

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Abstract

Background: Cognitive changes are often reported in Parkinson's disease (PD). Numerous studies showed that there are changes in the patterns of inflammation when vascular dementia progressed, but the role of inflammation in PD is unknown.

Methods: 75 consecutive diagnosed PD patients included. Patients divided into idiopathic PD (n=55) and PDD (n=20) based on DSM-IV criteria for diagnosis of dementia. Serum levels of vascular and inflammatory biomarkers for interleukin-6 (IL-6), high sensitivity-C reactive protein (hs-CRP), soluble intracellular cell adhesion molecule (ICAM-1), soluble vascular cell adhesion molecule (VCAM-1) investigated by ELISA assay and compared between PD and PDD.

Result: The significant enhancement of the VCAM-1 only found in serum of PDD compared to PD ($56/06 \pm 58/16$ ng/ml vs. $30/43 \pm 38/30$, $P=0/04$), even after adjustment age, gender and hypertension ($OR=1/01$, $P=0/05$). Cut-off point of VCAM-1 levels was equal to or greater than as 40/14 ng/ml for differentiating dementia in PD from PD without dementia with sensitivity and specificity were 73%, 64%.

Conclusion: PDD patients had significant higher levels of VCAM-1 than PD, suggesting the serum levels of VCAM-1 may be a useful marker for PDD diagnosis. Future studies are needed to investigate possible association between VCAM-1 levels in PDD in larger sample size.

Keywords: Dementia; Neurodegenerative disorders; Cognitive; Elisa; Biomarkers; Parkinson's disease; DSM-IV

Introduction

Dementia in neurodegenerative disorders such as Parkinson's disease (PD) was as an impairment in the structure and function of cerebral blood vessels and associated cells (neurovascular unit), and these effects are mediated by inflammation [1]. Systemic and central immune systems can communicate in the presence of an intact brain blood barrier (BBB). In AD (Alzheimer's disease), where there is evidence of a breakdown in BBB permeability [2-5], there is an even greater likelihood of communication by means of inflammatory mediators between the CNS and periphery. Some studies showed that plasma levels of inflammatory markers such as Interleukin-6 (IL-6) and high sensitivity Creative protein (hs-CRP) increased in the early stages of PD and in the early stages of Cognitive decline leading to AD [6]. Recently there is an activated research field to an early role for inflammatory processes in disease onset and progression, accumulating research also focuses a more complicated picture, in which pro-inflammatory markers inconsistently and at times inversely relate to cognitive decline. Several large comprehensive studies declared no association between baseline inflammation and future risk of AD or non-AD dementia or have noted no independent effects over and above traditional vascular risk factors [7-9]. Due to the activated primary response of immune system, it has been observed that endothelial dysfunction markers such as soluble inter-cellular adhesion molecule (ICAM-1) and soluble vascular cell adhesion molecule (VCAM-1) increased in neurodegenerative disease [10]. However, other studies have reported no association [11,12] in identifying the diagnostic biomarker in dementia in Parkinson's patients help clinician that select right patients for appropriate treatment. The Present study designed to answer the question whether the inflammatory biomarkers have a suitable power in comparing to vascular biomarkers for diagnosis of dementia in PD, so, we investigate the serum concentration of hs-CRP and IL-6 as representative of systemic inflammation and ICAM-1 and VCAM-1 as vascular biomarkers.

Materials and Methods

Population

Seventy-five consecutive diagnosed PD patients seen in an outpatient primary care setting who presented movement symptoms were enrolled. PD patients were evaluated by trained neurologists and diagnosed based on the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria for Parkinson's disease. We excluded patients with secondary causes of Parkinsonism (e.g. Wilson's disease, neuroleptic drug use or psychiatric diseases) [13-15]. PD patients with a cerebrovascular disease or focal neurological signs of cerebral disease were also excluded. None of the subjects included in this study had a recent out- or inpatient history of recent infection, a history of surgery or trauma during the previous month, cardiovascular disease, and use of NSAIDs. Informed consent was obtained from the participants before entering the study. The study was approved by the local ethics committee of Islamic Azad University, Iran.

Measurements

Dementia was diagnosed by DSM-IV criteria [16] and by Mini-Mental state exam (MMSE) [17] scores adjusted for educational adjustment. In addition, we defined hypertension, diabetes mellitus, hypercholesterolemia, and cigarette smoking based on medical histories to examine relationships between these atherosclerosis risk factors and biomarkers levels. Hypertension was defined as a systolic blood pressure of >140 mmHg, a diastolic blood pressure of >90 mmHg, or the current use of antihypertensive medications. Diabetes mellitus (DM) was defined as a history of a fasting glucose >110 mg/dl or the current use of hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol

concentration of >220 mg/dl or the current use of lipid-lowering agents. Cigarette smoking was described as the patient stating any cigarette smoking during the previous 5 years.

Blood sampling and biological assays

Venous blood samples for biomarkers analysis were obtained from all 75 non-fasting subjects. Biomarker levels in PD patients were measured in the morning before antiparkinsonian therapy was administered. The serum samples were obtained within 1 hour of blood sampling by centrifugation at 3,000 rpm for 10 minutes. Serum samples were stored at -70°C until required for laboratory evaluations. Levels of ICAM-1 by Boster biological Technology – Human ICAM-1 ELISA kit, levels of VCAM-1 by Boster Biological Technology- Human VCAM-1 ELISA Kit, levels of hs-CRP by LDN –CRP – high sensitivity Human Elisa kit, levels of IL-6 by Orgenium IL-6 human Elisa kit.

Statistical analysis

Calculation was performed using the SPSS version 19.0 software. Group results are expressed as means \pm standard deviations (SD). Pearson's Chi-square analysis was used to compare group categorical variables, and independent t-tests were used to compare continuous variables. Binary logistic regression analysis was used to adjust for potential confounders. Statistical significance was determined using an error level of 5%.

Results

The demographic and baseline clinical features of the PDD patients and PD patients presented in **Table 1**.

Table 1 Baseline characteristics of all subjects in each group.

Characteristics	PDD (n=20)	PD (n=55)	P value
Demographics			
Male, n (%)	6 (30)	33 (60)	0.43
Age (year), mean \pm SD*	70/25 \pm 9/04	61/03 \pm 10/23	0/001
Illiterate	15 (75%)	30 (54%)	0/12
MMSE Score*	17/35 \pm 4/17	27/07 \pm 2/65	0/000
Biomarker studies			
hs-CRP (mg/dl), mean \pm SD	0/15 \pm 0/19	0/10 \pm 0/03	0/06
IL-6 (ng/ml), mean \pm SD	78/61 \pm 69/05	56/20 \pm 50/15	0/13
ICAM-1 (ng/l), mean \pm SD	779/57 \pm 611/79	796/00 \pm 612/94	0/92
VCAM-1 (ng/ml), mean \pm SD*	56/06 \pm 58/16	30/43 \pm 38/30	0/04
Clinical features			
Symptom duration (years), mean \pm SD	4/18 \pm 3/84	5/98 \pm 5/96	0/21

H & Y stage	2/001 ± 1/01	1/69 ± 0/82	0/203
HO	1 (5%)	5 (9/09%)	0/58
Hypertension (%)	10 (50)	16 (29)	0/09
Diabetes mellitus (%)	5 (25)	8 (14/5)	0/29
Hypercholesterolemia (%)	5 (25)	8 (14/5)	0/29
Smoking (%)	3 (15)	7 (12/7)	0/47

PDD: Parkinson disease with dementia, PD: idiopathic Parkinson's disease, hs-CRP (high sensitivity C-reactive protein), MMSE: Mini Mental Status Examination, H & Y stage: Hoehn and Yahr Stage, HO: Hypotension Orthostatic, Values was expressed as mean ± standard deviation, Gender was analyzed by Pearson chi-square test among 2 group, *P-value: PD vs. PDD <0.05

There were no significant differences in gender or symptom duration, although PDD patients were older. When evaluating serum levels of hs-CRP and VCAM-1 between PDD and PD after adjustment for age, sex and atherosclerotic risk factors, binary

logistic regression analysis demonstrated no significant association between hs-CRP level and dementia in PD (P=0.99), but VCAM-1 has a significant difference between two groups (P =0/04) (Table 2).

Table 2 Cut-off point for VCAM-1, IL-6 and hs-CRP for diagnosis of dementia in Parkinson's disease.

Variables	Cut off Point	Specificity (%)	Sensitivity (%)	NPV (%)	PPV (%)	Under area
VCAM-1 (ng/ml)	40.14	64	73	92.3	57.9	0/64
IL-6 (ng/ml)	38.12	49	73	90.4	26.3	0/62
Hs-CRP (mg/dl)	0.09	58	68	88.5	42.1	0/65

Negative Predictive Value (NPV) and Positive Predictive Value (PPV)

By binary logistic regression analysis, the odds ratio (with a 95% confidence interval) for PDD based on a VCAM-1 level was 1/01 (95% confidence interval=1/00–1/02, P= 0/04) (Table 2). Regarding association between VCAM-1 level and atherosclerosis risk factors, smoking had the largest effect on the VCAM-1 levels in PDD group, although this was not statistically significant (Table 3).

Table 3 Comparison of VCAM-1 by atherosclerotic risk factors in PDD patients.

Variables	VCAM-1 in PDD (ng/ml) (no/yes)	P-value
Hypertension	51.92 ± 60.65/60.66 ± 58.55	0.75
Diabetes mellitus	62.36 ± 64.85/38.42 ± 32.07	0.44
Hypercholesterolemia	55.76 ± 65.51/57.18 ± 16.31	0.96
Smoking	45.76 ± 47.68/111.01 ± 89.54	0.07

*P value: positive vs. negative <0.05

The MMSE in general neuropsychological tests showed significant difference related to age, VCAM-1 and hs-CRP at determined levels of cognitive function in Parkinson's disease because there was significant difference among normal cognitive function and mild cognitive impairment as follow: (P=0/01, P=0/04) and ICAM-1 levels was significant among mild and severe Cognitive Impairment.

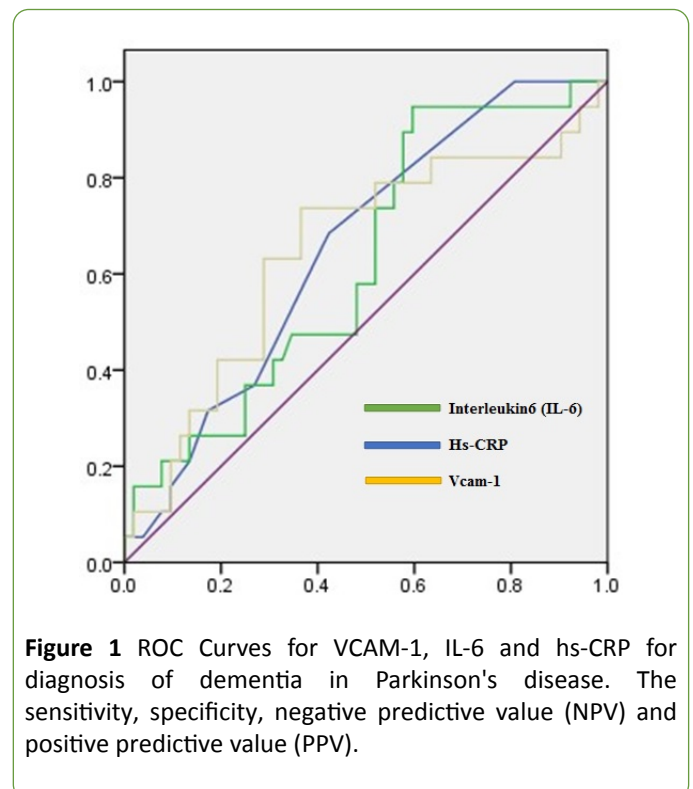


Figure 1 ROC Curves for VCAM-1, IL-6 and hs-CRP for diagnosis of dementia in Parkinson's disease. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV).

The fluctuation of IL-6 based on cognitive function from Normal to sever dysfunction showed in Figure 1. Used by ROC, the best cut-off point for differentiating dementia in PD from PDD was VCAM-1 levels equal to or greater than as 40/14 ng/ml. At this cut-off point, the sensitivity and specificity were

73% and 64%, The cut-off point calculated for IL-6 and hs-CRP levels equal to or greater than as 38/12 ng/ml and 0/09 with sensitivity and specificity were (73%, 49%, 68%, 58%) (Table 4 and Figure 1). In the group of patients with a cut-off value of

VCAM-1 (40/14 ng/ml) according to our results, the PDD patients with positive value, the average age was 71/81 ± 8/09 vs. 71/81 ± 8/09 years.

Table 4 hs-CRP and VCAM-1 comparisons between PDD and PD after adjustment for risk factors.

Variables	Odds ratio	P value	95% CI
Hypertension Gender	1.20 1.29	0.78 0.71	0.35-5.00 0.38-6.34
AGE *	1.09	0.01	1.02-1.18
Hs-CRP	2.33	0.99	0.00-1.70
VCAM-1 *	1.01	0.04	0.99-1.02

PDD group, PD normal MMSE result, hs-CRP high-sensitivity C-reactive protein, CI confidence interval, P value by binary logistic regression analysis

Duration of symptoms disease and the score of H & Y was 4/51 ± 3/93 years and 2/29 ± 0/96, only the MMSE score (16/07 ± 4/39) has a significant difference according to positive vs. negative values of VCAM-1 (P=0/03) (Table 5).

Table 5 Comparison of the clinical profiles by VCAM-1 cut point for the PDD patients.

Characteristics	VCAM-1 in PDD (cut point=40/14 ng/ml)		P value
	Negative	Positive	
Age (Mean ± SD)	69/80 ± 11/94	71/81 ± 8/09	0/85
Sex (Male, N (%))	4 (80%)	10 (66/6%)	0/70
Duration of symptoms (Mean ± SD)	2/30 ± 2/28	4/51 ± 3/93	0/25
H & Y stage (Mean ± SD)	1/51 ± 1/00	2/29 ± 0/96	0/14
MMSE Score (Mean ± SD)	20/60 ± 0/54	16/07 ± 4/39	0/03
VCAM-1 (Ng/ml) (Mean ± SD)	5/24 ± 2/88	80/94 ± 63/84	0/01

*P value: positive vs. negative <0.05

Discussion

To answer the question whether the inflammatory biomarkers have suitable power in comparing to vascular biomarkers for diagnosis dementia in Parkinson disease, our first finding that the higher serum levels of VCAM-1 appears to play role in PDD. Serum levels of IL-6, hs-CRP and ICAM-1 did not show any significant differences among PDD and PD. PDD is a multifactorial illness that the vascular pathologic interaction with the neuroinflammatory changes progresses to dementia. More knowledge about the mechanism of dementia in PD result to control modifiable risk factors. Our results proposed VCAM-1 as a modifiable vascular risk factor for PDD. This is supported by Zuliani et al. [2] showed that the levels of VCAM-1 was elevated among Alzheimer's disease than healthy controls, the differences was not statistically significant, while VCAM-1 positively correlated with age (and alcohol consumption and negatively associated with HDL-C levels). The

level of VCAM-1 in presence of smoking is significantly increasing in PDD patients. For comparison between mechanisms of dementia in Alzheimer's disease and Vascular dementia, Engelhart et al. showed no changes in the plasma levels of VCAM-1 and ICAM-1 in Dementia, AD and VD [5], also, Hochstrasser did not reveal that VCAM- affected in monocytes of AD and MCI patients [17,18]. ICAM-1 can be induced by different cytokines, such as, e.g. interleukin-1. It has been shown that ICAM-1's plasma levels were increased in AD but another study shown that ICAM-1/CD14 has not changed in MCI and AD [5]. Our study find that the IL-6 level as a proinflammatory cytokine has no significant correlation with PDD, other factors may be involve to induce adhesion molecules in this regard. Kravitz et al. proposed inflammation is typically thought as a risk factor for AD, so, CRP as a systemic inflammatory biomarker was in association with the plaque and tangle pathology in AD brain [19]. Doung et al. showed that the concentrations of CRP similar to those detected in the serum of AD patients are neurotoxic *in vitro* [20]. CRP may also contribute to atherosclerotic processes used by increase the expression of adhesion molecules such as vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1) in vascular endothelial cells [21-23], the relationship between CRP and atherosclerotic processes which can underlie VD may account for the relationship between this inflammatory marker and VD [24,25].

Conclusion

Previous studies have further suggested that the association between CRP and dementia in VD is stronger than AD [20,26]. While cerebrovascular dysfunction and neurodegeneration exist independently, both conditions can impact cognition, cerebrovascular dysfunction directly impacts dementia, a broad clinical determination for specific impairments. Importantly, global evaluation of vascular pathologies allows for greater attention to prevention of dementia and AD.

Limitations

Our study has several limitations: (1) the present study is a cross-sectional study; therefore, we cannot draw any

conclusions how the markers will change when disease progresses, or in the case of MCI remains stable or reverses. (2) The number of patients in this study is small and the differences are very small. (3) We extracted proteins by sonication of cells, thus we analyzed soluble cytoplasmic proteins. We do not know how membrane-bound proteins are changed. (4) The stability of the protein extracts was not tested. (5) Clinical diagnosis of dementia is made through specific impairments, meaning cognitive testing does not always have the sensitivity to discriminate specific underlying pathological conditions. It seems the serum level of VCAM1 may be a useful marker for diagnosis of PDD, However, it is unclear whether VCAM-1 can predict the risk of progression from mild cognitive impairment to dementia in Parkinson's disease. The role of blood brain barrier dysregulation mediated by VCAM-1 in progression of Parkinson's disease with dementia should be investigated in the future.

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Conflict of Interest

We have no conflicts of interest in this study.

Author Contributions

Homa Ebrahimi, Mohammad Saadatnia and Ahmad Sobhani conceived and designed the experiments.

Homa Ebrahimi, Ali Ebrahimi and Heshamtallah Orooji performed the experiments.

Homa Ebrahimi and Ali Ebrahimi analyzed the data.

Ahmad Chitsaz contributed the reagents/ materials/analysis tools.

Homa Ebrahimi and Mohammad Saadatnia wrote the paper.

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