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Review Article

Diagnosis and Management of Cognitive Dysfunction In Systemic Lupus Erythematosus Patients

Ernes Mahardini[1], Perdana Aditya Rahman[2], Cesarius Singgih Wahono[2], Handono Kalim[2]
[1]*Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya – RSUD Dr. Saiful Anwar Malang, Indonesia*
[2]*Supervisor Division of Rheumatology and Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya – RSUD Dr. Saiful Anwar Malang, Indonesia*

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Corresponding Author:
Perdana Aditya Rahman
Supervision Division of Rheumatology and Immunology, Departemen of Internal Medicine, Faculty of Medicine, Universitas Brawijaya – RSUD Dr. Saiful Anwar Malang, Indonesia
Email: perdana.aditya@ub.ac.id

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ABSTRACT

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with diverse clinical manifestations. One of the frequent manifestations of SLE is cognitive dysfunction. Cognitive dysfunction is a hidden and often undiagnosed manifestation of SLE but can severely impair quality of life even in mild cognitive dysfunction. Early detection of cognitive dysfunction in SLE patients can determine interventions to help patients adapt to the effects of this decline in cognitive function. However, currently, screening and diagnosis of cognitive dysfunction in SLE are often delayed, and monitoring cannot be done properly. This may be due to the most appropriate assessment tool for cognitive screening in SLE patients has not been agreed upon. The management of cognitive dysfunction in SLE patients today is still challenging due to the SLE pathophysiology is still in debate and research. This literature review will discuss the approach of diagnosis and management of cognitive dysfunction in SLE.

Keywords: cognitive dysfunction, SLE, NPSLE

INTRODUCTION

Cognitive dysfunction is one of 19 neurological and psychiatric syndromes that occur in SLE patients According to the Classification of the American College of Rheumatology (ACR).[(1)] It occurs twice as much in SLE patients than the general population, with a prevalence range of about 20 – 80%.[(2)] The wide range of prevalence is likely due to the lack of uniform examination tools for cognitive dysfunction in SLE.[(3)] It is also known to be the most frequent manifestation of NPSLE, with a prevalence of 55 – 80% in NPSLE patients.[(4)]

Bland et al. researched the effects of cognitive dysfunction on quality of life in SLE patients and found a decrease in quality of life-based on the SF-36 and Lupus QoL scales.[(5)] In

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another study by appenzeller et al. it is also said that 19 – 52% of SLE patients should lose their job within 12 months after experiencing cognitive dysfunction. SLE patients with cognitive dysfunction also seem to prefer to withdraw from social life, which is sometimes unnoticed by the patient himself but known to others.

Definitions & Manifestations of Cognitive Dysfunction on SLE

Cognitive dysfunction is defined as the presence of significant deficits in one or all of the following primary cognitive functions, i.e. memory (learning and remembering), complex attention, simple attention, executive skills (planning, organizing, and sequencing), visual-spatial processing, language (e.g. verbal, fluency), reasoning/problem solving and psychomotor speed.[1] Cognitive dysfunction is one of 19 neurological and psychiatric syndromes that occur in SLE patients according to the Classification of the American College Of Rheumatology (ACR)[1] shown in table 1. The ACR committee also distinguished between cognitive impairment and decreased cognitive function where it said cognitive impairment when the score ≥ 2SD below average in critical domains, namely concentration, memory and psychomotor speed compared to standard data using ACR neurocognitive battery. The decrease in cognitive function is defined if the score is 1.5 - 1.9 SD below the average score. Cognitive dysfunction is focal when one domain is impaired and multifocal when a disorder is found in two or more domains.[8] Although there is no specific pattern of cognitive dysfunction of patients with SLE, Hanly et al. note that decreased attention, impaired working memory, and executive function (e.g., planning and multitasking abilities) are the cognitive domains most commonly affected in SLE patients in addition to the overall cognitive slowdown.[11] Other studies from Mikdashi et al. previously showed that attention, memory, and verbal fluency are among the most severely affected domains in SLE patients.[1]

Table 1. The Classification of Neuropsychiatric Disorders in SLE based on ACR Criteria [9]

Manifestations of the Central Nervous System	Manifestations of the Peripheral Nervous System
Aseptic Meningitis	*Acute Inflammatory Demyelinating*
Acute Conventional Status	*Poliradiculoneuropathy*
Anxiety Disorders	Autonomy disorder
Cerebrovascular Disease	Cranial Neuropathy
Cognitive Dysfunction	Mononeuropathy
Demyelination syndrome	Myasthenia Gravis
Headaches	Plexopathy
Movement Disruption	Polyneuropathy
Mood Disorders	
Myelopathy	
Psychosis	
Stiff	

Characteristics of Cognitive Dysfunction in SLE

Some studies to assess the characteristics of patients with cognitive dysfunction on SLE are shown in Table 2.

Table 2. Characteristics Of Cognitive Dysfunction In SLE Patients

Author	Subject	Methods / Inclusion	Result
Ali Duarte – Garcia, et al, 2018 [12]	100 SLE patients in outpatient therapy with the age of > 16 years. Sixteen patients had mild/moderate cognitive dysfunction.	16 years cohort prospective cohort study, Use ACR criteria ≥4 for SLE.	Patients with moderate/severe cognitive dysfunction had lower levels of education, a high BMI, anti-cardiolipin IgG antibodies in serum were higher and increased levels of CCL2 in cerebrospinal fluid compared to patients who did not have cognitive dysfunction.
Barraclough, et al, 2020 [13]	60 SLE patients in therapy who has no previous medical record of NPSLE.	SLE was assessed with ACR and SLICC criteria. Cognitive dysfunction was assessed with CANTAB. The average age of subjects 36 years. The average duration of the disease 11 years.	In SLE, several risk factors for cardiovascular disease (anti-cardiolipin antibodies, arterial stiffness, metabolic syndrome) are independently associated with the occurrence of several domains of cognitive dysfunction and are related to SLE in white substances.
Lilis,et al, 2018 [14]	115 SLE patients in therapy. 72 patients with cognitive dysfunction.	Cross-Sectional Research SLE criteria using ACR criteria. Disease activity using SELENA – SLEDAI	Cognitive dysfunction in SLE is significantly associated with pain, sleep disorders and depressive symptoms.
Murray, et al, 2012 [15]	694 SLE patients in therapy. 107 patients had cognitive dysfunction. 587 have no cognitive dysfunction.	Cohort Research Uses The Hopkins Verbal Learning Test-Revised (HVLT-R) and Controlled Oral Word Association Test (COWAT) to assess cognitive dysfunction	Cognitive dysfunction in SLE is associated with the presence of antiphospholipid antibodies, hypertension and stroke.
Rogers, et al, 2019 [16]	205 lupus patients 17% have active nephritis 16% have remission nephritis 67% without a history of nephritis.	Lupus Criteria Using ACR and SLICC criteria 2012. Cognitive impairment is assessed with ACR criteria for fibromyalgia.	Both patients with active and inactive lupus nephritis had a lower incidence of fibromyalgia, fatigue, sleep disorders and cognitive impairment compared to patients without lupus nephritis.
Plantinga,et al, 2017 [17]	777 adult SLE patients (> 18 years), 41.7% experienced easy to forget and 29.5% had difficulty concentrating.	Stress level assessed by Perceived Stress Scale (PSS)	SLE patients especially with high disease activity are reported to experience higher cognitive symptoms where stress is a modifiable factor.

From table 2, it can be seen that patients with cognitive dysfunction usually also experience cardiovascular disease (hypertension), pain, sleep disorders, depression, have high antiphospholipid antibodies, high BMI, high-stress levels and have had strokes. Hypertension is associated with the occurrence of cognitive disorders in SLE, but the mechanism is still unknown. Studies show a link between hypertension and hypertensity of white matter

and also brain atrophy, especially in the prefrontal cortex. Positive antiphospholipid antibodies are also known to be significantly related to cognitive dysfunction, but the mechanism of whether through pathogenic effects directly on neurons or thrombotic mechanisms is still unclear. Antiphospolipid antibody are also crucial with stroke, where the stroke is also known as a cause of cognitive dysfunction SLE patients.[15] Pain in SLE is also associated with cognitive dysfunction due to mood disorders and sleep disorders.[14] High BMI and anticardiolipin antibody are also well linked to cognitive dysfunction with suspected vascular cognition and high BMI is also an independent predictor of brain atrophy.[12] In lupus nephritis patients, study shows that compared to patients without lupus nephritis, it turns out to have a lower incidence of cognitive dysfunction than in lupus patients without nephritis, but the reason is still unknown.[16] Stress levels are also known to be high in patients with cognitive dysfunction in SLE, and it is said that stress levels are a predisposing factor to uncontrollable disorders in SLE.[17]

Pathophysiology of Cognitive Dysfunction in SLE

Cognition is a functional product of a process in which learning and memory abilities are generated from communication between neurons, glia cells, astrocytes, and immune cells through various neurotransmitters, cytokines, transcription factors and chemokine. Hippocampus is the main structure in the brain that plays a role in memory function and cognition. Therefore, good cognitive function relies heavily on the circuitry of neurons, the process of good neurogenesis and the mechanism of uninterrupted neuroimmune signals in the hippocampal.[18,19] Overall, several factors that affect the occurrence of cognitive dysfunction in SLE patients can be seen in table 3.

Autoantibodies such as DNRAb (anti-DNA antibodies) and anti-ribosomal-P (anti-P), antiphospholipid antibodies (aPL) in serum and cerebrovascular fluid, especially IgG anti-cardiolipin (ACL) and anti-coagulant Lupus (LAC) contribute to the occurrence of cognitive dysfunction in SLE.[20,22,23] DNRAb intercedes with the GluN2A and GluN2B subunits of N-methyl-D-aspartate (NMDAR) receptors causing NMDA receptor activation causes excitotoxic cell death due to numbers of calcium influx into the cells.[21] Anti-P recognizes NSPA and also inducing calcium influx and glutamatergic transmission in neurons.[22] Some pro-inflammatory cytokines play a role in the decline in affective and cognitive function that usually accompanies the emergence of an acute condition. [35]

Table 3. Factors that Play Role in the Pathophysiology of Cognitive Disorders in SLE

Factor	Molecules	Mechanism	References
Immunology	**Autoantibodies**		
	DNRAb	**DNRAb** inter binds to the GluN2A and GluN2B subunits of N-methyl-D-aspartate (NMDAR) receptors that cause NMDA receptor activation and cause exotoxic cell death [20,21]	Tay et al, 2017 [20] ; Hirohata et al, 2014 [21]
	Anti-P	**Anti-P** recognize surface neuronal antigens of Neuronal Surface P Antigens (NSPA) that induces the occurrence of calcium influx and glutaminergic transmission in neurons [23]	Segovia-Miranda et al, 2015 [22]

	Antiphospholipid Antibodies	**Antiphospholipid antibodies** mediate prothrombotic and nonthrombotic vascular such as the direct toxic effects of aPL on neuron and glia cells [23]	Yelnik et al, 2016 [23]
Inflammation	**Cytokine**		
	IFN-α	**IFN-α** stimulate microglia to become active and ingest neuronal synapses in studies using lupus-prone mice [24]	Bialas et al., 2017[24]
	IFN-γ	**IFN-γ** can interfere the monoamine pathway through 3 pathways i.e., indoleamine pathway 2.3 – dioxygenase (IDO), P38MAPK and tetrahydrobiopterin (BH4) [25,36] **IFN-γ** inhibits dendritic growth and induces dendritic retraction and inhibits the speed of dendritic synapse formation [26]	Monteiro et al,2016[25] ; Korte et al, 2019[26] ; Schwartz et al, 2019 [36]
	TWEAK	**TWEAKs** increase MMP-9 activity and vascular permeability of the brain and induces expression of ICAM-1, IL-8 and IL-6 in cultured astrocyte [27]	Stock et al, 2013 [27]
	IL – 6 IL – 8	**IL-6** and **IL-8** causing astrocytes or neurons damage[28]	Kwieciński et al, 2009 [28]
Microglia Activation		Microglia activation will lead to phagocytosis or pruning of dendritic synapses which will eventually lead to reduced dendritic collection and density of the bone marrow [24]	Kello et al,2019[3] ; Bialas et al, 2017 [24]
Blood-Brain Barrier Leakage		Autoantibody in circulation includes anti – NMDAR, anti-P antibodies are able to enter the central nervous system which is need a blood-Brain Barrier leakage[30]	Hirohata et al, 2014 [21] Yoshio et al, 2006 [30] Mahajan et al, 2016[31] Delgado et al[32]
Exitotoxic Mediator	HMGB1	C1q uses HMGB1 as an intermediary connecting with NMDAR to be targeted for microglia [29]	Nestor et al, 2018 [29]
	Angiotensin II	Angiotensin II directly affects microglia activity and increases the production of inflammatory mediators[44]	Petri, et al, 2011 [44]
	MMP-9	MMP – 9 has been linked to the occurrence of NPSLE through degradation of the basic protein myelin [33]	Ainiala et al, 2004 [33]
Aging Marker	Increased memory T cells (CD4+CD45RO+, CD8+CD45RO+)	Accumulation of end stage memory T cells releases large amounts of pro-inflammatory cytokines including IFN- γ. IFN-γ has cytotoxic activity of modulating MHC class I and II inhibiting cell growth and apoptosis that induces cell death [34]	Ulfah, et al, 2020 [34]

Autoantibodies through cellular interaction will increase cellular signals and pro-inflammatory cytokines such as IFN-α, IFN-γ,IL-6, IL-8, TWEAK that modify immune regulatory mechanisms and cause local inflammation and tissue damage with damage to the blood-brain barrier.[36] IFN-α stimulates microglia to become active and ingest neuronal synapses in studies using lupus-prone mice.[24] IL-6 and IL-8, are related to known neuronal damage that their presence in cerebrospinal fluid is related to the presence of proteins related to damage astrocytes or neurons.[28] TWEAK, a Tumor Necrosis Factor (TNF) family, increased MMP-9 activity and increased BBB permeability. TWEAK also induces ICAM-1, IL-8 and IL-6, another effector of blood-brain leakage.[27] IFN- γ interfere the monoamine pathway through 3 pathways, namely indoleamine pathway 2,3 – dioxygenase (IDO), P38MAPK and tetrahydrobiopterin (BH4).[25,36] Pro-inflammatory cytokines also

known to increase the transporter of serotonin (SERT), dopamine (DAT) and Nor Epinephrine (NET) so that reuptake of the neurotransmitter where the condition relies on P3MAPK.[27]

Microglia activation can cause cognitive dysfunction through phagocytosis or pruning of dendritic synapses, which will eventually lead to reduced dendritic com collection and density of the bone marrow. Activation of microglia can be through several mechanisms, including interferon type 1.[24] Complement, especially C1q, also plays a role in the pruning of microglia-mediated synapses. [3] The presence of leakage in the blood-brain is also needed for a direct access of antibodies in the CNS for the occurrence of antibody-mediated damage; this is suspected due to evidence that antibodies are not produced in CNS in SLE patients. Some conditions that can interfere the integrity of blood-brain barrier vessels include viral and bacterial infections, systemic inflammation, stress (epinephrine), ischemia, aging, hypertension, nicotine, alcohol and specific inflammatory cytokines such as TNFα, IL-1β, IL-6, and IL-8.[30] High cytokine expression in the brain reduces the expression of tight junction proteins related to increased permeability and migration of leukocytes and also inducing the expression of ICAM-1 and VCAM-1 adhesion molecules in extracellular fluids that facilitate the diapedesis of leukocytes in the brain. DNRAb also directly affects the integrity of blood brain barrier by activating endothelial cells to produce pro-inflammatory cytokines [29] Leakage of the blood-brain can also be a consequence of antiphospholipid syndrome and activation of C5a complement in SLE patients with the active disease [29,31]

Excitotoxicity, a death of neuron cells caused by the hyperactivity of excitotoxic mediators in the central nervous system can also cause cognitive dysfunction. This activity causes an excessive cellular influx of ions, especially calcium, which leads to activation of protease, phospholipase and endonuclease.[37] Some inflammatory mediators can play a role in the occurrence of excitoxicity, including HMGB1, MMP-9 and Angiotensin Converting Enzyme (ACE).[29] Another condition that also causing cognitive dysfunction is immune cell aging or immunosenescence that was characterized by the reverse ratio of CD4 and CD8, increased memory T cells, loss of CD28 molecules, and the presence of terminal differentiated cell markers CD57 and KLRG1. Patients with this immune risk profile showed cognitive dysfunction, especially the ability to recall and concentrate. There is a relationship between immunosenescence marker where there is a negative correlation between memory CD4+ T cells with recall and visuospatial domains and a negative correlation between CD8+ CD28 T cells- recall and attention.[37] Serre-Miranda et al. also showed better cognitive function in patients with lower levels of effector memory cells.[34]

Screening for Diagnosis of Cognitive Dysfunction in SLE

Determination of cognitive dysfunction in SLE patients should include a clinical history of impaired function delivered by the patient and the results of neuropsychological tests. Neuropsychological examination becomes the standard for the diagnosis of cognitive dysfunction in NPSLE. In addition to a neuropsychological examination, neuroimaging examination is also a promising

modality for understanding the pathogenesis of cognitive dysfunction in SLE and monitoring therapeutic responses.[3] Neuropsychological examination using the comprehensive battery is an ideal method to evaluate cognitive dysfunction and severity. However, due to the lengthy examination time of 4 hours, the ad hoc committee of the American College of Rheumatology (ACR) proposes testing with a battery test of 1 - 2 hours, namely ACR-SLE battery. ACR - SLE battery is validated and has good reliability compared to comprehensive neuropsychological battery.[39] Table 4 shows the types of checks performed on the ACR neuropsychological battery.

Table 4. ACR Neuropsychological Test Battery (ACR-NB)[1]

North American Adult Reading Test (For measuring IQ)
Digit Symbol Substitution Test
Trail Making Test (Part a and B)
Stroop colour-word TestCalifornia Verbal Learning Test
Rey - Osterrieth Complex Figure Test
Waist - III letter - Number Sequencing
Controlled Oral Word Association Test
Animal Naming
Finger Tapping Test

However, ACR - SLE battery is not always available; this must be done by trained personnel, time-consuming and associated with cost burden so that it is less practical as a screening tool in all patients with potential cognitive decline.[39,9] Therefore it has been researched using several other cognitive assessment tools, such as, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), The Hopkins Verbal Learning Test-Revised (HVLT-R), Controlled Oral Word Association Test (COWAT) as listed at Table 5.

MMSE is widely used to examine cognitive function and determine whether or not a patient is referred. MMSE has a maximum score of 30 grouped on 11 inspection items to check the following domains: time orientation and place (assess cerebral hemisphere and brain stem = 10 points), short-term memory (Recording and recalling 3 words = 6 points), attention and counting process (5 points), language (8 points) and visual construction (1 point). MMSE work time is 5 - 10 minutes [1] and will usually take > 15 minutes in patients with dementia.[41] Internal consistency of MMSE assessed with Cronbach's alpha of 0.78 with a specificity of 70% and sensitivity of 88%.[42] For dementia, screening used a threshold of < 21 in individuals with a basic education level and < 23 for individuals with higher education levels, and < 24 for individuals with a bachelor's degree level. Its usefulness in detecting mild-moderate cognitive dysfunction in SLE patients is still limited as the initial design of this instrument is intended for dementia screening. However, it is still considered a relevant first stage test tool for assessing cognitive function and will provide better result if continued with another instrument test.[41]

MOCA was developed to detect the same domain as MMSE, but more in-depth include using the clock-drawing test and trail test (connecting point points). MoCA assesses attention, concentration, executive function, memory, language, visuoconstruction ability, the concept of thinking, calculation and orientation. The maximum point of this check is 30, with a score of ≥ 26 is considered normal. The examination takes about 5-10 minutes and is available in 36 languages and dialects.The use of MoCA instruments with a threshold value of < 26/30 to assess impaired cognitive function on SLE showed reasonable sensitivity

(83%) and 73% specificity with an accuracy rate of 75%.[41] The internal consistency of the MoCA method using Cronbach's alpha is 0.81.[42]

HVLT-R measures verbal learning abilities as well as short-term and long-term verbal memory. HVLT-R assesses the efficiency of verbal learning, the ability to access newly learned information, and retention. HVLT-R uses 12 items of words - words presented on 3 consecutive learnings where the examiner reads the words in the list and asks the patient to repeat the words on the list. A reminder for long-term memory is performed by having participants recall a word after more than 25 minutes. HVLT-R showed adequate sensitivity (74%) and specificity (68%) in identifying patients with cognitive dysfunction compared to ACR - SLE batteries. COWAT is used to measure verbal fluency where each participant must mention as many words as possible within a minute, starting with a specific letter (e.g., "Mention words beginning with 'F'). There are three one-minute trials in one test. COWAT show a 79% strong sensitivity and 67% specificity in identifying cognitive dysfunction in SLE compared to ACR-SLE batteries.[43]ANAM is a computerized cognitive test battery that is self-carried out by the patient. These checks are given to a single session in a fixed order and take approximately 40 minutes to complete. ANAM uses basic symbols and involves simple task instructions that can be provided in multiple languages, making it suitable for individuals from various educational backgrounds and mother tongues.

ANAM includes various subtests that researchers or doctors can choose from to measure cognitive function in relevant cognitive domains. Examples of subtests include Simple Reaction Time (simple attention), Continous Performance (continuous alertness/attention), Code Substitution (scanning and visual learning) with immediate, delayed memory, simultaneous (visual perception and mental rotation), Stenberg test (continuous attention/working memory), mathematical processing (simple mental arithmetic), and Matching to Sample (visuospatial perception and working memory). ANAM is built to be an

Table 5. Tools of Neuropsychological Examination in SLE Patients

Neuropsychology Examination	Subject	Result	Author
ACR Neuropsychological Test Battery (***ACR - SLE Battery***)	The study used 31 sample of SLE patients with a history of NPSLE and 22 patients without a history of NPSLE, 25 healthy patients, a comparison between comprehensive battery and ACR - SLE Battery results	Good validity and reliability when compared to comprehensive battery sensitivity of 80%, specificity of 81%	Kozora et al, 2004 [40]

Montreal Cognitive Assessment (***MoCA***)	54 SLE patients performed measurements with MoCA instruments compared to ANAM	Good sensitivity (83%) and specificity of 73% with an accuracy rate of up to 75%	Larner, 2017 [41]
Mini-Mental State Examination (***MMSE***)	Of the 11 studies that used MMSE compared to the comprehensive battery (CB)	Internal consistency assessed with Cronbach's alpha 0.78, specificity 70%, sensitivity 88 %	Kabátová et al.,2016 [42]
The Hopkins Verbal Learning Test-Revised (***HVLT-R***)	Methane research conducts HVLTR validation compared to a comprehensive battery.	Sensitivity 74% and specificity 68% compared to a comprehensive battery	Al Rayes, 2018 [1]
Controlled Oral Word Association Test (***COWAT***)	139 SLE patients performed COWAT examination compared to a comprehensive battery	COWAT has a strong sensitivity of 79% and a specificity of 67%	Julian, et al, 2012 [43]
Automated Neuropsychological Assessment Metrics (***ANAM***)	Methane research, comparing ANAM with a comprehensive battery	Sensitivity 76%, and specificity is 83% compared to Comprehensive Battery. Significantly less affected by age, education, and at lower levels, ethnicity, glucocorticoid doses, and depression than Comprehensive Battery	Al Rayes, 2018 [1]

easy-to-use program for patients. Patients use two standard mouse keys ("Left" and "right") to respond, reducing long reaction times when unfamiliar with computer keyboards or problems with joint mobility. The compiler automatically generates multiple performance scores for each ANAM subtest. ANAM sensitivity is 76%, and specificity is 83% compared to Comprehensive Battery 2 hours. ANAM is significantly less affected by age, education, and at lower levels, ethnicity, glucocorticoid doses, and depression than Comprehensive Battery 2 hours.[1]

Neuroimaging Examination

Magnetic resonance imaging (MRI) is a non-invasive examination to assess the cognitive function of patients with SLE. Other MRI techniques, including Fluid Attenuation Inversion Recovery (FLAIR), can detect SLE with hypertension. Diffusion-weighted imaging (DWI) is capable of detecting SLE in white substantia. Functional MRI (fMRI) specifically records blood-oxygen-level-dependent (BOLD) signals, which are a measure of neuron metabolism and a proxy measure of neuron activity.[3] In patients with NPSLE, greater frontoparietal activation was obtained during working memory than in healthy people's control. During administrative function work, it was also found an increased contralateral cerebellar-frontal activity to compensate for the disrupted cortico-basal ganglia thalamic-cortical circuit in SLE patients to maintain cognitive test performance to be comparable to healthy person control [33]

Cognitive dysfunction Management in SLE

To date, there has been no specific therapy recommended for cognitive dysfunction on SLE. Therapeutic approaches can be both pharmacological and non-pharmacological. EULAR recommends that

management of cognitive dysfunction in SLE should include factors related to its SLE and non-SLE factors, including psycho-educational support.[3] Some study on cognitive dysfunction therapy on SLE can be seen in table 6.

Non-Pharmacological Therapy

Not all cognitive dysfunction require pharmacological therapy. Non-pharmacological approaches are also thought to improve cognitive dysfunction. The severity of cognitive dysfunction in SLE is associated with the results of 6 – minute walk test, lung function test, so it is suspected that a regular exercise program with supervision may be a practical approach to improving cognitive function. [40] Other non-pharmacological therapies that can be administered include cognitive behavioral therapy and cognitive rehabilitation.[2]

Table 6. Study on Cognitive Dysfunction Therapy in SLE

Author	Subjects and Interventions	Information	Result
Nestor et al 2018 [29]	Experimental mice injected with DNRAb and Lipopolisakarida were then given captopril.	Spatial memory is assessed by behavioral test examination. Hippocampal activity is assessed with electrophysiology.	Cognitive performance and complexity of dendrites were more awake in experiment mice given captopril.
Petri, et al, 2011 [44]	Randomized double-blind studies with 51 SLE patients administered memantine 20 mg per day for 12 weeks.		No significant difference in ANAM scores in the memantine-rated group than the controls after being followed for 6 – 12 weeks
McLaurin,et al, 2005 [45]	123 SLE patients were performed for 3 years. 26 using aspirin 97 not using aspirin	Cognitive examination is performed using ANAM.	Consistent aspirin use was associated with improved cognitive function (higher ANAM values)
Navarette, et al, 2010 [46]	45 patients with lupus who experienced stress daily as a control group, and given CBT for 10 weeks		There was a significant reduction in depression and daily stress in the group given therapy and quality of live and somatic complaint improvement

Cognitive behavioural therapy can help SLE patients cope with negative emotions that indirectly affect cognitive function, several sets of behavioural therapies, including stress management and relaxation exercises can help patients to regain control of the chronic phase of SLE.[2] Cognitive rehabilitation that includes psychoeducation, use of memory aids, prioritization and optimization of time and cognitive exercise. Psychoeducation provides information in patients with SLE on the basic mechanisms of cognitive function and how SLE causes cognitive dysfunction using lay language. In memory aid, SLE patients with cognitive dysfunction are taught to use reminders or cell phones to alert them. Memory assistance helps patients stay focused and keep up with their daily routine. Time optimization includes prioritizing heavy duty

at the beginning of the day so that patients can have lighter tasks for the rest of the day and prioritize their tasks on one day and focus on one task before switching to another. Cognitive exercises such as sudoku, chess, risk and mahjong (for Asian patients) will improve executive function and problem-solving abilities.[2]

Pharmacological Therapy

To date, there has been no treatment of cognitive dysfunction on SLE and data on the use of immunosuppressive drugs on SLE are still limited. Large clinical trials are still needed, some therapeutic strategies seem promising potential, but there is still much research needed to determine which biomarkers are referenced at the endpoint of a clinical trial. Administration of memantine, an NMDAR antagonist, showed no significant differences or improvements in cognitive performance in SLE patients with cognitive dysfunction compared to those given a placebo.[44] It is also said that long-term inhibition of NMDAR has a damaging effect on brain function, making memantine a less preferred therapeutic alternative.[3]

Although no studies examine the benefits of anticoagulant or antiplatelet administration in SLE patients with cognitive dysfunction without the thromboembolic phenomenon, administration of antiplatelets such as low-dose aspirin or antimalarial may be considered in SLE patients with cognitive dysfunction with positive antiphospholipid antibodies. A 3-year prospective observational study that assessed predictive factors of cognitive dysfunction in SLE showed that low-dose aspirin administration improved cognitive dysfunction in patients without positive antiphospholipid antibodies compared to those not given aspirin.[45]

Administration of ACE inhibitors may also be possible as an alternative therapy. As mentioned in the previous chapter, ACE enhancement plays a role in neuroinflammation in cognitive dysfunction. Where angiotensin II can activate microglia and, if expressed excessively, it will be directly neurotoxic, causing neuronal damage and cell death. ACE inhibitors may also inhibit bradykinin inactivation mediated by ACE, which has an anti-inflammatory effect and suppresses microglial activation and stops in-type responses. In cognitive dysfunction in Alzheimer's, ACE inhibitors are known to slow cognitive dysfunction. This data supports the potential use of ACE inhibitors as a novel neuroprotective therapy of cognitive dysfunction in SLE.[3]

In experiments using mice with DNRAb+ given LPS, it was found that ACE inhibitior indicates the suppression of microglial activation.[29] Minocycline, a second-generation semi-synthetic tetracycline, is also a potent inhibitor of microglial activation with benefits in some neurological disorders. However, minocycline's toxicity profile and potential risks are limited to its use. Acetylcholinesterase inhibitors (Donepezil, Rivastigmine and Galantamine) have been introduced as dementia therapy for About 30 years and to date are still a crucial therapy.[47] However, some studies assess their effectiveness in cognitive dysfunction in SLE patients.[2]

CONCLUSION

Cognitive dysfunction is a hidden manifestation of SLE and is often undiagnosed but can severely impair quality of life. The prevalence range is quite broad, which is about 20 - 80% which is thought to be due to the absence of uniform examination tools to detect cognitive dysfunction in SLE. Some underlying mechanism including immunological factor, inflammation factor, microglial activation, blood barrier leakage, excitotoxic mediator, and also aging marker.

Diagnosis of cognitive dysfunction in SLE assisted by several tools, some of them are 4-hour Comprehensive Battery, ACR Neuropsychological Test Battery (ACR-NB) MMSE, MoCA, HVLTR, COWAT and ANAM. Neuroimaging examination is also quite promising in the diagnosis of cognitive dysfunction in SLE, but currently, its importance is limited to research or monitoring therapy results. Management of cognitive dysfunction in SLE including non-pharmacological intervention and pharmacological intervention despite no definitive treatment currently. Non pharmacological intervention including exercise, cognitive behaviour theraphy and other cognitive excercise. Some agent use to treat cognitive dysfunction with limited evidence and study. Aspirin, anti malaria, ACE inhibitor are some of studied agent but no recent RCT.

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