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ASSESSMENT OF SYSTEMIC INFLAMMATORY INDICATORS AND THEIR CORRELATION IN ALZHEIMER'S DISEASE PATIENTS

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ABSTRACT

Background: The identification of Alzheimer's disease biomarkers can aid in tracking the disease's progression. Serum IL-6 levels are higher in people with Alzheimer's disease than in healthy individuals, according to a number of earlier research. Serum CRP levels in Alzheimer's disease patients have been found to rise in a small number of investigations. There are few research on albumin evaluation.

Aim: The purpose of this study was to determine whether systemic inflammatory indicators, such as albumin levels, C-reactive protein (CRP), and interleukin-6 (IL-6), may play a part in the onset of Alzheimer's disease (AD) and whether they are related to the severity of the disease.

Methods: In this cross-sectional investigation, individuals with Alzheimer's disease and vascular dementia (VaD) from the neuropsychiatry department were compared to non-demented controls (NDCs) who were evaluated from the general population. Serum levels of albumin, CRP, and IL-6 were measured in 220 individuals aged 50 years or older who had vascular dementia, Alzheimer's disease, and non-demented controls. A clinical dementia rating scale was employed in order to stage the degree of dementia. In dementia subgroups, the degree of dementia was evaluated and serum albumin, CRP, and IL-6 levels were compared.

Results: IL-6 serum levels were substantially higher in persons with Alzheimer's disease and vascular dementia (6.62 and 7.77, respectively) than in non-dementia controls (2.96, $p<0.001$).

The three study groups' albumin and CRP levels did not differ significantly from one another. Serum CRP and IL-6 levels were positively correlated with the severity of Alzheimer's disease, although only IL-6 showed a meaningful association. Serum albumin level and illness severity were found to be statistically correlated negatively.
Conclusions: The current study finds a strong correlation between the severity of Alzheimer's disease and systemic inflammatory indicators, especially IL-6 levels, which suggests a possible involvement for these markers in the pathophysiology of the disease. By focusing on these markers, novel approaches to Alzheimer's disease treatment can be developed.

Keywords: vascular dementia, inflammatory indicators, albumin, CRP, IL-6, and Alzheimer's disease

INTRODUCTION

A clinical entity and syndrome known as dementia is characterized by a severe enough acquired cognitive decline to interfere with day-to-day functioning. It may be linked to a number of behavioral and mental health issues. There are various varieties of dementia, with vascular dementia and Alzheimer's disease being the two most prevalent causes in older

adults. Alzheimer's disease is a neurodegenerative condition that manifests as extracellular amyloid deposition and intracellular neurofibrillary tangles (NFTs) in the afflicted brain regions.[1]

In patients with AD or Alzheimer's disease, neuroinflammation and neurodegenerative processes interact intricately. The pathophysiology of Alzheimer's disease is significantly influenced by neuroinflammation, which contributes to amyloid pathology and neuronal death. Neuroinflammation was formerly thought to be a result of amyloid accumulation and NFTs. Currently, it is thought that amyloid precursor protein triggers the release of inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP), which further encourages the formation and deposition of amyloid plaques.[2]

Additionally, the activation of microglial cells brought on by amyloid deposition results in the production of several cytokines, such as IL-6, which start the inflammatory response. The deposition of cerebral β-amyloid (Aβ) protein has been linked to the study of albumin, another inflammatory systemic marker, with varying degrees of success. The development of neuronal injury is accelerated by these inflammatory reactions. It is thought that inflammatory markers may be present in the serum of these individuals as it is evident that a chronic inflammatory state exists prior to the clinical onset of Alzheimer's disease.3

The detection of Alzheimer's disease biomarkers can aid in tracking the disease's progression. Data from other available research has demonstrated that patients with Alzheimer's disease have higher serum IL-6 concentrations than healthy controls. Serum CRP levels have been found to rise in Alzheimer's disease in a small number of research reviews. However, there aren't many research in the literature evaluating albumin in Alzheimer's disease. In light of these, it is necessary to assess systemic inflammatory markers in individuals suffering from Alzheimer's disease.4

The current study sought to determine whether systemic inflammatory markers, such as albumin levels, C-reactive protein (CRP), and interleukin-6 (IL-6), may play a part in the onset of Alzheimer's disease (AD) and whether they are related to the severity of the disease.

MATERIALS AND METHODS

The goal of the current cross-sectional clinical investigation was to determine if systemic inflammatory indicators, such as albumin levels, C-reactive protein (CRP), and interleukin-6 (IL-6), may play a part in the onset of Alzheimer's disease (AD) and whether they are related to the severity of the disease. The study participants came from the Institute's Department of Neuropsychiatry. Prior to their involvement in the study, all subjects gave their written and verbal informed consent. The study sample was drawn from participants at the Institute's outpatient neurology and psychiatry department. The study evaluated 88 participants who were at least 50 years old and had a verified clinical diagnosis of Alzheimer's disease.

The study's control group consisted of forty-four voluntary participants who had been clinically diagnosed with vascular dementia. Normal subjects who were matched for age and gender from the study group made up the non-dementia control group. The study's exclusion criteria for vascular dementia and Alzheimer's disease included people who were mentally ill and difficult to evaluate, subjects who did not consent to participate in the study, and subjects who did not provide their assent. Every participant was right-handed and evaluated using the Edinburgh Handedness Inventory.5

Following final inclusion, a single qualified psychiatric specialist in the field performed a thorough neuropsychiatric evaluation on each participant. Cognitive functions were evaluated using the Hindi Mental State Examination (HMSE), which is the Indian version of the Mini-Mental Status Examination. The EASI (Everyday Abilities Scales of India) was used to assess activities of daily living.6

One of the examiners from the department of neurology and psychiatry subsequently evaluated these people in order to establish a clinical diagnosis. Alzheimer's disease and vascular dementia were diagnosed using the International Classification of Disease-10 criteria.7

NINDS-AIREN8 and NINCDS/ADRDA9 were utilized for Alzheimer's disease and vascular dementia, respectively. The severity of dementia was evaluated using the clinical Dementia Rating Scale. EASI and HMSE were evaluated in NCDs. After obtaining informed consent, 10 ml of intravenous blood was drawn from participants with vascular dementia, Alzheimer's disease, and non-dementia controls. Within 30 minutes of sample collection, the serum was extracted and quickly kept at -200°C. An ELISA (enzyme-linked immunosorbent test) was performed using a commercially available kit to measure IL-6. A Random Access Discrete Auto analyzer was used to determine the serum CRP levels. Serum albumin levels were measured using a commercial kit and the photometric technique.

The collected data was statistically evaluated using the chi-square test, Pearson test, one-way ANOVA (analysis of variance), and SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk, NY, USA) for evaluating descriptive measures. The findings were presented as frequency, percentages, mean, and standard deviation. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

The goal of the current cross-sectional clinical investigation was to determine if systemic inflammatory indicators, such as albumin levels, C-reactive protein (CRP), and interleukin-6 (IL-6), may play a part in the onset of Alzheimer's disease (AD) and whether they are related to the severity of the disease. Serum levels of albumin, CRP, and IL-6 were measured in 220 individuals aged 50 years or older who had vascular dementia, Alzheimer's disease, and non-demented controls.

The average age of the research participants was 66.92±8.39 years, with the AD, VaD, and NDC groups having respective ages of 70.12±8.57, 66.84±4.64, and 68.54±5.65. The percentage of males in the Alzheimer's, VaD, and NDC groups was 59.09%, 59.1%, 72.7%, and 52.3%, respectively. The educational years for the Alzheimer's, VaD, and NDC groups were 5.03±4.51, 4.3±4.54, and 4.91±4.31 years, respectively. In contrast, alcohol use was 16.4%, 11.4%, 18.2%, and 20.5% in the Alzheimer's, VaD, and NDC groups, respectively, while smoking status was 21.7%, 27.1%, 22.5%, and 15.7%. While CDR was 6.03±3.88 and 4.96±3.34 in the AD and VaD groups, it was not applicable in the overall and NDC groups. The overall, AD, VaD, and NDC groups had EASIs of 2.83±3.20, 5.09±3.03, 4.03±2.42, and 0 respectively. For the overall, AD, VaD, and NDC groups, the corresponding HMSEs were 17±11, 13.1±3.97, 14.66±3.77, and 28.93±1.01 (Table 1).

Serum albumin levels in the AD, VaD, and NDC groups were statistically equivalent with p=0.42 when comparing the albumin, CRP, and IL-6 levels in study participants with Alzheimer's disease, vascular dementia, and non-demented controls. Serum CRP values were 1.03±1.13, 0.97±1.15, and 0.59±0.19 mg/dl, with a p-value of 0.32 indicating a statistically non-significant difference. Alzheimer's disease patients had significantly higher serum IL-6 levels (7.77±9.72 pg/ml), followed by vascular dementia patients (6.62±10.35 pg/ml) and non-demented control subjects (2.96±1.87, p=0.000) (Table 2).

In research participants with Alzheimer's disease, it was shown that serum albumin levels were considerably higher in mild dementia, followed by intermediate dementia, and were lowest in severe dementia (p=0.02) when comparing albumin, CRP, and serum IL-6 levels to dementia severity. Subjects with mild, moderate, and severe dementia showed non-significant differences in serum CRP levels (p=0.14). Subjects with severe dementia had significantly higher serum IL-6 levels (31.85±29.22 pg/ml), followed by those with moderate dementia (9.37±3.07 pg/ml) and those with mild dementia (4.12±2.18 pg/ml) (Table 3).

Serum albumin levels were 3.93±0.46, 3.76±0.24, and 3.53±0.47 g/dl in mild, moderate, and severe vascular dementia, with p=0.47 indicating statistical non-significance, according to the study's findings on the relationship between albumin, CRP, and serum IL-6 levels and dementia severity in study participants with vascular dementia. Serum CRP in the groups with mild, moderate, and severe vascular dementia showed a comparable non-significant difference (p=0.08). The groups with severe vascular dementia had the highest serum IL-6 levels (32.73±24.38 pg/ml), followed by those with moderate vascular dementia (8.16±2.58 pg/ml) and those with mild vascular dementia (2.92±1.42 pg/ml) with p=0.003 (Table 4).

DISCUSSION

220 participants aged 50 years or older were evaluated in this study. Serum levels of albumin, CRP, and IL-6 were measured in people with Alzheimer's disease and vascular dementia as well as in controls who were not affected by dementia. The average age of the research participants was 66.92±8.39 years, with the AD, VaD, and NDC groups having respective ages of 70.12±8.57, 66.84±4.64, and 68.54±5.65. The percentage of men in the Alzheimer's, VaD, and NDC categories was 59.09%, 59.1%, 72.7%, and 52.3%, respectively. The educational years for the Alzheimer's, VaD, and NDC groups were 5.03±4.51, 4.3±4.54, and 4.91±4.31 years, respectively.

In contrast, alcohol use was 16.4%, 11.4%, 18.2%, and 20.5% in the Alzheimer's, VaD, and NDC groups, respectively, while smoking status was 21.7%, 27.1%, 22.5%, and 15.7%. While CDR was 6.03±3.88 and 4.96±3.34 in the AD and VaD groups, it was not applicable in the overall and NDC groups. The overall, AD, VaD, and NDC groups had EASIs of 2.83±3.20, 5.09±3.03, 4.03±2.42, and 0 respectively. The overall, AD, VaD, and NDC groups had HMSEs of 17±11, 13.1±3.97, 14.66±3.77, and 28.93±1.01 respectively. These findings were comparable to those of studies conducted by Pu Z et al and Altunoglu E et al, in which the authors evaluated participants with comparable clinical, illness, and demographic characteristics.

Serum albumin levels were statistically equal in the AD, VaD, and NDC groups (p=0.42) when comparing the albumin, CRP, and IL-6 levels of study participants with vascular dementia, Alzheimer's disease, and non-demented controls. Serum CRP values were 1.03±1.13, 0.97±1.15, and 0.59±0.19 mg/dl, with a p-value of 0.32 indicating a statistically non-significant difference. Alzheimer's disease patients had considerably higher serum IL-6 levels (7.77±9.72 pg/ml), followed by vascular dementia patients (6.62±10.35 pg/ml) and non-demented control subjects (2.96±1.87, p=0.000).

These findings were in line with earlier research by Cankurtaran M et al. (2012) and Can M et al. (2013), who, like the authors of the current study, found that IL-6 levels were significantly higher in Alzheimer's disease, vascular dementia, and non-dementia control subjects.

Additionally, it was noted that among research participants with Alzheimer's disease, albumin, CRP, and serum IL-6 levels were strongly correlated with the severity of dementia. Serum albumin levels were highest in mild dementia, followed by moderate dementia, and lowest in severe dementia (p=0.02). Subjects with mild, moderate, and severe dementia showed non-significant differences in serum CRP levels (p=0.14).

Subjects with severe dementia had considerably higher serum IL-6 levels (31.85±29.22 pg/ml), followed by those with moderate dementia (9.37±3.07 pg/ml) and those with mild dementia (4.12±2.18 pg/ml) (p=0.000). These results were consistent with those of Singh Manoux A et al. (2014) and Koyama A et al. (2013), who found that patients with severe dementia had considerably greater serum levels of IL-6 than subjects with mild and moderate dementia who had Alzheimer's disease.

Serum albumin levels were 3.93±0.46, 3.76±0.24, and 3.53±0.47 g/dl in mild, moderate, and severe vascular dementia, with p=0.47 indicating statistical non-significance, according to the study's findings on the relationship between albumin, CRP, and serum IL-6 levels and dementia severity in vascular dementia study participants.

Serum CRP in the groups with mild, moderate, and severe vascular dementia showed a comparable non-significant difference (p=0.08). Serum IL-6 levels were highest in groups with severe vascular dementia (32.73±24.38 pg/ml), followed by moderate vascular dementia (8.16±2.58 pg/ml) and mild vascular dementia (2.92±1.42 pg/ml) (p=0.003). These findings were published by Lai KSP et al and Cooper J et al, who also noted that patients with severe dementia had considerably greater serum levels of IL-6 than subjects with mild and moderate dementia who had vascular dementia.

CONCLUSIONS

Within its limitations, the present study concludes that there is a remarkable association of systemic inflammatory markers with the severity of Alzheimer's disease, particularly in IL-6 levels that depicts its potential role in disease pathogenesis. Targeting these markers can help achieve new ways in therapeutic strategies for Alzheimer's disease. In the future, longer studies in varying geographical areas are needed to attain a definitive conclusion.

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S. No	Parameters	Overall (n=220)	Alzheimer's (n=88)	Vascular dementia (n=44)	NDC (n=88)
1.	**Mean age (years)**	66.92±8.39	70.12±8.57	66.84±4.64	68.54±5.65
2.	**Male gender (%)**	59.09	59.1	72.7	52.3
3.	**Education years**	4.87±4.44	5.03±4.51	4.3±4.54	4.91±4.31
4.	**Smoking status (%)**	21.7	27.1	22.5	15.7
5.	**Alcohol intake (%)**	16.4	11.4	18.2	20.5
6.	**CDR**	N/A	6.03±3.88	4.96±3.34	N/A
7.	**EASI**	2.83±3.20	5.09±3.03	4.03±2.42	0
8.	**HMSE**	17±11	13.1±3.97	14.66±3.77	28.93±1.01

Table 1: Clinical and sociodemographic data in study subjects

S. No	Parameters	Alzheimer's (n=88)	Vascular dementia (n=44)	NDC (n=88)	p-value
1.	**Serum albumin (g/dl)**	3.92±0.43	3.87±0.43	3.96±0.44	0.42
2.	**Serum CRP (mg/dl)**	1.03±1.13	0.97±1.15	0.59±0.19	0.32
3.	**Serum IL-6 (pg/ml)**	7.77±9.72	6.62±10.35	2.96±1.87	**0.000**

Table 2: Albumin, CRP, and IL-6 levels in study subjects with non-demented controls, vascular dementia, and Alzheimer's disease

S. No	Dementia severity	Mild (CDR=1) (n=520	Moderate (CDR=2) (n=30)	Severe (CDR=3) (n=6)	p-value
1.	**Serum albumin**	4.06±0.46	3.74±0.28	3.65±0.52	**0.02**
2.	**Serum CRP**	0.85±0.89	1.12±1.27	2.14±1.73	0.14
3.	**Serum IL-6**	4.12±2.18	9.37±3.07	31.85±29.22	**0.000**

Table 3: Association of albumin, CRP, and serum IL-6 levels to dementia severity in study subjects with Alzheimer's disease

S. No	Dementia severity	Mild (CDR=1) (n=520	Moderate (CDR=2) (n=30)	Severe (CDR=3) (n=6)	p-value
1.	**Serum albumin**	3.93±0.46	3.76±0.24	3.53±0.47	0.47
2.	**Serum CRP**	0.61±0.32	1.60±2.17	2.63±1.89	0.08
3.	**Serum IL-6**	2.92±1.42	8.16±2.58	32.73±24.38	**0.003**

Table 4: Association of albumin, CRP, and serum IL-6 levels to dementia severity in study subjects with vascular dementia