Assessment Of Anti-Inflammatory Cytokine Interleukin-10 In Mild Cognitive Impairment In Elderly

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Abstract

Background: Mild cognitive impairment (MCI) is decline and disturbance of cognitive, little impairment of complex skills, ability to conduct ordinary daily functions, and the absence of dementia are all features of MCI. Interleukin-10 (IL-10) has anti-inflammatory effects and may suppress neurodegenerative disorders.

Objective: This study aimed to investigate the possible association between serum interleukin 10 (IL-10) levels and mild cognitive impairment (MCI) in the elderly population.

Material and methods: The study was carried out on 90 subjects aged 65 years or older] divided into Group I (MCI patients): including 45 patients. in Group II (Control): which included 45 subjects with normal cognition. All subjects underwent detailed history taking, clinical examination, and assessment of cognitive function. Laboratory investigations included: Serum interleukin-10(IL-10), C-reactive protein (CRP), ESR, CBC, fasting blood glucose (FBS), postprandial blood glucose (PPS), urea, creatinine, and liver enzyme levels.

Results: IL-10 levels in the MCI group ranged from 4.60 –16.31 with a mean value (S.D) of 9.75 ±2.26. IL-10 among the control group ranged from 4.91 –to 12.15 with a mean value (S. D) of 8.87 ±1.80.IL-10 was significantly higher among the MCI group (p=0.044)

Conclusion: There was a statistically significant difference between the serum levels of IL-10 in patients with MCI and controls.

Keywords: Mild cognitive impairment (MCI), Inflammation, Interleukin 10(IL-10)

INTRODUCTION

Mild cognitive impairment (MCI) causes serious changes that are noticeable by the person affected and by family members and friends but do not affect the individual's ability to perform everyday activities. Approximately 15 - 20% of people aged 65 years or older have MCI. People living with MCI, especially those with MCI involving memory problems, are more likely to develop Alzheimer's disease or other dementias than people without MCI. [1]

Mild cognitive impairment (MCI) is four times more common than dementia. [2]

MCI became a novel topic in current research with the hypothesis it represents the "grey line" or "transitional zone" between normal cognition and dementia, such as Alzheimer's disease (AD). Up to 50% of patients with MCI develop dementia within three years. [3,4]

Chronic low-grade inflammation is characteristic of biological aging. This long-term process has been termed "inflamm-aging," and is a major cause of disease and mortality in the elderly. Inflamm-aging plays an important role in the onset and progression of diseases associated with old age such as type II diabetes, mild cognitive impairment, Alzheimer's disease, cardiovascular disease, frailty, osteoporosis, sarcopenia, and cancer. [5]

Emerging data suggest that inflammation plays a causal role in disease etiology and that understanding and controlling immune-nervous system interactions could be essential to prevent or delay the onset of most late-onset central nervous system disorders. Neuroinflammation is not a passive system induced by amyloid plaques and neurofibrillary tangles in Alzheimer's disease; rather, it plays an equal (or greater) role in pathogenesis than plaques and tangles. Initial findings of mild cognitive impairment that occur before Alzheimer's disease show an early and significant role of inflammation in disease etiology. [6]

Neuroinflammation is a response that involves neurons, microglia, and other cells of the central nervous system (CNS). Microglia and complicated neuroinflammatory pathways are activated by several factors, including initial injury, genetic background, environmental conditions, and age or previous experience. [7,8]

MCI already exhibits extracellular plaque formation and many neuropathological characteristics of Alzheimer's disease. [9]

Microglia and astrocytes are arguably the most important sources of cytokines in neuroinflammation. Cytokines are involved in every aspect of neuroinflammation, including both pro and anti-inflammatory processes, neuronal damage, chemoattraction, and microglial reactions to Aβ deposition. Increased quantities of proinflammatory cytokines such as TNF-α, interleukin 6, interleukin 1α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are linked to higher levels of Aβ. [10] In the brains of people with mild cognitive impairment or Alzheimer's disease, caspase 1 activity, which is required for the cleavage of interleukin 1β to its active form, is also enhanced. [11] In MCI patients' brains and cerebrospinal fluid (CSF), inflammatory markers were shown to be upregulated. [12] For example Patients with elevated levels of TNF-α and lower levels of transforming growth factor-β (TGF-β) in the CSF are prone to developing Alzheimer's disease after mild cognitive impairment. [13]

Macrophage migration inhibitory factor (MIF), which increases the production of various inflammatory mediators such as TNFα, IL-6, and interferon-gamma (IFN-γ), is another pro-inflammatory cytokine that has recently been studied. CSF MIF levels are significantly higher in patients with AD and MCI. [14]

Anti-inflammatory cytokines are important for balancing the immune response and preventing the steady state of immunological homeostasis from tipping into inflamm-aging

and disease-causing states. Anti-inflammatory cytokines play a major role in the resolution of inflammation. They inhibit or control the production of IL-1α, TNF- α, and other important pro-inflammatory cytokines and the inflammatory response, allowing inflammation to be resolved. The anti-inflammatory route of inflammation management is dominated by these cytokines (TGF-β, IL-37, and IL-10) and variations in their synthesis and expression have been frequently observed in aging and age-related diseases. [15]

Interleukin-10 (IL-10) has anti-inflammatory and immunosuppressive effects, and Polymorphonuclear leukocytes (including mast cells, eosinophils, and neutrophils), dendritic cells, natural killer cells, macrophages, B lymphocytes, and T lymphocyte subtypes, particularly T helper 2 (TH2) and T regulatory cells (Tregs), all produce interleukin-10 (IL-10). [16] In the central nervous system, the main producers of IL-10 are astrocytes, microglia, and neurons. Macrophages are the main source of IL-10 at the periphery. [17]

Suppression of monocyte and macrophage function is one of the most important actions of IL-10. In addition, IL-10 inhibits the production of IL-1β and TNF-α. The major histocompatibility complex (MHC) class II glycoproteins of the histocompatibility complex are expressed by IL-10. IL-10 also suppresses co-stimulatory and adhesion molecule clusters of differentiation (CD86 and CD54), which drive a pro-inflammatory response within macrophages. IL-10 also inhibits the actions of IL-12 and IL-23, which are known mediators of the inflammatory immune response. [18] IL-10 promotes Treg differentiation .[19]

One of the most essential features of IL-10's immunomodulatory activity is the TH1/TH2 balance. TH1 plays a key role in cell-mediated immunity, whereas TH2 plays an important role in mucosal immunity. B cells are vital in mucosal defense against bacterial toxins and intestinal parasites and IL-10 increases their activation and proliferation. [20]

Several aspects of B cell function are stimulated by IL-10, such as differentiation, proliferation, survival, and production of antibodies. Mast cells and thymocytes proliferate in response to IL-10. IL-10, on the other hand, can decrease T cell activation and proliferation by suppressing IL-2 synthesis and CD28 signaling. [21]

Finally, angiogenesis suppression and decreased production of IL-1β, TNF-α, and IL-6, all of which play essential roles in neovascularization and decrease the expression of vascular endothelial growth factors within tumor-associated macrophages, may all have anti-cancer effects. [22]

IL-10 concentration and function are affected by many variables. Many diseases and immunodeficiency disorders have been linked to altered IL-10 function, including infections, allergies, autoimmune reactions, tumor growth, and transplant tolerance. [23,24]

Increased IL-10 levels have been demonstrated to protect tissues against harm, such as diabetic wounds, cerebrovascular ischemic stroke, and myocardial remodeling. [25] IL-10 also has positive benefits in physiological settings such as learning and cognition, pregnancy and breastfeeding, nutritional therapy, and a variety of metabolic and homeostatic problems. [26,27] One of IL-10's most essential physiological functions is to protect neurons from hypoxic and ischemic stress, glutamate-induced excitotoxicity, and neuronal death. [28]

Peripheral proinflammatory and counter-regulatory anti-inflammatory cytokines are thought to mediate intricate interactions between the central and peripheral nervous immune systems that contribute to "normal" and pathological cognitive decline in the context of age-related chronic low-grade inflammation. Changes in sleep patterns, apoptosis, demyelination, regulation of neurotransmitters, the risk of thrombosis, and vascular endothelial injury are some of the mechanisms by which cytokine dysregulation may adversely affect cognition through synaptic regression and neuronal death. [29]

Proinflammatory markers, especially acute phase C-reactive protein (CRP), are increasingly linked to cognitive performance. Although CRP has been shown to predict future cognitive deterioration in some studies, a link between specific cognitive domains and proinflammatory markers has been described. [30] CRP levels, for example, have been shown in certain studies to be inversely associated with episodic memory performance and predict poor memory performance. [31]

Inflammatory indicators in the blood, such as IL-6, IL-10, and TNF-α, may be used to identify those at risk for poor cognitive outcomes. Following the increased expression of inflammatory cytokines, elevated levels of IL-10 could indicate an anti-inflammatory reactive response in patients with MCI. [32]

this study aimed to investigate the possible association between serum interleukin 10 (IL-10) levels and mild cognitive impairment (MCI) in the elderly population.

Subjects

The study was carried out at the Alexandria Main University Hospital, Geriatric Department, or Outpatient Clinic. The study was approved by the Medical Ethics Committee of the Alexandria Faculty of Medicine. All participants were informed about the nature of the study and written informed consent was obtained from all subjects.

The study was carried out on 90 subjects of both sexes (male and female) aged 65 years or older and divided into the following categories:

- Group I (MCI patients): included 45 patients who had a score of 20 to 24 on the Mini-Mental Status Examination MMSE and a score of 22 to 26 on the Montreal Cognitive Assessment (MoCA). [33,34]
- Group II (Control): included 45 subjects with normal cognition (MMSE score more than 24 and MoCA score more than 26)

Patients with one or more of the following were excluded:

1. The presence of severe dementia.
2. Severe neurological or psychiatric illness.
3. History of diabetes mellitus.
4. History of angina pectoris or myocardial infarction.
5. History of head trauma.
6. Patients with hearing or speech impairment.
7. Patients with any identifiable acute, intermittent or chronic infection or being on routine anti-inflammatory or immunosuppressive therapy.

METHODS

The following data were obtained for each patient:

Socio-demographic data:

- Name.
- Age (in years).
- Sex (male and female).
- Occupation (employed, unemployed, retired……etc).
- Marital status (single-married-divorced-widow).
- Smoking (smoker -non-smoker).
- Sleep duration was collected in hours per day (h/day).

• Full history taking for the present condition regarding duration, course, and medication received.

• Complete physical examination was done for all participants.

• Cognition was assessed using:

1. Mini-Mental Status Examination (MMSE). [33]
2. Montreal Cognitive Assessment (MoCA). [34]

• The following laboratory investigations were done for all participants:

- Complete blood count (CBC).
- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP)
- Liver enzymes: ALT, AST.
- Serum protein, albumin, and total bilirubin.
- Renal function tests: blood urea, serum creatinine, complete urine analysis.
- Fasting and postprandial blood glucose.
- Serum Interleukin 10 (IL-10)

RESULTS

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). the significance of the obtained results was judged at the 5% level.
The used tests were

1 - Chi-square test

For categorical variables, to compare different groups
2 - Monte Carlo correction
Correction for chi-square when more than 20% of the cells have an expected count of less than 5
3 - Student t-test
For normally distributed quantitative variables, to compare two studied groups
4 - Mann Whitney test
For not normally distributed quantitative variables, to compare two studied groups
8 - Pearson coefficient
To correlate between two normally distributed quantitative variables

Table (1):   demographic data and clinical characteristics of the patients.

	Cases (n = 45)		Control (n = 45)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	26	57.8	23	51.1	$\chi^2=$ 0.403	0.525
Female	19	42.2	22	48.9		
Age (years)						
Min. – Max.	65.0 – 86.0		65.0 – 85.0		t= 0.486	0.628
Mean ± SD.	70.84 ± 6.98		71.51 ± 6.0			
Median (IQR)	68.0 (65.0 – 76.0)		70.0 (65.0 – 77.0)			
Occupation						
Retired	12	26.7	21	46.7	$\chi^2=$ 4.934	MCp= 0.055
Unemployed	31	68.9	24	53.3		
Employed	2	4.4	0	0.0		
Marital status						
Single	4	8.9	0	0.0	$\chi^2=$ 6.260	MCp= 0.074
Married	22	48.9	31	68.9		
Widow	18	40.0	13	28.9		
Divorced	1	2.2	1	2.2		
Smoking						
No	30	66.7	34	75.6	$\chi^2=$ 0.865	0.352
Yes	15	33.3	11	24.4		
Sleep						
Min. – Max.	5.0 – 11.0		5.0 – 11.0		t= 0.928	0.356
Mean ± SD.	7.76 ± 1.69		7.42 ± 1.71			
Median (IQR)	8.0 (6.0 – 9.0)		7.0(6.0 – 8.0)			

IQR: **Inter quartile range**   SD: **Standard deviation**   t: **Student t-test**
χ^2: **Chi square test**   MC: **Monte Carlo**
p: p value for comparing between the studied groups

Table (2): cognitive assessment of studied two groups

	Cases (n = 45)	Control (n = 45)	t	p
MMSE				
Min. – Max.	20.0 – 24.0	25.0 – 30.0		
Mean ± SD.	22.07 ± 1.45	27.64 ± 1.35	18.864[*]	<0.001[*]
Median (IQR)	22.0(21.0 – 23.0)	28.0(27.0 – 29.0)		
MOCA				
Min. – Max.	22.0 – 26.0	27.0 – 30.0		
Mean ± SD.	23.33 ± 1.31	28.02 ± 1.08	18.516[*]	<0.001[*]
Median (IQR)	23.0(22.0 – 24.0)	28.0(27.0 – 29.0)		

IQR: **Interquartile range**   SD: **Standard deviation**   t: **Student t-test**

p: p-value for comparing the studied groups

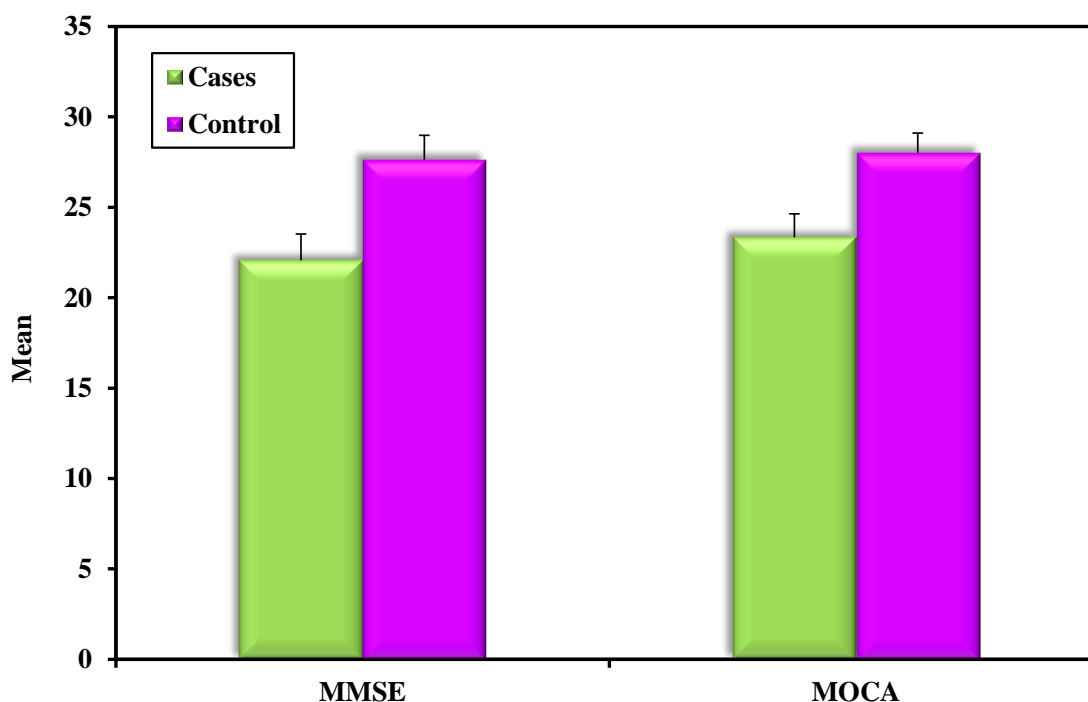*: Statistically significant at $p \leq 0.05$

Figure (1): Comparison between the two studied groups according to MMSE and MOCA

Table (3): Comparison between the two studied groups according to inflammatory markers

	Cases (n = 45)	Control (n = 45)	U	p
CRP				
Min. – Max.	1.01 – 19.20	0.70 – 17.60		
Mean ± SD.	13.10 ± 4.83	6.77 ± 4.36	328.50*	<0.001*
Median (IQR)	15.0 (11.30 – 16.0)	5.20 (3.0 – 10.0)		
ESR 1st				
Min. – Max.	5.0 – 40.0	3.0 – 35.0		
Mean ± SD.	22.0 ± 10.75	15.87 ± 6.79	694.50*	0.010*
Median (IQR)	23.0 (10.0 – 30.0)	15.0 (12.0 – 20.0)		
ESR 2nd				
Min. – Max.	13.0 – 60.0	9.0 – 50.0		
Mean ± SD.	41.18 ± 15.16	30.82 ± 12.09	602.50*	0.001*
Median (IQR)	45.0 (27.0–55.0)	28.0 (22.0 – 44.0)		

IQR: **Interquartile range**   SD: **Standard deviation**   U: **Mann Whitney test**
p: p-value for comparing the studied groups
*: Statistically significant at $p \leq 0.05$

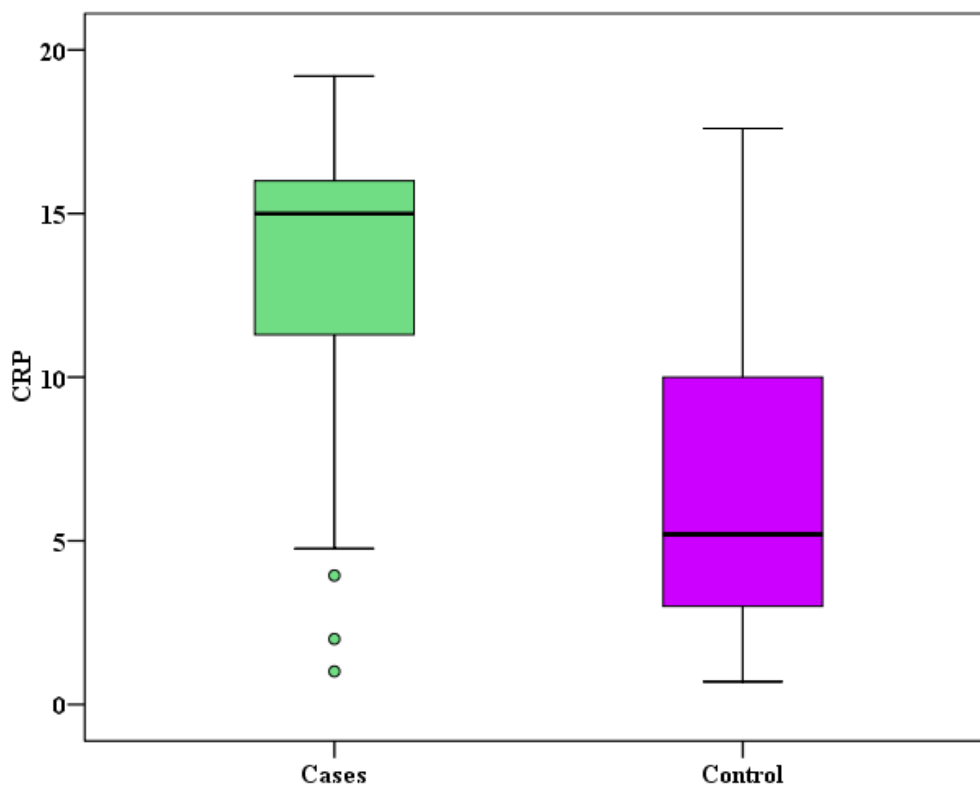**Figure (2):   Comparison between the two studied groups according to CRP**
Table (4):   Comparison between the two studied groups according to IL-10

IL-10	Cases (n = 45)	Control (n = 45)	t	p
Min. – Max.	4.60 – 16.31	4.91 – 12.15	2.047*	0.044*
Mean ± SD.	9.75 ± 2.26	8.87 ± 1.80		
Median (IQR)	9.32 (8.77 – 10.74)	9.01 (8.05 – 10.20)		

IQR: **Interquartile range**   SD: **Standard deviation**   t: **Student t-test**
p: p-value for comparing the studied groups
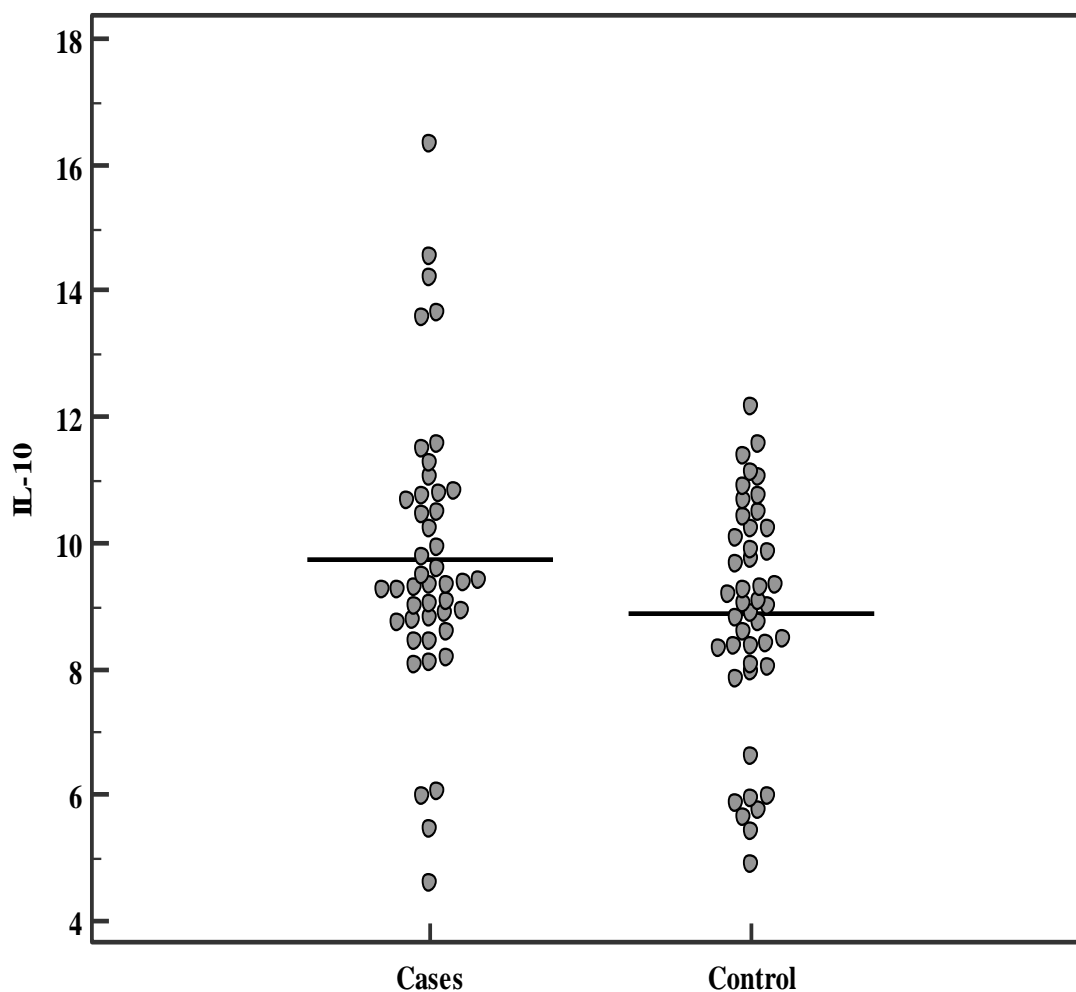*: Statistically significant at $p \leq 0.05$

Figure (3):   Comparison between the two studied groups according to IL-10

Table (5): **Correlation between IL-10 with different parameters in cases group (n = 45)**

IL-10 vs.	r	p
CRP	-0.211	0.165
WBCs	-0.114	0.456
MMSE	-0.051	0.742
MOCA	0.101	0.508

r: Pearson coefficient

Table (6): Correlation between CRP with MMSE and MOCA in the cases group

(n = 45)

CRP vs.	r	p
MMSE	0.044	0.776
MOCA	0.038	0.805

r: Pearson coefficient

DISCUSSION

For a variety of reasons, the idea of MCI is extremely important in the subject of aging and dementia. MCI patients have an increased rate of dementia progression in a short amount of time. Patients who revert to normal cognition have a higher risk of recurring MCI or dementia than those who never develop MCI. A greater understanding of MCI and its characterization could lead to the development of better diagnostic mechanisms such as imaging and fluid biomarkers, as well as therapeutic and non-therapeutic measures for MCI.[35]

MCI and MMSE

Our study found a significant discrepancy between the two studied groups concerning MMSE (p<0.001). The mean for the MCI group was 22.07 ± 1.45 and for the control 27.64 ± 1.35.

In line with our findings, Wang et al.[36] conducted a cross-sectional study from January 2009 to June 2012, the study included 120 Alzheimer's patients, 120 MCI patients, and 120 controls. MMSE was done for the three groups, and a significant difference between MCI and control regarding MMSE score was found (P < 0.001).

Zheng et al. [37] recruited 126 patients with type 2 DM (63 cases with MCI and 63 controls) in a cross-sectional study at the Hospital of Tianjin Medical University from 2016 to 2017.MMSE was done for all participants. Compared with the subjects in the control group, those in the MCI group had lower MMSE scores (P < 0.001).

Also, Wang et al.[38]enrolled 71 patients with chronic renal failure (CRF) and divided them into the MCI group and non-MCI group using MMSE. There was a significant discrepancy between the two groups regarding MMSE (P <0.05).

MCI and MoCA

Our study found a significant discrepancy between the two studied groups concerning MoCA (p<0.001). The mean for the MCI group was 23.33 ± 1.31 and for the control was 28.02 ± 1.08.

Cao et al.[39] conducted a study on three groups of elderly people aged 60-85 years: 121 patients with MCI, 131 patients with AD, and 100 healthy controls who were all examined at the same time. MMSE and MoCA were used to assess these groups. The MoCA and MMSE scores of the three groups were collected and analyzed. The results revealed that the Control group had significantly greater levels than the MCI group (P<0.05).

Shen et al.[40] used MMSE and MoCA to assess the cognitive function of the two studied groups and found a significant difference between them (p=0.001) for MMSE and MoCA.

MCI and CRP

Hepatocytes in the liver produce CRP, which is an acute-phase protein. It has a wide range of biological functions, but it is best known for activating the human complement, which is involved in innate immunity. It is also used as an inflammatory marker, with significant elevations in elderly inpatients reflecting serious disease and predicting poor prognosis. [41] Direct neuronal damage occurs due to its pro-inflammatory effect. Raised CRP concentrations can produce cerebral macro or micro-angiopathy. Both types of injuries compromise the integrity of frontal-subcortical networks, causing cognitive decline and dementia. [42]

Our study found a significant discrepancy between the two studied groups regarding CRP (p<0.001) as CRP level was higher in the MCI group than in the control group.

Results found by Gorska-Ciebiada et al. 2015 [43] are similar to our results regarding CRP as it was significantly higher in the MCI group as compared to the control.

Wang et al.[44] performed a prospective study on 1,800 patients from a health database at Tianjin Medical University General Hospital with normal cognitive function during their first health checkups. They were over 60 years old at the start of the study, with a 7-year follow-up period. At the time of data collection, 196 participants had MCI as determined by MMSE. The remaining 1,604 people had normal cognition. The results showed a significant discrepancy between the two groups at baseline and after follow-up. CRP was higher in the MCI group (p<0.001)

In the cross-sectional study conducted by Wang et al.[44] CRF patients' CRP was significantly greater in patients with MCI than in patients with normal cognition.

MCI and IL-10

Our study found a significant discrepancy between the two studied groups regarding IL-10 level (p= 0.044). The mean for the MCI group was 9.75 ±2.26 and for the control group was 8.87 ±1.80.

In line with our study, the cross-sectional and longitudinal study done by Wennberg et al.[45] as IL-10 level showed a significant difference between MCI and control group (p= 0.034) as it was significantly higher in the MCI group.

Wang et al.[44] measured IL-10 levels in the two studied groups and found a significant difference between the two studied groups but it was higher in CRF patients without MCI than in those with CRF and MCI.

Against our findings, Kim et al.[46] measured IL-10 levels in the MCI group and control, no significant difference was found.

Also, Fan et al.[47] measured Il-10 levels in 30 healthy control subjects, and 26 patients with MCI. There was no significant discrepancy between the two groups.

This discrepancy may be due to differences in the number of patients, heterogeneity of the studied population, and selection of different age groups.

CONCLUSION

There is a higher statistically significant discrepancy between serum IL-10 levels in patients with MCI and control subjects. CRP is also significantly higher in patients with MCI than in the control group. These findings may refer to that IL-10 and CRP are inflammatory indicators for poor cognition in high-risk elderly.

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