Relationship Between Disease Activity, Levels of IFN-α, IL-4, IL-6, and Anti-NMDA to Cognitive Dysfunction (MoCA-INA Score) in Systemic Lupus Erythematosus (SLE) Patients with Cognitive Dysfunction

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ABSTRACT

Background: *Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is a condition that impacts the patients' brain with SLE, and cognitive dysfunction (CD) is the most common manifestation. Subsequently, the CD hurts the life quality of SLE patients and creates impaired social function. Furthermore, the Montreal Cognitive Assessment (MoCA-INA) is a screening instrument to evaluate cognitive function. In the context of lupus, cytokines, and autoantibodies act as biomarkers in SLE disease control activities.* ***Purpose:*** *The aim of this study was to analyze the correlation between disease activity, IFN-a, IL-4, IL-6 and Anti-NMDA on CD (MoCA-INA Score) in SLE patients with CD.* ***Methods:*** *This analytical observational study was performed with a cross-sectional design and included a sample of 56 SLE patients. The independent variables were the degree of the disease activity, and levels of IFN-a, IL-4, IL-6, and anti-NMDA. The dependent variable consisted of the degree of CD (MoCA-INA score), while the confounding variables were age, DM, gender, hypertension, obesity, and dyslipidemia. Subsequently, the CD was described as a MoCA-INA score <26, and disease activity was estimated based on the SLEDAI score.* ***Results:*** *Increased IL-6 levels were correlated with decreased MoCA-INA scores (p=0.003; r= -0.387). Younger age was found to be associated with more severe CD (p=0.006)* ***Conclusion:*** *In conclusion, IL-6 levels can be used as a predictor severity of CD in SLE patients.*

Keywords*: Cognitive dysfunction, Systemic Lupus Erythematosus, Disease activity, IFN-a, IL-4, IL-6, Anti-NMDA*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a persistent autoimmune rheumatic disease that impacts many bodily systems. It is characterized by alternating episodes of disease attacks and periods of remission. Within SLE, there is a subgroup known as neuropsychiatric lupus (NPSLE), which refers to patients experiencing neurological or psychiatric symptoms associated with the central nervous system. To diagnose NPSLE, other potential causes must be ruled out through laboratory tests, clinical evaluations, neuropsychological assessments, and neuroimaging tests.[1,2] Subsequently, a CD is the most familiar abnormality in NPSLE and significantly reduces the quality of life and increases morbidity and mortality. Based on the investigation by Zhang Y, et al, it was reported that CD occurred in 42.1% of NPSLE patients. [3]

The MoCA is a widely used screening tool for evaluating CD. The MoCA-INA also has high sensitivity and specificity for assessing CD in adults. This assessment tool evaluates several cognitions including attention, orientation, memory, executive function, conceptual thinking, language, visuospatial skills, and concentration. Using a cutoff score of 26, the MoCA-INA has a sensitivity of 83% for detecting CD.[4]

To evaluate SLE disease activity, several assessment questionnaires were used. SLEDAI is a commonly used scoring system due to its practicality. Given the significant role of cytokines in lupus, their use as biomarkers for disease movement in SLE is of particular interest.[5] Several cytokines are used as markers that describe SLE disease activity in patients, including interferon-alfa (IFN-α), interleukin-4 (IL-4), -6 (IL-6), and anti-NMDA. The objective of this study was to analyze the connection between disease activity, IFN-α, IL-4, IL-6, and Anti-NMDA, with CD (MoCA-INA score) in SLE patients with CD.

METHODS

We conducted this cross-sectional analytic study, from February 2023 to April 2023, at the Rheumatic Internal Medicine Polyclinic and Internal Medicine Ward at RSUP Dr. Kariadi Semarang. The sample was 56 SLE patients who met the inclusion criteria and did not have exclusion. Inclusion for males and females aged 18 years and older diagnosed with SLE based on the 2019 EULAR/ACR classification criteria and CD with a MoCA-INA score of <26, 2). Additionally, participants are required to have a minimum educational level equivalent to graduating from elementary school and express willingness to participate. Exclusion criteria included the exclusion of SLE patients with retinal disorders (retinopathy). In this study, the independent variables examined were disease activity, IFN-α, IL-4, IL-6, and anti-NMDA levels. The dependent variable was the degree of cognitive dysfunction (MoCA-INA score), with confounding variables being age, DM, gender, hypertension, obesity, and dyslipidemia. Subsequently, the CD is defined as having a MoCA-INA score of <26. Illness activity was counted based on the SLEDAI score (mild <3; moderate 3-12; severe >12).

This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University – Dr. Kariadi with reference letter number 786/EC/KEPK-RSDK/2021 and carried out in accordance with the principles of the Declaration of Helsinki.

RESULTS

The average of participants' age is 34.31 ± 9.25 years, which was mostly dominated by females (98.2%). On average, they had been experiencing symptoms of SLE for 46.38 ± 42.72 months. The SLEDAI score was 5.13 ± 2.9 where 14 (25%) participants had mild LES activity and 42 (75%) had moderate SLE activity, and no participants had severe LES activity.

In terms of cognitive function, the Visuospatial MoCA had an average of 0.23 ± 1.05, the Naming MoOCA had an average of 2.85 ± 0.35, and all participants scored 0 in Memory MoCA. The Attention MoCA had an average of 4.18 ± 1.07, and the MoCA scores for language, delayed recall, abstraction, orientation, and the total MoCA score averaged at 1.67 ± 0.81, 1.47 ± 0.53, 3.07 ± 1.59, 5.69 ± 0.57, and 22.8 ± 2.39, respectively. All participants experienced CD.

The IL-4 levels had a mean of 206.91 ± 276.77 pg/mL, and a median value of 75.7 pg/mL (10-1028 pg/mL). IL-6 levels had a mean of

18.88±12.71 pg/mL, and a median value of 14.95 pg/mL (1.5-53 pg/mL). INF-α levels had a mean of 21.59 ± 31.42 pg/mL, and a median value of 9.1 pg/mL (0.1-138.3 pg/mL). Anti-NMDA levels had a mean of 7.25±11.98 pg/mL, and a median value of 0.8 pg/mL (0.3-41.7 pg/mL).

Table 1. Study subject demographics

Variables	n (%)	Mean ± SD	Median (min-max)
Age		34,31 ± 9,25	34 (18-53)
- ≤ 20 years	2 (3,6)		
- 21-30	22 (39,3)		
- 31-40	15 (26,8)		
- 41-50	15 (26,8)		
- 51-60	2 (3,6)		
Gender		-	-
- Male	1 (1,8)		
- Female	55 (98,2)		
SLE Duration	-	46,38 ± 42,72	33 (0-163)
SLEDAI		5,13 ± 2,9	4 (0-10)
- Mild	14 (25)		
- Moderate	42 (75)		
- Severe	0 (0)		
MoCA Visuospatial	-	0,23 ± 1,05	4 (0-5)
MoCA Naming	-	2,85 ± 0,35	3 (2-3)
MoCA Attention	-	4,18 ± 1,07	4 (1-6)
MoCA Language	-	1,67 ± 0,81	2 (0-3)
MoCA Abstraction	-	1,47 ± 0,53	1 (0-2)
MoCA Delayed Recall	-	3,07 ± 1,59	3 (0-5)
MoCA Orientation	-	5,69 ± 0,57	6 (4-6)
MoCA Total		22,80 ± 2,39	23 (16-25)
- Cognitive dysfunction	56 (100)		
- Normal	0 (0)		
IL-4	-	206,91 ± 276,77	75,7 (10-1028)
IL-6	-	18,88 ± 12,71	14,9 (1,5-3)
IFN-α	-	21,59 ± 31,42	9,1 (0,1-138,3)
Anti-NMDA	-	7,25 ± 11,98	0,8 (0,3-41,7)

Table 2. Differences in cognitive dysfunction (MoCA-INA score) based on systemic lupus erythematosus activity.

Variables	Systemic Lupus Erythematosus Activity		*p*
	Mild	Moderate	
MoCA-INA Score	23,14 ± 2,14; 23,5 (18-25)	22,74 ± 2,48; 23,5 (16-25)	0,662

Independent T-test; significant p<0,05

Table 3. Correlation of IL-4, IL-6, INF-α and anti-NMDA levels on cognitive dysfunction (MoCA-INA score

Variables	Cognitive Dysfunction (MoCA-INA Score)	
	p	r
IL-4 Level	0,314	-0,137
IL-6 Level	**0,003**	-0,387
IFN-α Level	0,750	-0,044
Anti-NMDA Level	0,653	-0,061

Spearman test; significant p<0,05

A significant difference (p=0.662) was not discovered in the MoCA-INA score between subjects with mild as well as moderate SLE activity.

Table 4. Factors influencing cognitive dysfunction (MoCA-INA)

Variable		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	CI 95%	
		B	SE	Beta			Lower	Upper
Cognitive Dysfunction (MoCA-INA)	Constant	30.499	5.339		5.713	.000	19.776	41.222
	Age	-.101	.035	-.388	-2.858	**.006**	-.171	-.030
	Gender	-.348	2.359	-.019	-.147	.883	-5.086	4.390
	Hypertension	-1.570	.991	-.205	-1.585	.119	-3.560	.420
	IMT	-.265	.329	-.108	-.806	.424	-.927	.396
	Dyslipidemia	.067	.639	.014	.105	.917	-1.216	1.351

Linear Regression Test; significant p<0,05

Table 5. Correlation of age and IL-6 levels to components of MoCA-INA

MoCA-INA Components	Age		IL-6 Level	
	p	r	*p*	r
Visuospatial	0.147	-0.196	**0.009**	**-0.346**
Naming	0.844	-0.027	0.094	-0.226
Attention	0.502	-0.092	0.124	-0.208
Language	0.348	-0.128	0.377	-0.120
Abstraction	0.432	0.107	0.553	0.081
Delayed Recall	**0.049**	**-0.264**	0.459	-0.101
Orientation	**0.049**	**-0.265**	0.120	-0.210

Spearman test; significant p<0,05

A correlation of IL-6 levels and CD (MoCA-INA score) in SLE patients (p=0.003) was found, with a weak negative correlation level (r= -0.387). There was no relation between IL-4 levels (p=0.314), INF-α levels (p=0.750), as well as anti-NMDA levels (p=0.653) on CD (MoCA-INA score) in SLE patients.

Age was the most influencing factor for CD (MoCA-INA) in SLE patients, where younger age was associated with more severe CD (p=0.006; B= -0.101)

Examination of each component of the MoCA-INA indicated a correlation between age and delayed recall score (p=0.049) and orientation (p=0.049). Furthermore, the analysis of each component of the MoCA-INA showed a relation between IL-6 levels and the visuospatial score (p=0.009).

Increasing age is weakly correlated with decreasing delayed recall scores (r= -0.264) and decreasing orientation scores (r= -0.265). Increased IL-6 levels are correlated weakly with decreased visuospatial scores (r= - 0.346).

DISCUSSION

Most SLE patients are dominated by females with an average age of 34 years. SLE is described by an incidence ratio of 9:1 between males and females, with a higher predominance of females through the peak reproductive years. The peak incidence of SLE in female transpires during the reproductive (age 20–30).[6] Subsequently, Boodhoo KD, et al conducted a systematic review as well as a meta-analysis study on 11,934 SLE patients and obtained similar results that the ratio of the incidence of SLE between female: and male were 9.3:1. Several clinical symptoms were significantly different between female and male, including alopecia, photosensitivity, as well as oral ulcers were significantly higher in female patients (OR 0.36, 95% CI 0.29–0.46, P < 0.00001; OR 0.72, 95% CI 0.63–0.83, P<0.00001; as well as OR 0.70, respectively, 95% CI 0.60–0.82, P<0. 00001). The occurrence of malar rash was found to be significantly higher in female (OR 0.68, 95% CI 0.53–0.88, P = 0.003), whereas arthritis was significantly less frequent in male patients (OR 0.72, 95% CI 1.25–1.84, P < 0.00001). Whereas serositis as

well as pleuritis were significantly more common in females (OR 1.52, 95% CI 1.25-1.84, P < 0.0001; as well as OR 1.26, 95% CI 1.07-1.48, P = 0.006, respectively). Male patients, on the other hand, had a higher likelihood of experiencing renal involvement (OR 1.51, 95% CI 1.31–1.75, P < 0.00001). In males, most of the diagnoses of SLE were performed between the ages of 30-50 years, while in female patients the diagnosis of SLE was carried out between the ages of 30-45 years.[7]

Several studies conducted on LES rat models have indicated that the presence of estrogen can worsen autoimmunity. In vitro studies on people's cells also indicate that estrogen exposure increases the exposure to inflammatory cytokines in dendritic cells. Conversely, progesterone has been found to inhibit TLR7-mediated IFN-α production by dendritic cells. Females with SLE have abnormal active estrogen metabolite levels and abnormally low progesterone levels. Therefore, in females predisposed to SLE due to another factor, low progesterone levels or high estrogen levels may ease disease progression or infection activity by modulating the IFN-α pathway. Several studies highlight the involvement of IFN-α in the SLE pathogenesis, with raised levels of IFN-α correlating with higher disease activity.[8]

A sign of SLE is the excessive production of autoantibodies, leading to irreversible resistant complex-mediated end-organ defeat. This antibody production is very dependent on CD4+ T cells, which have an important part in the formation of the germinal center from which high-affinity B cells and memory B cells are selected. In T cells of SLE patients, signal transduction pathways are altered by estrogen compared to normal T cells.[9]

The mean duration of suffering from SLE was 33 months with moderate activity based on the SLEDAI score. The total MoCA score has a median value of 23, in which all participants have CD. The MoCA score with the lowest score is visuospatial MoCA.

According to Koelmeyer R, et al., the median duration of suffering from SLE in patients was reported to be 5.1 years.[10] In research conducted by Shamim et al. investigated the relationship midst SLE activity and clinical characteristics in patients, it was found that 87% of patients had a SLEDAI score higher than 6. Furthermore, the mean SLEDAI score was found to be more elevated in patients with kidney involvement (p=0.06). Increased sedimentation rate (r=0.48, p=0.02), anti-dsDNA (r=0.44, p=0.05), as well as low levels of complement protein (p=0.03) were very positively correlated with the SLEDAI score, while hemoglobin levels (r= -0.43, p=0.04) has a negative relation with the SLEDAI score.[11]

Rame AS, et al which examined the MoCA-INA relationship in 83 participants found that the mean MoCA-INA score was 21.06 with a standard deviation of 4.56 (range 5-30).[12] Anjalia S, et al which assessed memory function in SLE patients using MoCA-INA found that the mean total MoCA-INA score was 24.97 ± 3.14. Subsequently, 50% of SLE patients experienced cognitive impairment, with the domains included being delayed recall (86.67%), language (56.67%), attention (60%), abstraction (53.33%), as well as visuospatial/executive function (36.67%). Cognitive impairment in SLE patients is likely due to damage to the front-subcortical circuits.[13] The process of memory forming involves encoding, retention, and retrieval of information, with encoding and retrieval taking place in the prefrontal cortex and retention in the hippocampus.[14]

Neuropsychiatric involvement in SLE patients is declared in 6% to 91% of cases, and this condition is known to cause severe mortality and morbidity.[13] One of the neuropsychiatric manifestations is cognitive impairment, which occurs in 80% of neuropsychiatric lupus patients. Previous studies showed that SLE patients have decreased cognitive abilities compared to non-SLE individuals, with observed impairments in attention, working memory, visuospatial abilities, and simple reaction times. Impaired memory is the most common manifestation, possibly caused by circulating antibodies blocking neurotransmitter transmission and causing vasculopathy.[15]

Although there was no relationship between LES activity and CD in SLE patients, there is a tendency for a negative correlation between LES activity and the MoCA-INA score (r= -0.059),

this means that the more severe the LES activity is associated with a higher the MoCA-INA score. lower (tendency to occur cognitive dysfunction).

Saepudin A, et al., in their investigation of the correlation between cognitive function and SLE activity, found a median MoCA-INA score of 25 and a mean SLEDAI-2K score of 6. Subsequently, the CD was proved in more than half of the participants (52.63%), where the memory domain (78.95%) was most often disturbed. Most of the participants were active SLE patients (63.2%). The correlation test found no connection between the SLEDAI-2K as well as the MoCA-INA score ($r=0.023$, $p=0.445$).[16] Ragunath S, et al found similar results that in SLE patients, CD was positively related to organ damage, but not related to disease activity.[17]

The development of NPSLE is influenced by multiple factors and involve a variety of inflammatory cytokines, immune complexes, and autoantibodies. This intricate interplay can result in vasculopathy, cytotoxic effects, and neuronal injury mediated by autoantibodies. Microvasculopathy, triggered by complement activation and antiphospholipid antibodies, stands as the prevailing histopathologic characteristic of SLE.[18]

Within the neuropathology of SLE, the blood-brain barrier is compromised, leading to functional alterations in endothelial cells and elevated levels of ICAM-1. Diamond et al. proposed a potential mechanism for NPSLE involving circulating anti-DNA autoantibodies that exhibit cross-reactivity with the NR2 subunit of the anti-N-methyl-D-aspartate receptor. This cross-reactivity occurs during the inflammatory processes that contribute to the disruption of the blood-brain barrier.[18]

The median values for IL-4, IFN-α, and anti-NMDA levels were 75.5 pg/mL, 9.1 pg/mL, and 0.8 pg/mL, respectively. Therefore, there was no observed correlation between IL-4, IFN-α, and anti-NMDA levels and CD as measured by the MoCA-INA score. On the other hand, IL-6 levels had a median value of 14.95 pg/mL and showed a relation between IL-6 levels and CD (MoCA-INA score) in SLE patients. More elevated levels of IL-6 existed correlated with decreased MoCA-INA scores (more severe cognitive dysfunction).

Ruchakorn N, et al., conducted a study on cytokine performance in predicting LES activity and obtained similar findings. They reported a significant increase in active LES and correlated with the SLEDAI score. IL-6 levels also have higher sensitivity and specificity than anti-dsDNA and C3 for predicting lupus nephritis.[19] Another study by Bradburn S, et al., involving 15,828 participants, revealed that high serum IL-6 levels were associated with a 1.42 times greater risk of experiencing global cognitive decline after 2-7 years follow-up.[20]

In patients with active SLE, serum IL-6 levels increase, and several studies showed correlations between IL-6 levels and disease activity or anti-DNA levels. Increased levels of IL-6 are associated with B-cell hyperactivity as well as production of autoantibodies and anti-DNA IgG antibodies, and decreased secretion of anti-DNA IgG antibodies, which can be reversed by neutralizing IL-6 or administering exogenous IL-6 in vitro. IL-6 is also implicated in local inflammation, such as in lupus nephritis, where it is believed to contribute to mesangial cell proliferation, a characteristic feature of proliferative lupus nephritis. IL-6 levels increased during cardiopulmonary complications of SLE, and NPSLE patients show elevated levels of IL-6 in the cerebrospinal fluid.[21]

IL-6 has been evident to directly cross the blood-brain barrier in studies using mouse models, even at low levels. In addition, it is also suspected that cytokines circulating in the plasma have a greater ability to penetrate the central nervous system through the circumventricular organs (CVO), areas of the brain that have high permeability. There is an effective relationship between IL-6 levels in plasma as well as cerebrospinal liquid. The central nervous system of older individuals is also more susceptible to inflammatory cytokines. Montagne et al., suggested that the blood-brain barrier is damaged and its permeability increases in areas responsible for learning and memory functions, including the hippocampus.[22] In addition, repeated injury to the blood-brain barrier, either because of repeated infections or increased exposure to exogenous IL-6, proved to increase the permeability of the blood-brain barrier.[23] Consequently,

dysfunction of that barrier may occur in the elderly population, especially in the presence of age-related factors and underlying infection.

Prolonged exposure to IL-6 in the brain has been related to various neuropathological problems. In vitro, a study involving rat hippocampal precursor cells incubated with recombinant IL-6 showed a 50% decrease in neurogenesis and an upgrade in apoptotic cell count. In addition, the overproduction of IL-6 by astroglia in transgenic rats decreased the rate of neurogenesis in the dentate gyrus by 63% as well as decreased proliferation, survival, as well as differentiation of neural progenitor cells. Studies using MRI found a strong association between heightened blood IL-6 concentrations and hippocampal gray matter volume, total brain volume, and intensified rate of cortical thinning over time.[24-26] These results imply that long-term exposure to IL-6 in the brain can directly inhibit neurogenesis and neuronal health, thereby indicating cognitive decline.

In male and female patients, as well as healthy siblings of both genders, there appears to be a correlation between younger age and more severe CD. Specifically, there is an inverse connection among age and serum IFN-α activity, with higher levels observed in younger individuals.[27] Raghunath S, et al., found a negative relation between age and the domain of cognitive function, including visual memory (r= -0.04), verbal memory (r= -0.02), working memory (p= -0.01), processing speed (r= -0.03), complex attention (r= -0.04), and psychomotor speed (r= -0.03).[28]

In this study, a noteworthy finding was the significant increase in IFN-α activity observed among female SLE patients between the ages of 12 and 22 and males between 16 and 29. Interestingly, healthy male as well as female first-degree relatives exhibited a significant decrease in IFN-α activity after the age of 50. The year range exhibiting the highest serum IFN-α levels in SLE patients is the same as the age range during which peak SLE events occurred for each gender. These findings suggest that elevated serum IFN-α levels are prevalent in the early stages of SLE onset and may have a role in influencing the pattern of SLE events.[29]

CONCLUSION

There was a relationship between IL-6 levels and CD (MoCA-INA score) in SLE patients, where increased IL-6 levels correlated with decreased MoCA-INA scores (more severe cognitive dysfunction). Additionally, younger age was associated with greater CD.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest or personal relationships that could have influenced the findings or interpretation of this study.

REFERENCES

1. Netto TM, Zimmermann N, Rueda-Lopes F, Bizzo BC, Fonseca RP, Gasparetto EL. Neuropsychiatric lupus: classification criteria in neuroimaging studies. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2013;40(3):284–91.
2. Hanly JG, Urowitz MB, Sanchez-Guerrero J, et al. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: An international inception cohort study. Arthritis Rheum. 2007;56(1):265–73.
3. Zhang Y, Han H, Chu L. Neuropsychiatric lupus erythematosus: future directions and challenges; a systematic review and survey. Clinics. 2020;75: e1515.
4. Smith T, Gildeh N, Holmes C. The montreal cognitive assessment: validity and utility in a memory clinic setting. The Canadian Journal of Psychiatry. 2007;52(5):329–32.
5. Yap DYH, Lai KN. Cytokines and their roles in the pathogenesis of systemic lupus erythematosus: from basics to recent advances. J Biomed Biotechnol. 2010; 2010:1–10.
6. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: Estimates obtained using hospitalization data. Arthritis Rheum. 2007;56(6):2092–4.
7. Boodhoo KD, Liu S, Zuo X. Impact of sex disparities on the clinical manifestations in patients with systemic lupus erythematosus. Medicine. 2016;95(29):e4272.
8. Weckerle CE, Niewold TB. the unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. Clin Rev Allergy Immunol. 2011;40(1):42–9.

9. Walters E, Rider V, Abdou NI, et al. Estradiol targets T cell signaling pathways in human systemic lupus. Clinical Immunology. 2009;133(3):428–36.
10. Koelmeyer R, Nim HT, Nikpour M, et al. High disease activity status suggests more severe disease and damage accrual in systemic lupus erythematosus. Lupus Sci Med. 2020;7(1): e000372.
11. Shamim R, Farman S, Batool S, Anwer Khan SE, Raja MKH. Association of systemic lupus erythematosus disease activity index score with clinical and laboratory parameters in pediatric onset systemic lupus erythematosus. Pak J Med Sci. 2020;36(3).
12. Rambe AS, Fitri FI. Correlation between the Montreal cognitive assessment-Indonesian version (Moca-INA) and the mini-mental state examination (MMSE) in elderly. Open Access Maced J Med Sci. 2017;5(7):915–9.
13. Conti F, Alessandri C, Perricone C, et al. Neurocognitive dysfunction in systemic lupus erythematosus: association with antiphospholipid antibodies, disease activity and chronic damage. PLoS One. 2012;7(3): e33824.
14. Anjalia S, Ong PA, Atik N, Hamijoyo L. Memory performance in patient with systemic lupus erythematosus using moca-ina in hasan sadikin genneral hospital Bandung. Indonesian Journal of Rheumatology. 2018 Feb 9;9(1).
15. Kowal C, DeGiorgio LA, Lee JY, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. Proceedings of the National Academy of Sciences. 2006;103(52):19854–9.
16. Saepudin A, Ong PA, Hidayat S, Rahmadi AR, Hamijoyo L. Correlation between cognitive function with disease activity of systemic lupus erythematosus patients in Dr. Hasan Sadikin Hospital Bandung: An analytical cross-sectional study. Indonesian Journal of Rheumatology. 2019;11(1).
17. Raghunath S, Glikmann-Johnston Y, Golder V, et al. Clinical associations of cognitive dysfunction in systemic lupus erythematosus. Lupus Sci Med. 2023;10(1): e000835.
18. Popescu A, H. Kao A. Neuropsychiatric systemic lupus erythematosus. Curr Neuropharmacol. 2011;9(3):449–57.
19. Ruchakorn N, Ngamjanyaporn P, Suangtamai T, et al. Performance of cytokine models in predicting SLE activity. Arthritis Res Ther. 2019;21(1):287.
20. Bradburn S, Sarginson J, Murgatroyd CA. Association of peripheral interleukin-6 with global cognitive decline in non-demented adults: A meta-analysis of prospective studies. Front Aging Neurosci. 2018;8:9.
21. Ohl K, Tenbrock K. Inflammatory cytokines in systemic lupus erythematosus. J Biomed Biotechnol. 2011; 2011:1–14.
22. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015;85(2):296–302.
23. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun. 2017; 60:1–12.
24. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biol Psychiatry. 2008;64(6):484–90.
25. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: The 3C-Dijon Study. Neurology. 2012;78(10):720–7.
26. McCarrey A, Pacheco J, Carlson O, et al. Interleukin-6 is linked to longitudinal rates of cortical thinning in aging. Transl Neurosci. 2014;5(1):1–7.
27. Niewold TB, Adler JE, Glenn SB, Lehman TJA, Harley JB, Crow MK. Age- and sex-related patterns of serum interferon-α activity in lupus families. Arthritis Rheum. 2008;58(7):2113–9.
28. Raghunath S, Glikmann-Johnston Y, Golder V, et al. Clinical associations of cognitive dysfunction in systemic lupus erythematosus. Lupus Sci Med. 2023;10(1): e000835.
29. Niewold TB, Adler JE, Glenn SB, Lehman TJA, Harley JB, Crow MK. Age- and sex-related patterns of serum interferon-α activity in lupus families. Arthritis Rheum. 2008;58(7):2113–9.