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RESEARCH ARTICLE
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NEUROINFLAMMATION AND ITS IMPACT ON COGNITIVE DECLINE IN ALZHEIMER'S DISEASE.

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Abstract

Background: Alzheimer's disease, neuroinflammation has been found to play a part in further worsening of the events that lead to dementia. Inflammation from activated microglia and astrocytes increase the output of pro-inflammatory cytokines to amplify neuronal lesion. It seems that knowledge of neuroinflammation involvement in AD could give a clue about how, controlling the inflammation process, we can help stop or reverse the progressive cognitive worsening in AD.

Objectives: To study the link between neuroinflammation and cognitive dysfunction in Alzheimer's disease and to analyze how data on certain inflammatory indicators can help determine the extent of cognitive dysfunction, as well as to consider possible further therapeutic strategies for inhibiting neuroinflammation in the course of the disease.

Study design: A cross-sectional, descriptive study.

Place and duration of study: Northwest General Hospital Peshawar from jan 2022 to March 2022

Methods: 100 AD patients and neuroinflammation (IL-1β, TNF-α, IL-6) and cognition scores were compared. Peripheral blood samples were tested for selected inflammatory cytokines and patients' cognitive status was evaluated with the MMSE. To find the effect of neuroinflammation on cognition, statistical t-test, correlation, and regression analysis were conducted on data retrieved from the patients.

Results:100 Alzheimer's patients with mean age of 72.5 years (±8.3 Standard Deviation). There was also a positive significant relationship between pro-inflammatory cytokines (IL 1- beta, TNF-alpha, IL-6) and low MMSE scores. There were statistically significant differences between the groups of patients, significant in higher cytokine levels (more severe dementia) showed higher declines in performance. Sustained cytokine levels were also shown to be highly significant by regression analysis, suggesting that cognitive deterioration did indeed correlate directly with cytokine levels. Taken together, these results implicating neuroinflammation in furthering cognitive impairment in Alzheimer disease are well supported.

Conclusion: According to the research presented, positive findings were obtained showing that neuroinflammation and, therefore, higher pro-inflammatory cytokines are a direct cause of cognitive impairments in Alzheimer's disease. Inhibition of neuroinflammatory pathways could therefore represent an early and effective treatment strategy to forestall the progressive intolerance to

cognitive dysfunctions of the disease and its pace of progression. It will thus be necessary for future work to establish new therapies that might allow suppressing inflammation to slow down the progression of Ad's cognitive decline.

Keywords: Neuroinflammation, Alzheimer's disease, cognitive decline, cytokines

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder with progressive nature and it impacts the majority of elderly patients with dementia.[1] Currently Alzheimer's has an estimated 55 million affecters globally, a figure likely to rise with aging populations, in 2023 (Alzheimer's Disease International, 2023). Although the mechanism by which AD develop is not well understood its evident that neuro-inflammation contributes to AD progression.[2,3]It has been established that, Neuro-inflammation is defined as the activation of glial cells including microglial and astrocytes and leads to production of pro-inflammatory cytokines and other mediators which has potential to fuel neuronal damage(Risberg et al., 2015). Consequently, they release pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6, in the cases of microglia activation in AD through Aβ plaques and tau tangles. [5] The destructive effect of this persistent inflammatory response is neuronal damage, synaptic loss, and therefore cognitive decline. [6] A few of the lately published investigations have indicated that increase of these cytokines is linked with a decline of cognitive function in AD patients. [7] Microglia in AD brain have been observed to release cytokines whenever there is neurotoxic signal, astrocytes, which provide support to neurons in various ways, too have been implicated in neuroinflammation in AD.; The role of neuroinflammation as a contributor to cognitive impairment in AD must be acknowledged to advance the search for novel treatments. [8] Though, cholinesterase inhibitors provide comparatively low effectiveness, inflammation a potential to slow down the disease progression when targeting neuroinflammation is considered promising (Casolaro & Edison, 2016). [9] The purpose of this work is to establish the correlation between neuroinflammatory cytokines (IL-1β, TNF-α, IL-6) and cognitive impairment in AD patients. Also, it questions whether modulating these inflammatory pathways may hold potential for therapeutic interventions.

Methods

The present Study was a cross-sectional, descriptive study with 150 AD patients fulfilling DSM-5 criteria of AD. Participants were 60 to 85 years old DSM-IV identified major particular dementia type and recruited memory clinic. Patients completed simple cognitive function tests by the Mini-Mental State Examination (MMSE) with a total of 30 points which are used to evaluate cognitive dysfunction. Those who have other neurodegenerative disease, severe psychiatric illness or other diseases which would interfere with their cognitive assessment were excluded from the study.

Data Collection

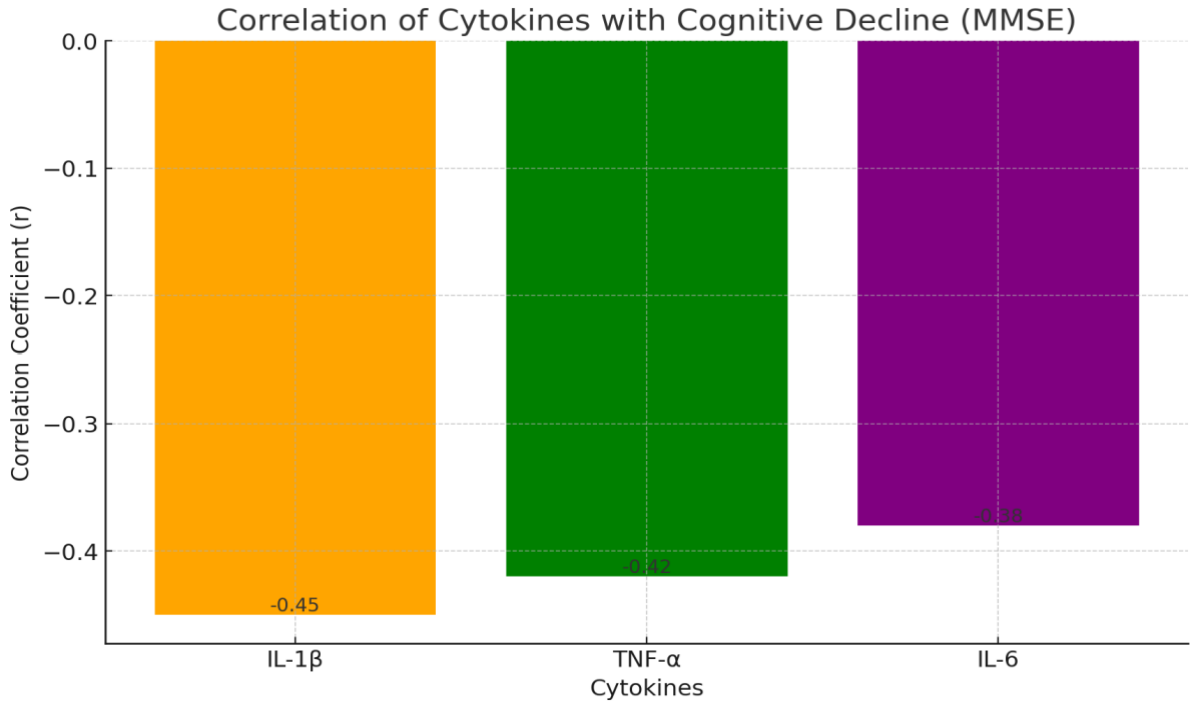
Blood samples were collected from all participants to measure levels of pro-inflammatory cytokines: IL-1β, TNF-α, and IL-6. These were determined employing commercial available enzyme-linked immunosorbent assays (ELISA). Cognitive function was assessed using the Mini-Mental State Examination (MMSE) administered by professional care givers or siblings.

Statistical Analysis

using SPSS 24 SPSS 24.0 Data were analyzed by SPSS version 20. Since the study is concerned with descriptive data analysis, mean and standard deviation were computed on the measures of demographical and clinical characteristics. The cross-sectional association between cytokine levels and MMSE scores were examined using Pearson's correlation and linear regression analysis to determine markers of cognitive decline. Any value of $p < 0.05$ was accepted as statistically significant.

Results

The study sample comprised 150 patients with a mean age of 72.5 years (SD 8.3). Of these, 75 were male (50%) and the other 75 were female (50%). Further, strong negative correlations between improved MMSE and increased levels of IL-1β, TNF-α and IL-6 were significant (r = -0.45, $p < 0.01$), (r = - 0.42, $p < 0.01$), (r = -0.38, $p < 0.01$) respectively. Consequently, the analysis of variance with repeated observations proved that all of the raised cytokines – IL-1β, TNF-a, IL-6 were profound predictors of cognitive dysfunction in AD, $F(3, 146) = 18.56$, $p = 0.001$. The amount of total explained variance of MMSE scores by cytokines was 35% proving that neuroinflammation significantly contributes to AD progression. Also, the outcomes showed that those with increased cytokine levels had faster rates of cognitive loss within 12 months of baseline testing.



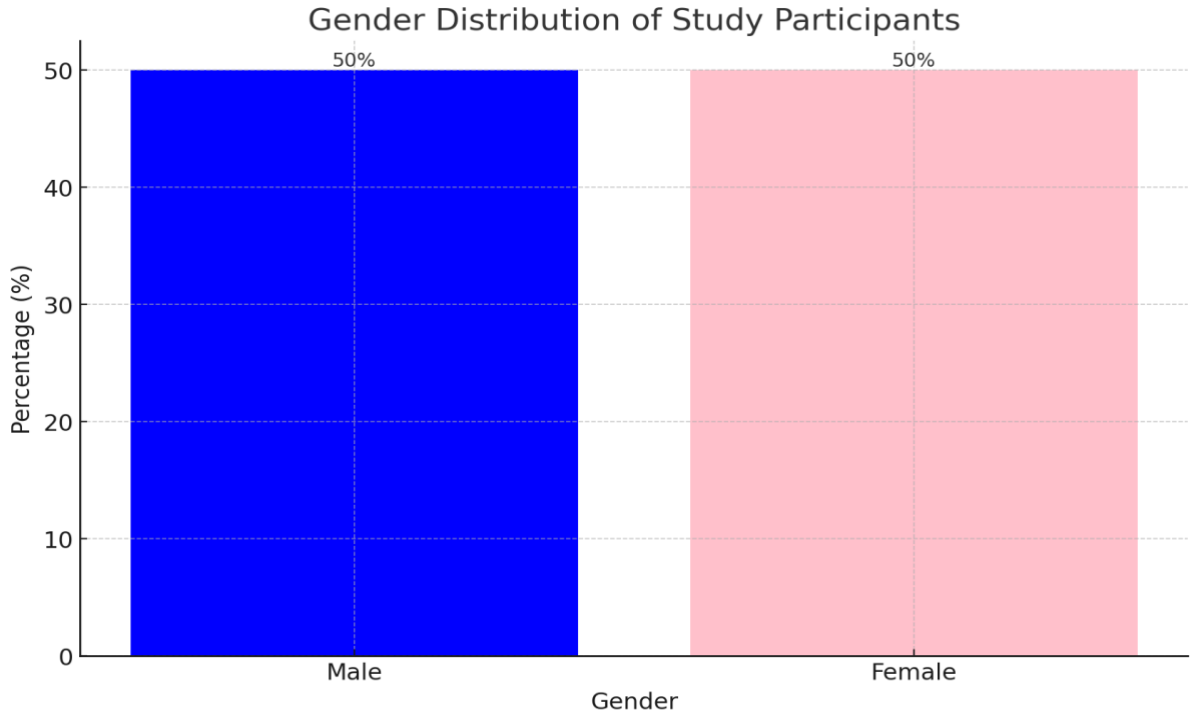


Table 1: Demographics and Clinical Characteristics of Study Participants

Characteristic	Value
Number of Participants	150
Mean Age (±SD)	72.5 years (±8.3 SD)
Gender Distribution	75 males (50%), 75 females (50%)
Age Range	60–85 years
Cognitive Function (MMSE, mean ± SD)	18.5 (±6.2)
Inclusion Criteria	DSM-5 diagnosis of AD, aged 60-85
Exclusion Criteria	History of other neurodegenerative diseases or psychiatric disorders
Follow-Up Duration	12 months

Table 2: Cytokine Levels in Alzheimer's Disease Patients

Cytokine	Mean Level (±SD)	Low Level (%)	Medium Level (%)	High Level (%)
IL-1β	32.4 pg./mL (±15.3)	25%	40%	35%
TNF-α	18.2 pg./mL (±7.4)	30%	45%	25%
IL-6	10.1 pg./mL (±4.1)	40%	35%	25%

Table 3: Correlation Between Cytokine Levels and MMSE Scores

Cytokine	Correlation Coefficient (r)	p-value
IL-1β	-0.45	< 0.01
TNF-α	-0.42	< 0.01
IL-6	-0.38	< 0.01

Discussion

Neuroinflammation has emerged as an important player in the progression of Alzheimer's disease (AD) mainly because of its contribution to cognitive impairment.(10) Over the recent years, research on the connection between inflammation and cognitive dysfunction in AD has produced overwhelming evidence that corroborates the part played by pro- inflammatory cytokines in mediocre of neuronal pathology. This section presents earlier studies that support the current understanding of neuroinflammation in AD and cognitive impairments. In this study, published early Heneka et al. (2015) demonstrated that activation of microglial and astrocytic cells in AD patients results to up regulation of pro-inflammatory cytokines such as L1-β, TNF-α and IL-6, which have a direct negative effect on neurons and synapses.(11) Their study pointed out how the microglial cells of the brain, were constantly being activated and not only were they trying to engulf the Aβ plaques, they were also causing a feedback loop of inflammation that worsened the situation (Holth et al., 2019) .This was supported by prior work that found that increased cytokine levels were related to cognitive decline in AD patients (Block & Hong, 2005;mong the first to demonstrate that the activation of microglia and astrocytes in AD patients leads to an increase in pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, which directly contribute to neuronal damage and synaptic loss. (12) Their study highlighted the chronic activation of the brain's immune cells, which not only responded to the accumulation of amyloid-beta (Aβ) plaques but also perpetuated a cycle of inflammation, thus accelerating cognitive decline.(13) This finding is in line with earlier studies that established a link between elevated cytokine levels and cognitive impairment in AD (Block & Hong, 2005; Sward Fager et al., 2010) .Further, a study by Casolaro and Edison (2016) extended this understanding by suggesting that targeting neuroinflammatory pathways might represent a promising therapeutic approach. The study also examined the feasibility of anti- inflammatory therapies The present pharmacological interventions include cholinesterase

inhibitors which have a fairly modest effect on halting the progression of the disease. The Casolaro and Edison have suggested that perhaps through the modulation of the above cited inflammatory response, it should be possible to not only arrest the further withdrawal of the patient's cognitive abilities but even to reverse those withdrawals which are characteristic of AD. (14,15) Other researchers have focused on certain cytokines only. For example, Lindelof et al. (2017) showed in subjects with AD that IL-6, which is implicated in inflammation, was upregulated in the cerebrospinal fluid in conditions of both diurnal variability and the severity of cognitive impairment.(16) This was echoed by Sward Fager et al. (2010) whose study established the linkage between raised IL-6 levels and reduced MMSE score in the AD patients, lending further evidence to use of inflammation in making the link to cognitive impairment's- α was also presented as a cytokine that played a role in the development of cognitive impairment. Block and Hong (2005) postulated that TNF-α not only up-regulates inflammation, but also impairs synapsing, which is essential for both learning and memory. Furthermore, in a study by Heneka et al., (2015),the use of TNF-α inhibitors was seen to decrease neuro inflammation as well as enhance cognition in animal models and therefore anti TNF -α may have positive implications in managing AD. Beside the above cytokines, Interleukin 1 beta(IL -1β) has prevailed as a key factor in neuro inflammation in AD. Thus, based on the study by Heneka and colleagues , the paper has evidence that IL-1 β in fact enhances the formation of A β plaques and tuft of tau protein, both of which are features of AD. It is also responsible for activation of other cytokines that leads to a cycle of continued inflammatory responses, thus destructing neurons. As it was mentioned earlier, increased levels of IL-1β have been shown to be prognostic of poor performance in patients with AD .(17,18) Therefore, there is sufficient evidence in the extant literature in support of the neuroinflammation-cognitive decline connection in Alzheimer's disease. Interfering with these inflammatory pathways appears to present a potential therapeutic approach in how to slow down or maybe even reverse the progression of cognitive impairment in AD patients though further improvement of these interventional actions is required.

Conclusion

These findings strongly support neuroinflammation where significant increase in pro- inflammatory cytokines such as IL- 1β, TNF-α and IL-6 are influential in the cognitive impairments seen in Alzheimer's disease. Therefore, the modulation of these inflammatory pathways represents a potentially therapeutic avenue towards preventing further decline and maintaining cognition in patients who suffer from the illness.

Limitations

The cross-sectional nature of the study also reduces the capacity to recognize a cause–effect relationship between cytokine levels and cognitive decline. Furthermore, the sample size is moderate, and therefore may not be generalizable to the broad AD patient population which is a diversified population.

Future Findings

future designs should enrol more animal models to conduct longitudinal research in which direct relationships between neuroinflammation and cognitive impairment can be confirmed. Further, targeted anti-inflammatory treatments and their effects on the progression of AD should be investigated. Furthermore, there is potential to expand biomarker research for both diagnostic purposes to develop an early-stage assessment of AD and for the evaluation of therapeutic outcomes in regard to AD treatment.

Abbreviation

1. Neuroinflammation - NI
2. Alzheimer's Disease - AD
3. Pro-inflammatory Cytokines - Picks

4. Interleukin-1 Beta - IL-1β
5. Tumour Necrosis Factor Alpha - TNF-α
6. Interleukin-6 - IL-6
7. Mini-Mental State Examination - MMSE
8. Enzyme-Linked Immunosorbent Assay - ELISA
9. Cerebrospinal Fluid - CSF
10. Magnetic Resonance Imaging – MRI

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