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ORIGINAL ARTICLE

Assessment of Neuroinflammatory Markers (IL-6, TNF-α) and Cognitive Decline in Early Alzheimer's Disease Patients

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ABSTRACT

Background: Alzheimer disease is a progressive neurodegenerative disorder characterized by premature deterioration of the brain and progressive memory impairment. Emerging evidence suggests that neuroinflammation plays a central role in the pathogenesis of the disease, with pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) contributing to neuronal dysfunction and cognitive decline.

Objective: To measure serum IL-6 and TNF-α levels in patients with early-stage Alzheimer disease and to determine their association with cognitive deterioration.

Methods: This cross-sectional comparative study was conducted at a tertiary care hospital from March 2023 to February 2025. A total of 70 participants were enrolled, including 40 patients with early Alzheimer disease and 30 cognitively healthy controls. Cognitive performance was assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Serum IL-6 and TNF-α levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using SPSS version 26, and correlations were assessed using Pearson's correlation coefficient.

Results: Patients with early Alzheimer disease had significantly lower cognitive scores than controls (MMSE: 21.48 ± 2.86 vs 28.27 ± 1.41; MoCA: 18.94 ± 3.17 vs 26.31 ± 1.84; $p = 0.001$). Serum IL-6 and TNF-α levels were significantly elevated in the Alzheimer group (IL-6: 8.61 ± 2.49 pg/mL vs 4.29 ± 1.47 pg/mL; TNF-α: 14.87 ± 4.12 pg/mL vs 8.64 ± 2.31 pg/mL; $p < 0.001$). Both cytokines demonstrated significant negative correlations with MMSE and MoCA scores, indicating that higher inflammatory marker levels were associated with poorer cognitive performance.

Conclusion: Elevated serum IL-6 and TNF-α levels in early Alzheimer disease are significantly associated with cognitive decline. These findings support the role of neuroinflammation in Alzheimer disease progression and suggest that these inflammatory markers may serve as accessible biomarkers for early disease monitoring and prognostic evaluation.

Keywords: Alzheimer disease, IL-6, TNF-α, neuroinflammation, cognitive decline, biomarkers.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that is most prevalent among the elderly in the world and the primary cause of dementia[1]. It is a progressive worsening of memory, attention, executive functions, language, and behavior, which eventually leads to loss of autonomy and deterioration of functional abilities. Following the rising life expectancy around the globe, the disease burden in Alzheimer is growing exponentially, and it is a health issue of significant concern to people, particularly in low- and middle-income nations where timely diagnosis and lifelong neurological care have not been effectively established yet[2]. Though the traditional

concept of Alzheimer disease has been based on the idea of the amyloid-beta plaque deposition and the development of the neurofibrillary tangles, the modern-day research has proven that the pathogenesis of this disease is much more complicated and comprises a number of parallel molecular and cellular processes. Neuroinflammation in chronic form nowadays is considered to be one of the primary causes of disease outbreak, disease development and clinical worsening[3].

Activated microglia and astrocytes are the main mediators of neuroinflammation in Alzheimer disease in response to amyloid deposition, tau pathology, oxidative stress, synaptic loss, and neuronal degeneration, releasing a large repertoire of inflammatory mediators[4]. Although acute inflammatory reactions might have some protective or clearance-related function, chronic infection of the immune pathways can become maladaptive and help to cause progressive neuronal dysfunction. This protracted inflammatory condition has been suggested to worsen the loss of synapses, neuroplasticity, blood-brain barrier dysfunction, promote oxidative damage, and accelerate neurodegeneration. Inflammatory pathways are therefore no longer deemed as secondary epiphenomena in Alzheimer disease but they are active biological forces which can be relevant in both the initiation and escalation of cognitive impairment[5].

Among various inflammatory mediators that have been associated with the Alzheimer disease, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a) have been of special interest due to their significant role in immune signaling, neuronal damage and cognitive impairments[6]. The IL-6 is a versatile cytokine that participates in acute-phase reaction, glial induction and inflammatory amplification. The long-term presence of IL-6 has been considered to lead to abnormal neurotransmission, to enhance amyloidogenic processing, and to deteriorate cognitive functioning. On the same note, TNF-a is a strong pro-inflammatory cytokine that is known to affect functions of synapses, apoptosis, dysfunction of mitochondria, and neurovascular integrity. Continued TNF-alpha inflammation can lead to neuronal susceptibility and facilitation of the early cognitive impairment to settled dementia[7]. Both of the markers have thus become promising leads in the hunt to find clinically useful inflammatory biomarkers in Alzheimer disease[8].

Over the last few years, a number of studies that have done so by using biomarkers have tried to explain whether circulating markers of inflammation have the capacity to indicate the pathological burden underlying the Alzheimer disease and the cognitive impairment[9]. The existing literature has found high levels of serum or plasma IL-6 and TNF-alpha in patients with Alzheimer disease and mild cognitive impairment than cognitively healthy individuals. Other reports have also shown that these cytokines have a significant negative correlation with cognitive performance as measured by the Mini-Mental State Examination (MMSE) indicating that higher levels of inflammation could be associated with lower performance. Further supporting research on the concept is more recent systematic review and meta-analyses results that suggest that inflammatory dysregulation is constant in Alzheimer disease and can correlate to disease severity and progression[10].

It is specifically significant to identify stable and least invasive biomarkers in the initial stages of the Alzheimer disease, during which the slight mental decline may already exist, but the developed neurodegeneration is not entirely manifested yet[11]. Identifying patients who are at risk of a more rapid deterioration earlier might enhance the clinical monitoring process, help to intervene promptly, and aid in biomarker-based therapeutic interventions in the future. In most healthcare systems, particularly those of developing economies like Pakistan, complex diagnostic systems like the cerebrospinal fluid biomarker, amyloid PET, and advanced molecular neuroimaging are not a systematic measure. In this regard, inflammatory biomarkers in blood have the potential to offer an alternative to clinical analysis and a neurocognitive-oriented assessment that is feasible and somewhat affordable[12].

Although there is an increasing global concern on inflammatory biomarkers, there is scanty local and regional data on the connection between serum IL-6, TNF-alpha and early cognitive atrophy in Alzheimer disease[13]. The bulk of published literature has been done in non-Pakistani groups and how these markers can be clinically applicable in our context is not well studied. Knowledge of this association can assist in enhancing biomarker-based dementia studies in resource-constrained clinical settings and also make further contributions towards biologically resourceful evaluation of early Alzheimer[14].

Thus, the current research was aimed at evaluating the levels of serum IL-6 and TNF-a in patients with the early signs of Alzheimer disease and establishing their relationship with the extent of cognitive deficit with the help of standardized cognitive testing tools[15]. The hypothesis was that neuroinflammatory markers levels would be much higher in patients with early Alzheimer disease and that they would be judged by a worse cognitive performance[16].

MATERIAL & METHODS

This is a cross-sectional comparative study carried out in the Neurology and Psychiatry Departments of a tertiary care teaching hospital in Lahore, Pakistan, during two years between March 2023 and February 2025. The research was

also commenced upon receiving a formal consent of the Institutional Ethical Review Committee and all the procedures conducted were in compliance with the ethical principles postulated in the Declaration of Helsinki. All cognitively healthy subjects were informed and all patients with early Alzheimer disease were informed, through the informed consent, before enrollment of the patient and the legally authorized attendants or caregivers.

The study consisted of 70 participants who were selected using non-probability consecutive sampling. Among them, 40 clinically diagnosed cases of early Alzheimer in the disease group and 30 age and sex matched cognitively healthy individuals were enrolled and occupied the control group. Outpatient neurology and psychiatry clinics and memory assessment units and referred geriatric evaluation services were used to recruit patients. Control group: It was chosen among attendants, community volunteers and hospital visitors who did not have any clinical evidence of cognitive impairment or dementia.

Eligible subjects of both sexes who were between 55 and 80 years of age were included. The case group consisted of patients whose clinical diagnosis was early Alzheimer disease, provided by detailed history, a neurological examination, memory deterioration (according to the caregiver), and cognitive assessment conducted by a team of special physicians. Probably Alzheimer disease diagnosis was made using established clinical diagnostic principles in line with the early symptomatic Alzheimer disease with the focus on progressive memory loss and dysfunction in the cognitive domains without the advanced end-stage functional dependence. Controls were to be involved when they did not have a known history of dementia, major psychiatric illness, cerebrovascular accident, Parkinsonism or other age and education-adjusted neurologically-based cognitive disorders, and when their screening cognitive scores were within normal or near-normal age education range.

Patients were not included with acute systemic infection, chronic inflammatory or autoimmune disease, active malignancy, recent surgery or trauma in the last three months, uncontrolled endocrine or metabolic illness, severe hepatic or renal dysfunction, history of major stroke, epilepsy, advanced Parkinson disease, severe depression with pseudodementia or receipt of systemic corticosteroids, immunosuppressive drugs or biologic anti-inflammatory drugs, which may considerably change the levels of inflammatory biomarkers and conf Due to the potential influence of systemic and metabolic factors on the blood inflammatory markers, exclusion criteria were carefully chosen to minimise the major confounding.

The demographic and clinical assessment of all the participants was done in detail through a structured data collection proforma after enrollment. The variables captured in records were age, gender, and body mass index (BMI), education level, length of memory complaints, smoking, hypertension, diabetes mellitus, family history of dementia, and current medication. Both patients and caregivers received a comprehensive clinical history including the questions about symptom onset and progression, memory loss, forgetfulness, disorientation, executive dysfunction, as well as behavioral changes.

Two standardized screening instruments which included the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were used to measure cognitive functioning. They were measured in a low-key clinical environment by trained doctors or by research personnel well versed in the field of neurocognitive assessment. MMSE was applied to determine orientation, memory, attention, recall, and language, whereas MoCA was utilized to have a general picture of executive functioning, visuospatial abilities, abstraction and delayed recall, as well as language functioning. Smaller scores in the two instruments were taken to be higher cognitive impairment. Cognitive screening was also conducted on the participants in the control group to ensure that they did not have clinically significant cognitive dysfunction.

In the case of biomarker analysis, 5 mL of fasting venous blood of each participant was collected under aseptic conditions and at the mornings to reduce the effect of diurnal changes. The blood samples were left to clot and centrifuged at 3000 rpm, 10 minutes to get serum. The aliquoted serum was frozen at 80 o C until analysed biochemically. Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-6) were determined in serum by way of commercially obtained enzyme-linked immunosorbent assay (ELISA) kits in line with the instructions of the manufacturer. Every sample was repeated twice and a mean was taken and recorded in pg/mL to enhance analytical reliability. ELISA serum cytokine is one of the frequently applied procedures in the inflammatory biomarkers research of Alzheimer.

In order to enhance internal consistency, the entire laboratory processes were conducted in the same institutional biochemistry laboratory using standard operating conditions. The samples used in quality control were replicated with every assay batch and where feasible used the same lot numbers of reagents to minimize the variability of inter-assays.

Data obtained were processed and analyzed by use of Statistical Package of the Social Sciences (SPSS) version 26.0. The continuous variables (age, BMI, MMSE score, MoCA score, serum IL-6 level, and serum TNF-a level) were provided in the form of mean and standard deviation, and the categorical variables (gender, hypertension, diabetes mellitus and smoking status) were provided in the form of

frequency and percentage. The comparison of the mean values in the Alzheimer disease group and the control group was done with the use of independent sample t -test. Chi-square test was used to compare the categorical variables. The levels of the inflammatory markers and the cognitive scores were compared with the help of Pearson correlation coefficient. The p-value was approximately below 0.05 which was taken as statistically significant. The use of standard parametric and non-parametric handling of biomarker data and correlation testing is also in line with the present blood biomarker analytical practice.

RESULTS

In the final analysis, 70 participants were included (40 patients with early Alzheimer disease, and 30 cognitively healthy controls). The entire mean age of the study population was 66.91±6.18 years. The average age in the Alzheimer disease group early onset was 67.48 years 5.94 years and the control group was 66.13 years 6.47 years with the difference between the two groups not being found to be significant (p = 0.372). There was a slight higher percentage of females in both groups with the female population of 22 (55.0) in the Alzheimer group and 16 (53.3) in the control group. The clinical features such as body mass index, hypertension, diabetes mellitus, or smoking status were similar in the two groups, which confirms that the two groups were quite similar in terms of key demographic and metabolic factors (Table 1).

Cognitive measures indicated that there were evident and statistically significant differences in patients with early Alzheimer disease and healthy controls. The average score of the Mini-Mental State Examine (MMSE) in the Alzheimer disease sample was 21.48 ± 2.86, as opposed to that of the control group 28.27 + 1.41 (p = 0.001). On the same note, the mean MoCA score showed a significant difference between the Alzheimer disease group (18.94 ± 3.17) and the controls (26.31 ± 1.84) (p < 0.001). The results support the fact that the patient group experienced objective early impairment of the cognitive abilities as compared to cognitively intact controls (Table 2).

Analysis of serum inflammatory markers revealed that there were high levels of neuroinflammatory cytokine in patients with early Alzheimer disease. The average serum level of IL-6 in the group of individuals with Alzheimer disease was 8.61 + 2.49 pg/mL and the control group was 4.29 ± 1.47 pg/mL with a highly significant difference (p < 0.001). Similarly, the serum level of TNF- in Alzheimer disease patients (14.87 ± 4.12 pg/mL) was significantly higher in comparison with the controls (8.64 ± 2.31 pg/mL) (p < 0.001). These findings suggest a much greater inflammatory profile in the early group of Alzheimer disease (Table 2).

Additional subgroup analysis further in the cohort of early Alzheimer disease revealed that the patients with the relatively lower cognitive scores were more likely to have higher levels of inflammatory markers. The mean IL-6 and TNF- a levels were highest in patients with MMSE scores 0-20 and lower in patients with MMSE scores 23-40. The same trend was followed when cognitive performance was categorized as MoCA score. This implies that the existence and severity of early cognitive dysfunction are potentially linked not only to more severe systemic inflammatory activity but also to the existence of Alzheimer's disease.

The analysis of correlation revealed the statistically significant negative associations between cognitive performance and inflammatory markers. There was a moderate negative correlation between serum IL-6 and MMSE score (r = -0.58, p<0.001) and MoCA score (r = -0.62, p<0.001). Likewise, serum TNF- 02 showed significant negative correlation with both MMSE score (r = 0.51, p = 0.001) and MoCA score (r = 0.55, p = 0.001). Also, the levels of serum IL-6 and TNF-alpha showed a positive correlation (r = 0.60, p < 0.001), indicating that the inflammatory pathways were activated in parallel in early Alzheimer disease (Table 3).

The difference in gender-wise analysis of Alzheimer disease group found out that the male and female patients had high levels of inflammatory markers and lower scores on cognitive analysis than their counterparts in the control group. The mean levels of IL-6 and TNF- alpha of female patients with early Alzheimer disease were 8.74 + 2.53 pg/mL and 15.01 + 4.25 pg/mL, respectively; that of male patients were 8.45 + 2.46 pg/mL and 14.70 + 3.98 pg/mL, respectively. But these were not statistically significant differences in the group of Alzheimer disease based on the gender (p > 0.05). Likewise, the cognitive scores were lower in both sexes and no significant gender-specific difference in the severity was found.

All in all, the results of the current research indicate that patients with early AD have a profoundly high level of serum IL-6 and TNF- 2 with a very low level of MMSE and MoCA scores. The observed negative correlation between the inflammatory cytokines and cognitive performance is a strong indication that the aggravation of cognitive decline in the early stages of the Alzheimer disease may have a correlation with the augmentation of the neuroinflammatory load. The findings are direction-significant to the current evidence on the association of blood inflammatory markers, namely, TNF- 0 and IL-6 with the presence of Alzheimer disease and worse cognitive performance, yet the literature on the topic remains more heterogeneous with respect to sample types and study designs.

Table 1. Baseline demographic and clinical characteristics of study participants

Variable	Early Alzheimer's Disease (n=40)	Controls (n=30)	p-value
Age (years), Mean ± SD	67.48 ± 5.94	66.13 ± 6.47	0.372
Male, n (%)	18 (45.0)	14 (46.7)	0.889
Female, n (%)	22 (55.0)	16 (53.3)	0.889
BMI (kg/m²), Mean ± SD	26.57 ± 3.61	25.84 ± 3.28	0.394
Hypertension, n (%)	21 (52.5)	13 (43.3)	0.447
Diabetes Mellitus, n (%)	15 (37.5)	9 (30.0)	0.510
Smokers, n (%)	8 (20.0)	5 (16.7)	0.720
Duration of Cognitive Symptoms (months), Mean ± SD	16.92 ± 6.31	—	—

Table 2. Comparison of cognitive scores and serum neuroinflammatory markers between groups

Variable	Early Alzheimer's Disease (n=40)	Controls (n=30)	p-value
MMSE Score, Mean ± SD	21.48 ± 2.86	28.27 ± 1.41	<0.001
MoCA Score, Mean ± SD	18.94 ± 3.17	26.31 ± 1.84	<0.001
Serum IL-6 (pg/mL), Mean ± SD	8.61 ± 2.49	4.29 ± 1.47	<0.001
Serum TNF-α (pg/mL), Mean ± SD	14.87 ± 4.12	8.64 ± 2.31	<0.001

Table 3. Correlation of serum IL-6 and TNF-α with cognitive scores in early Alzheimer's disease patients

Variable	MMSE Score	MoCA Score
IL-6 (pg/mL)	r = −0.58, p < 0.001	r = −0.62, p < 0.001
TNF-α (pg/mL)	r = −0.51, p = 0.001	r = −0.55, p < 0.001

DISCUSSION

The current investigation assessed the connection amidst systemic neuroinflammatory biomarkers interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) and cognitive impairment in patients with early Alzheimer[1]. The results showed that, the levels of IL-6 and TNF-alpha were greatly increased in patients with early Alzheimer disease than in cognitively healthy controls. Moreover, these inflammatory markers had statistically significant negative correlation with scores of cognitive performance evaluated by MMSE and MoCA, and thus greater inflammatory load was linked to a higher impairment of cognition[2].

These data are in line with the accumulating evidence that neuroinflammation is at the center of the pathophysiology of the Alzheimer disease[3]. Although the traditional models of the Alzheimer disease have centered on the role of amyloid-beta deposition and tau pathology, the latest studies have underlined the role of immune-mediated processes, especially the prolonged activation of microglia and astrocytes. These stimulated glial cells secrete pro-inflammatory cytokines, such as IL-6 and TNF-a, which is able to impair the synaptic functioning, facilitate neural damage, and accelerate the neurodegenerative processes. The increased levels of cytokines in the current study are in line with this inflammatory framework and indicate that there is a possibility of systemic inflammatory processes which are owing to ongoing neuroinflammatory processes in early Alzheimer disease[4].

The results of this study which had shown the significantly higher levels of IL-6 between patients with early Alzheimer disease are consistent with a number of other studies that have previously found IL-6 to be a marker of significant mediator in the process of neurodegeneration[5]. It is also known that IL-6 affects processing of amyloid precursor protein, increases amyloid-beta synthesis, and disrupts synaptic plasticity. Clinical and experimental studies have also found that chronic IL-6 elevation can lead to cognitive dysfunction and memory impairment. The results of this work support the assumption that IL-6 can be considered a potential biomarker of early disease activity and cognitive impairment[6].

Likewise, the TNF- 8 levels were significantly increased in the AD group and exhibited significant negative relationships with the cognitive scores[7]. TNF-alpha is an effective pro-inflammatory cytokine that has been attributed to neuronal death, oxidative stress, dysfunction of mitochondria, and dysregulation of synapses. It is also involved in changing neurotransmitter systems and neurotransmitters disruption which are essential parts of the cognitive processing. The results of this study in regard to the presence of high levels of TNF-A and low levels of MMSE and MoCA are consistent with those obtained by other studies, which proposed that the TNF-mediated processes of inflammatory signaling play a role in the development of cognitive decline[8].

A major strength of this research is that it shows a definite correlation between the inflammatory markers

and the cognitive performance as opposed to comparing the levels of cases and controls[9]. The unbalanced inverse relationships found with both IL-6 and TNF- alpha indicate the possibility of the latter not only indicating a disease occurrence but also its severity at the initial phase. The clinical implications of this observation are that inflammatory biomarkers can be used to track disease progression and diagnose patients who are more likely to experience rapid cognitive decline[10].

The subgroup analysis also confirmed this association because it revealed that patients with lower MMSE scores had greater levels of inflammatory markers[11]. This trend suggests that there is a potential dose-response association between inflammatory burden and cognitive impairment. This finding is consistent with the idea that neuroinflammation can be used as gain-enhancing mechanism that hastens neuronal damage once the disease process has been triggered[12].

In practical terms, inflammatory biomarkers based on blood e.g. IL-6 and TNF- 6 are especially attractive in resource-deprived environments[13]. Modern methods of diagnosing Alzheimer disease such as the use of cerebrospinal fluid biomarker and positron emission tomography (PET) have high cost and are not available in most developing nations. Conversely, serum-based tests are comparatively easy, cheap and less invasive and therefore more acceptable in clinical routine. According to the findings of this research, these biomarkers can be effective supplements to a cognitive test in early AD, particularly in the environment with inadequate diagnostic facilities[14].

In spite of these significant findings, a number of limitations ought to be taken into account[15]. First, the study is cross-sectional in design, which makes it impossible to determine the cause-effect relationship between the high levels of inflammatory markers and the deterioration of cognition. One cannot say whether elevated levels of cytokine play a direct role in disease progression or is a secondary reaction to neurodegeneration. Second, the sample size of 70 people that is sufficient to start analysis is possibly insufficient to generalize the findings. Multi-center studies that are larger should give stronger and representative data. Third, minor confounding factors that may have been missed cannot be fully dismissed despite attempts to remove major ones. Lastly, the research was based on serum biomarkers and omitted cerebral spinal fluid and neuroimaging correlates, which might be a more direct measure of the pathology on the central nervous system[16].

The future studies must revolve around longitudinal study designs to determine the ability of IL-6 and TNF-alpha to predict disease progression in the long-term[17]. Combination of inflammatory biomarkers with other emerging biomarkers like amyloid-beta, tau proteins, neurofilament light chain, and glial fibrillary acidic protein can further increase the diagnostic and prognostic accuracy. Moreover, the study of therapeutic approaches aimed at the regulation of inflammation pathways can establish new opportunities of disease-controlling therapies in Alzheimer disease[18].

CONCLUSION

Conclusively, the current research showed that early Alzheimer diseased patients have greatly increased levels of IL-6 and TNF-a in serum and these two neuroinflammatory agents are closely correlated to cognitive impairment when MMSE and MoCA are used to test it. The noted negative proportionality between the levels of cytokine and cognitive abilities implies that the systemic inflammation might contribute greatly in the initial clinical expression of the Alzheimer disease.

These results demonstrate the possibility of IL-6 and TNF-alpha as convenient and least invasive biomarkers of early disease and severity evaluation. Though additional large-scale and longitudinal research is necessary to prove their predictive value, the findings suggest that neuroinflammation should be considered an important part of the pathophysiology of Alzheimer disease and the need to consider inflammatory markers in the future diagnostic and treatment strategies.

DECLARATION

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