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A Study Of Serum IL-1b & IL-6 Levels In Patients With Alzheimer's Disease

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Abstract:
Background*: Alzheimer's disease, the predominant type of dementia, accounts for approximately 75% of cases, either as a standalone condition or in conjunction with other forms of pathology. Interleukin-1 beta (IL-1β), which belongs to the IL-1 cytokine family, is widely recognized as a prominent proinflammatory cytokine within the brain and is known to significantly contribute to the advancement of Alzheimer's disease (AD). interleukin-6 (IL-6) has the potential to induce the activation of microglia and astrocytes, leading to the subsequent release of a series of proinflammatory cytokines and acute phase proteins, including C-reactive protein.*
Materials and Methods: *The present study was conducted in the department of Biochemistry, Jawahar Lal Nehru (J. L. N.) Medical College and its Associated Hospitals Ajmer. The study encompassed a total of 95 patients diagnosed with Alzheimer's disease and 95 normal controls.*
Results: *serum IL-1b & IL-6 levels were found to be considerably greater in patients with Alzheimer's disease than controls.*
Conclusion: *Higher levels of IL-1b & IL-6 are associated with Alzheimer's disease.*
Keywords- *Alzheimer's, Dementia, IL-1β, IL-1*

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I. Introduction

According to the World Health Organization (2010), the term **"dementia"** encompasses a collection of illnesses characterized by cognitive decline, which arises from the loss or impairment of brain cells. It is a syndrome involving chronic disease of the brain usually of progressive nature resulting in disturbance of multiple higher cortical functions such as memory loss, orientation, in thinking skills, comprehension, learning capacity, language and judgement. The state of consciousness is not characterized by muddled cognition. The cognitive function impairments are frequently accompanied, and sometimes preceded, by a decline in emotional regulation, social conduct, or motivation. This syndrome is observed in individuals with Alzheimer's disease, cerebrovascular disease, and other conditions that primarily or secondarily impact the brain (World Health Organization, 2010).

This prevalent issue poses a significant challenge to public health, impacting a global population exceeding 20 million individuals and exhibiting a rapid upward trend particularly in industrially-developed nations.

Dementia is a global health issue. According to a World Alzheimer Report 2014, the global prevalence of dementia is expected to increase by 44 million individuals. In the year 2015, the global prevalence of dementia was seen to impact approximately 47 million individuals, which accounted for approximately 5% of the aged population globally. Projections indicate that this number is expected to rise to 75 million by the year 2030 and further escalate to 132 million by the year 2050. According to recent evaluations, it has been estimated that approximately 9.9 million individuals worldwide are diagnosed with dementia annually. This statistic implies that a new instance of dementia arises approximately every three seconds. Approximately 60% of individuals diagnosed with dementia presently reside in low- and middle-income nations, with a projected majority (71%) of new cases anticipated to arise within these countries.

The clinical manifestation of dementia, which is defined by the emergence of functional dependence resulting from a gradual decline in cognitive abilities, can be attributed to several pathophysiological mechanisms. The predominant cause of dementia is Alzheimer's disease (AD), accounting for approximately 50-75% of cases, followed by vascular dementia (VD) at 20%, dementia with Lewy bodies (DLB) at 5%, and frontotemporal lobar dementia (FTLD) at 5%. It should be noted that due to considerable clinical and pathological similarities among these conditions, the provided percentages are approximate estimates. Less frequently encountered causes of

dementia, comprising around 3% of cases, include Huntington's disease, Creutzfeldt-Jakob disease, HIV/AIDS, and multiple sclerosis.

There exist five causes of dementia:
Alzheimer's disease (AD): It is the prevailing diagnosis for dementia among the elderly population. The etiology of this phenomenon can be attributed to neurobiological alterations, namely the presence of atypical accumulations of proteins, commonly referred to as amyloid plaques and tau tangles.
Frontotemporal dementia (FTD): is an infrequent manifestation of cognitive decline, typically observed in individuals under the age of 60.
Lewy body dementia (DLB): Abnormal quantities or configurations of the proteins viz. tau and TDP-43 are linked to this phenomenon. Lewy body dementia is a variant of dementia that arises due to the presence of atypical accumulations of alpha-synuclein protein, commonly referred to as Lewy bodies.
Vascular dementia: It is a type of cognitive impairment that arises from pathological disorders that inflict damage upon the blood vessels in the brain or disrupt the normal circulation of blood and oxygen to the brain.
Mixed dementia: It refers to the coexistence of two or more distinct kinds of dementia inside an individual.

Alzheimer's disease (AD) is responsible for approximately 60% of dementia cases (Fratiglioni et al., 2007). Its initial documentation dates back to almost a century ago, when the German psychiatrist Alois Alzheimer first described it. The initial identification of Alzheimer's disease in 1907 is attributed to Alois Alzheimer, a renowned Bavarian psychiatrist who is widely recognized as a pioneer in the field of neuropathology. The initial documentation involved the delineation of the neuropathological attributes exhibited by a female patient who experienced a gradual decline in cognitive function during her early fifties. The subject of interest pertained to a cohort of women, aged 51, who were admitted to the psychiatric institution under the supervision of Alois Alzheimer. Alzheimer's initial observations were the identification of degenerating neurons characterized by the presence of neurofibrillary tangles, which are bundles of fibrils. Additionally, he noted the presence of silver-staining deposits known as senile plaques, which were found distributed throughout the cortex. The confirmation of the presence of plaques and fibrils in the patient's brain through a biopsy led to the attribution of the ailment to these pathological features.

In the year 1910, Emil Kraepelin, under the direction of Alois Alzheimer, presented the expression "Alzheimer's illness" to separate a particular sort of dementia from the more pervasive decrepit variation. Alzheimer's sickness is a neurodegenerative problem portrayed by a dynamic decrease in mental capability. The period of beginning can be delegated either presenile or senile, in view of whether the illness appears previously or past the age of 65 years, separately. Clinically, the patient presents itself as a progressive dementia of insidious onset with subtle personality alterations eventually resulting in complete anomia, agnosia and apraxia. As per Cummings et al (2004), the disease is occasionally accompanied by steep disturbance, anxiety, aggression and agitation.

As per Taylor and Thomas et al (2013), during the underlying periods of the condition, people regularly have cognitive decline relating to ongoing occasions and experience challenges in tracking down words. As the disease advances, more pronounced memory loss and language issues become evident. This phenomenon gives rise to challenges in routine tasks such as engaging in commerce, managing financial transactions, and navigating across physical spaces. Additional symptoms may include anxiousness and a decrease in motivation. According to Steinberg et al. (2008), as the disease advances, the symptoms tend to exacerbate. Over time, the individual has a decline in their ability to independently perform activities related to personal care.

Brain changes: Alzheimer's disease, the predominant type of dementia, accounts for approximately 75% of cases, either as a standalone condition or in conjunction with other forms of pathology, commonly referred to as 'mixed dementia'. Within the context of Alzheimer's disease, the brain undergoes abnormal accumulation of insoluble 'plaques' composed of a fibrous protein known as β-amyloid (Aβ), as well as the formation of twisted fibers referred to as 'neurofibrillary tangles' (Attems and Jellingeret al 2020). The presence of atypical plaques and tangles disrupts the regular operation of neuronal cells in the brain. Additionally, there exists a deficit in the neurotransmitter acetylcholine, which plays a crucial role in the process of learning and cognition (Piggott et al 2013).

The most dependable diagnosis can be established through histopathological examination of senile plaques and neurofibrillary tangles, typically observed after autopsy or, in rare cases, when a biopsy is performed. Senile plaques refer to the agglomerations of degenerated nerve terminals that encompass extracellular accumulations of β-amyloid. Neurofibrillary tangles, consisting primarily of phosphorylated tau proteins, are tiny paired helical filaments (Kamphuis and Wurtman et al, 2009). These abnormalities are predominantly observed in the neocortex and hippocampal regions. Indeed, there exists a positive correlation between the density of these plaques in the neocortex and the severity of cognitive impairment in Alzheimer's disease (AD). AD has a

biochemical impact on specific neurotransmitters and neuromodulators. A significant depletion of acetylcholine has been observed in the brains of nearly all individuals with Alzheimer's disease, as documented in a study conducted by Shah et al, 2008. The serotonergic and noradrenergic systems also seem to be affected particularly when the onset of the disease is before the age of 75 years. Putative pathogenic mechanisms include glutamate neurotoxicity, free radical production, aluminium accumulation, apoptosis and inflammation (Silvestrelli et al., 2006).

IL-1 is an important initiator of the immune response, playing a key role in the onset and development of a complex hormonal and cellular inflammatory cascade. Elevated IL- 1β has been detected in the CSF and brain parenchyma within the early hours after brain injury in both humans and rodents. Nonetheless, IL-1 has been documented to play a role in neuronal degeneration. In astrocytes, IL-1 induces IL-6 production, stimulates inducible nitric oxide synthase (iNOS) activity, and induces the production of macrophage colony-stimulating factor (MCSF). In addition, IL-1 enhances neuronal acetylcholinesterase activity, microglial activation and additional IL-1 production, astrocyte activation, and expression of the beta-subunit of S100 protein (S100β) by astrocytes, thereby establishing a self-propagating cycle.

Interleukin-1 beta (IL-1β), which belongs to the IL-1 cytokine family, is widely recognized as a prominent proinflammatory cytokine within the brain and is known to significantly contribute to the advancement of Alzheimer's disease (AD). Interleukin-1 beta (IL-1β) is produced and secreted by activated microglia and astrocytes in its precursor forms, known as pro-IL-1β, within the cytoplasm, in response to various stimuli.

Interleukin-6 (IL-6) is a multifunctional inflammatory cytokine primarily synthesized by activated microglia and astrocytes located in various areas of the brain. Furthermore, interleukin-6 (IL-6) has the potential to induce the activation of microglia and astrocytes, leading to the subsequent release of a series of proinflammatory cytokines and acute phase proteins, including C-reactive protein.

II. Materials & Method

The present study was conducted in the department of Biochemistry, Jawahar Lal Nehru (J. L. N.) Medical College and its Associated Hospitals Ajmer. The study encompassed a total of 95 patients diagnosed with Alzheimer's disease & 95 individuals who met the criteria of being healthy and within the same age group were chosen as control subjects for this study. These individuals were either attending the outpatient clinics or were admitted to the wards of the Department of Psychiatry at J. L. N. Medical College and its Associated Hospitals in Ajmer. The selection process involved recruiting volunteers from various backgrounds, including doctors, resident doctors, paramedical workers, and healthy attendants of patients. The study acquired consent from all participants involved.

Body weight was assessed while wearing lightweight clothing and without shoes or a cap. A calibrated digital weighing scale with an accuracy of 0.1kg was used for the measurements. The measurement of height was conducted in the absence of shoes and headwear, use a wall-mounted stadiometer with an accuracy of 0.5 cm. The body mass index (BMI) was calculated by dividing an individual's weight by the square of their height (kg/m²). (Garrow and Webster,1985)

Subject included in the study were categorized as followings:
The study subject is divided into three groups:

Group 1: Healthy Control subject (n=95)
Mean Age: 66±7 years
Mean BMI value: (26.44 ±5.32) kg/m²

Inclusion criteria:

All participants in the healthy control group were individuals who did not smoke or consume alcohol, and had no known family history of diabetes mellitus, hypertension, obesity, or coronary artery disease.

2. Group 2: Alzheimer's disease subject (n = 95)
Mean Age: 67±8 years
Mean BMI value: (26.68 ±5.33) kg/m²

Exclusion criteria for Alzheimer's disease subject-

The presence of confounding factors that may potentially disrupt the biochemical analyses conducted on the study subjects and subsequently modify the obtained results were identified as follows:

1. Individuals with a medical background encompassing congestive heart failure, inflammatory conditions, and unregulated hypertension.
2. Individuals afflicted with renal and pulmonary disorders.
3.The individuals experiencing uncontrolled diabetes mellitus, cancer, and thyroid problems.
4.Individuals who have been diagnosed with additional autoimmune disorders.

5.The occurrence of hypophyseal and hypothalamic dysfunction has been found to be associated with serious psychiatric diseases.

Patient selection criteria Alzheimer's disease subject and Vascular dementia subject
Alzheimer's disease : DSM – IV-TR summarized as follows
A. The presence of memory impairment and/or impairment in another prominent cognitive area.
B. In addition to domain a, there must be impairment in at least one of the following domains: The topics under consideration include language, praxis, gnosis, and executive functioning.
C. Decline in social or occupational functioning relative to a previous level of functioning. Delirium should be considered as the primary cause, without any concurrent medical, neurological, or psychiatric conditions accounting for the observed symptoms.
D. Supportive features include the emergence of mood disturbances, behavioural changes, or the manifestation of psychotic symptoms.

The variables were reported in the form of mean ± standard deviation (SD). The parameters within the groups were examined using an analysis of variance (ANOVA) test, followed by a Tukey honestly significant difference (HSD) post hoc analysis.The study employed the Pearson's rho (r: correlation coefficient) correlation test to examine the associations between variables. The study employed a two-tailed P value with a significance level of $P < 0.05$ for all statistical analyses conducted.

Following biochemical parameters were analysed with plasma:
INFLAMMATERY MARKERS:
1. Plasma Interleukin-6 – by ELISA method
2. Plasma Interleukin-1 β– by ELISA method

III. Results-

Table 1: Mean difference in IL-6 between control and patients with Alzheimer's disease (AD)

Variable	Control subjects Mean (SD)	Alzeimers disease subjects Mean (SD)	Mean difference	95% CI of mean difference	t-statistics	p-value
IL-6 (pg/ml)	6.18 (1.97)	27.86 (30.12)	-21.69	-27.83- (-)15.54	-6.96	<0.01*

*- statistically significant

Table 2: Mean difference in IL-Ib between control and patients with Alzheimer's disease (AD)

Variable	Control subjects Mean (SD)	Alzeimer's disease subjects Mean (SD)	Mean difference	95% CI of mean difference	t- statistics	p-value
IL-Ib (pg/ml)	2.30 (0.83)	11.68 (3.37)	-9.38	-10.09- (-)8.68	-26.21	<0.01*

*- statistically significant

Table 3: Association between IL-6 and gender in patients with Alzheimer's disease (AD)

Variable	Male Mean (SD)	Female Mean (SD)	Mean difference	95% CI of mean difference	t- statistics	p-value
IL-6 (pg/ml)	24.18 (5.06)	31.04 (4.07)	-6.86	-19.15- 5.43	-1.11	0.271

Table 4: Association between IL-1b and gender in patients with Alzheimer's disease (AD)

Variable	Male Mean (SD)	Female Mean (SD)	Mean difference	95% CI of mean difference	t- statistics	p-value
IL-1b (pg/ml)	11.52 (3.54)	11.81 (3.24)	-0.29	-1.67- 1.09	0.419	0.676

Participants with Alzheimer's disease dementia had IL-6 levels that were (27.86 ± 30.12 pg/ ml) greater than the control participants, who had IL-6 levels that were (6.18± 1.97 pg/ml) . When comparing the IL-6 levels of healthy controls and people with Alzheimer's disease or dementia (AD dementia), a statistically significant ($p<0.01$) difference was detected. Our findings corroborate with studies of Shen X-N, et al. (2019) , Brosseron et al. (2014), and others that found elevated levels of IL-6 in people with Alzheimer's disease dementia.

Table 2 shows that IL-1β levels were substantially greater in participants with AD dementia (11.68 ± 3.37 pg/ ml) than in controls (2.30± 0.83 pg/ml). Subjects with Alzheimer's disease dementia had significantly higher IL-1β levels compared to controls ($p<0.01$). Our findings corroborate those of Shen X-N et al. (2019) and other research that found elevated IL-6 in Alzheimer's disease dementia patients.

The results of the study obtained agreed well with other researchers. IL-1 is a pleiotropic and immunomodulator cytokine family, with two isoforms, IL-1α and IL-1β that have similar biological activities (as noted by D'Anna et al., 2017). IL-1 is a cytokine with a significant involvement in neuroinflammation. It has a pivotal role in regulating local tissue responses to injury and disease in the central nervous system and serves as a prototypical proinflammatory cytokine. According to D'Anna et al. (2017) our results confirm prior findings revealing elevated levels of IL-1β in brain lesions, CSF, and blood of AD patients. It's believed that IL-1β can have both helpful and harmful impacts on AD aetiology .

Proinflammatory cytokines and chemokines, such as IL-1β, IL-6, and IL-8, have been shown to correlate with the presence and metabolism of amyloid-beta (Aβ) or tau proteins, which in turn lead to the neurodegenerative cascades of AD, and this has been confirmed by Shen X-N, et al (2019). Neuron dysfunction and progressive neurodegeneration have both been linked to IL-1β after Aβ deposition in AD. Consistent with prior meta-analyses; IL-6 was discovered to have a potential characteristic that detects the degree of cognitive impairment in patients with AD. The degenerative cascade of Alzheimer's disease may be hastened by the fact that microglia and astrocytes release IL-6 when they encounter Aβ deposits.

We discovered no statistically significant association between IL-6 and age or body mass index in Alzheimer's disease. Researchers Boccardi, V. et al. (2021) showed that elevated IL-6 levels were significantly correlated with age, but not with body mass index.

IV. Conclusion

In emerging nations like India, the prevalence of dementia is predicted to increase at a far faster rate than in developed nations like the United States. Acquired decline in cognitive ability that interferes with daily functioning; this is the definition of dementia. Dementia affects many cognitive abilities, but memory loss is the most prevalent. Dementia is a prevalent condition and because of its non-specific clinical presentation, it remains under-diagnosed. Patients with dementia have an increased risk of developing additional medical conditions. Dementia seemed to affect more women than males, according to our findings.

There is evidence that inflammation has a role in the development of Alzheimer's disease. The purpose of this research was to compare the levels of pro- and anti-inflammatory cytokines in the blood of persons with Alzheimer's disease (AD) to those of people without the disease (controls), and to determine where these cytokines originate. Plasma levels of interleukin (IL)-1β and IL-6 were measured. The senile plaques found in Alzheimer's disease brains are surrounded by reactive astrocytes and activated microglial cells that express a variety of inflammatory cytokines.

Multiple pro-inflammatory cytokines have been shown to be involved in the pathophysiology of AD through their dysregulation. Here, focus will be on IL-1β and IL-6 and hypothesize about their potential roles in the development of AD.

Microglia and astrocytes in various parts of the brain are responsible for the majority of IL-6 production, yet it is a pleiotropic inflammatory cytokine. Patients with Alzheimer's disease have been discovered to have considerably increased IL-6 levels in their brains, CSF, and plasma, especially in the areas immediately surrounding amyloid plaques. We found that IL-6 levels were significantly higher in the Alzheimer's dementia group compared to the control group. The connection between age and IL-6 in the Alzheimer's dementia study group was weak. The connection between IL-6 and body mass index (BMI) in the Alzheimer's dementia study group was weak and not statistically significant.

A member of the IL-1 cytokine family, IL-1β is thought to have a crucial role in the development of AD as a significant proinflammatory cytokine in the brain. Pro-IL-1β is synthesised and secreted in the cytoplasm by activated microglia and astrocytes in response to various stimuli. Pro-IL-1β must be cleaved by the protease caspase-1, which in turn is activated by cytosolic multiprotein complexes called inflammasomes, to generate mature and bioactive form. According to our findings, IL-1β levels are much higher in Alzheimer's dementia than in the control group. The link between age and IL-1β in the Alzheimer's dementia study group was not statistically significant. The connection between IL-1β and body mass index (BMI) in the Alzheimer's dementia study group was weak and not statistically significant.

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