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Review Article,

Memory and Cognitive Impairment in Myasthenia Gravis

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Introduction:

Myasthenia gravis (MG) is an autoimmune disease in the neuromuscular junction. This is a relatively uncommon disorder characterized by fluctuating muscle weakness, worst with exertion and improves with rest. This disease is treatable but can result in significant morbidity and mortality. The etiology of MG is commonly acquired autoimmune but, in some case, result from genetic abnormalities in the neuromuscular junction.[1] The incidence of MG is about 4.1-30 points million per year, and the prevalence rate ranges from 150-200 cases per million.[2] It is believed that MG incidence has increased worldwide over the past seven decades. The majority of MG was estimated at 1 in 200,000 from 1915 to 1934, grew to 1 per 20,000 after the introduction of anticholinesterase drugs in 1934, and rose to 1 per 17,000 population after the discovery of AChR antibodies in 1969.[3] Sex and age appear to influence the occurrence of myasthenia gravis. Below 40 years of age, the female: male ratio is about 3: 1; however, between 40 and 50 years, as well as during puberty, it is roughly equal. Over 50 years, it occurs more commonly in males.[3]

Cognitive impairment in patients with myasthenia gravis is still a matter of debate. There is some evidence that central nervous system involvement in myasthenia gravis contributes to cognitive impairment—nearly 60% of individuals with MG report memory difficulties.[4] Mao et al. reported in their metanalysis study that patients with suspected MG performed worse than healthy controls regarding verbal learning and memory.[5] Research by Klaus et al., 2022 on myasthenia gravis showed structural and functional changes in the patient's brain. Structural changes were seen in the form of a significant decrease in the volume of gray matter in the cingulate gyrus, inferior parietal lobe, and fusiform gyrus. Functional changes are characterized by decreased performance in cognitive function, working memory, and somatosensory-related spatial orientation.[6]

Memory Consolidation Process:

Memory is the storage of knowledge that has been obtained so that it can be recalled. Memory traces are changes in neurons associated with the retention or storage of expertise. Information storage is conveyed through 2 stages, short-term and long-term memory. Transferring and strengthening short-term memory into long-term memory is called memory consolidation. Learning (stimulus) will be accommodated storage of short-term memory that is quickly forgotten. When this short-term memory continues to be repeated, it will become long-term memory. Memory enters the brain through synapses. The hippocampus (limbic system), amygdala (center of emotional memory), striatum (to control motor skills), and mammillary bodies play an active role in the brain. There are three basic processes of memory storage: encoding (entering information), storage, and retrieval (generating back). The first is the process of remembering with the encoding stage, which is encoding what is perceived by changing certain symbols. So encoding is a process of converting information into a form that suits the memory properties of the organism itself. The information's that were store can be obtained intentionally or unintentionally. The second is the process of remembering storage or the operation of storing data and how to store what has been processed at the coding stage. The third is the process of placing related to returning information that has been stored or is commonly called retrieval. This process is a process of searching

and finding information stored in memory to be reused when needed.[7,8]

With the potentiation of long-term memory, modifications occur as a result of increased use of the synapse that will increase the ability of the presynaptic neuron to excite future postsynaptic neurons. The more often the connection is used, the stronger the link will be. This strengthening is related to forming more EPSPs (excitatory postsynaptic potential) on the postsynaptic neuron in response to chemical signals from specific presynaptic excitatory inputs. The increased excitatory response will be translated into more action potentials sent along the postsynaptic cell to other neurons. LTP (long-term potentiation) takes days or even weeks to consolidate short-term memory into long-term memory.[7,8]

Memory Impairment in Myasthenia Gravis:

Various studies provide contradictory results, regarding the relationship between MG and cognitive function, especially for the cognitive domain of memory. To date, four alternative explanations have been proposed to explain the possibility of memory impairment in MG patients: (1) Hypothesis of central cholinergic system disturbance in MG. Nicotinic receptors are distributed in subcortical and cerebral cortical regions, which participate in specific cognitive and non-cognitive processes. Peripheral acetylcholine receptor antibodies (AchR-Abs) have access to central receptors, and these findings have led to the claim that both central and peripheral function may be impaired in MG. (2) Nocturnal respiratory problems, such as hypoxia and hypercapnia due to respiratory muscle weakness, can cause cognitive deficits in MG. (3) As a result of increased physical and mental fatigue. Cognitive fatigue is defined as a decline in performance with sustained cognitive effort. (4) Possible influence of nonspecific immunological processes.[5,9]

1. Disturbance of the Central Cholinergic System

Central nervous system (CNS) involvement in MG has been a topic of debate for more than a decade. Acetylcholine receptors are located in the central and peripheral nervous systems, and several studies have shown that antibodies to peripheral receptors can cross-react with central receptors. However, there is no strong evidence suggest that central acetylcholine receptors are involved in MG.[10] In addition, nicotinic AChR is also found in the central nervous system, especially in the hippocampus, hypothalamus, midbrain, and cerebral cortex. It is known that the central cholinergic system plays a vital role in mediating cognitive processes, namely learning ability and memory, and this is interesting because it can explain the fact that the occurrence of fatigue is associated with impaired cognitive performance in MG patients.[11]

This assumption has prompted many studies to support the hypothesis of CNS cholinergic involvement in MG, which states that MG has central cholinergic deficits that manifest in cognitive dysfunction. In addition, various studies have shown that the CNS and muscles other than striated muscles can also be affected in MG. In addition, reports of decreased REM sleep phase, memory dysfunction, and detectable cerebrospinal fluid-AChR antibodies further confirm the hypothesis of CNS involvement in MG cases. Thus, if the CNS is indeed involved in MG cases, it can be expected that this will manifest in the form of specific cognitive abnormalities, given the scientific evidence on the role of cholinergic transmission in attention and memory processes. (Kaltsatou et al., 2015)[6,9,1112]

In the study conducted by Kaltsatou et al., the hypothesis of a central cholinergic receptor deficit in MG patients was investigated using neurophysiological and neuropsychological methods. The results of this study indicate that MG patients exhibit decreased cholinergic activity, which suggests that MG affects the cholinergic system and causes a decrease in cognitive performance. One of the central cholinergic activities can be seen in changes in pupil size which indicate the work of the neurotransmitter functions of the parasympathetic and sympathetic nervous systems, namely ACh and noradrenaline, respectively. MG patients showed significant impairment in cognitive abilities, as shown by poor performance on the WMS (Wechsler Memory Scale) test. A neuropsychological examination can evaluate a patient's memory function in relation to other cognitive abilities and is the type of standardized examination most widely used to assess memory function. This indicates the occurrence of various kinds of cognitive dysfunction in MG patients, which has also been reported in several other studies.[11] The fact that cholinergic deficits are found in MG patients and combined with the vital role of nicotinic AChR in carrying out higher

cognitive functions in the hippocampus, hypothalamus, and cerebral cortex further supports the hypothesis of CNS involvement.[11]

ACh is synthesized in the cytoplasm from Acetyl-CoA and Cholin through a catalysis process by the enzyme choline acetyltransferase (ChAT). Acetyl-CoA is synthesized in the mitochondria, which are found in large quantities at nerve endings. Choline is transported from the extracellular fluid to the terminal neurons by the sodium-dependent carrier membrane. ACh is produced in large quantities; in one vesicle it can reach 1000-50000 molecules. Ach release depends on the extracellular Ca^{2+} level and occurs when the action potential reaches the terminal and stimulates an influx of Ca^{2+} ions. The vesicle then fuses with the membrane and causes the exocytotic expulsion of Ach into the synaptic cleft. After leaving the presynaptic terminal, the ACh molecule will bind to the receptor and activate the ACh receptor (cholinoceptor). The rapidly released ACh is broken down by acetyl cholinesterase (AChE) into choline and acetate, which terminates ACh's action. Most cholinergic synapses have large amounts of AChE, so the half-life of ACh at the synapse is very short. AChE is also found in other tissues, such as red blood cells. Another cholinesterase with lower specificity is butyrylcholinesterase found in plasma, liver, and glia there are two known acetylcholine receptorr, muscarinic and nicotinic. The two are distinguished by differences in their affinity for substances that mimic the action of acetylcholine (cholinomimetic agents/ parasympathomimetic agents). Once released, a neurotransmitter is only effective when it interacts with its receptor on the target cell. The specificity of these neuronal interactions is determined by the type of transmitter released and the type of receptor. Receptors are tools that can detect information that enters the cell. Receptors have been known to have binding sites with rigid structures. The receptor usually binds to only one type of transmitter, although other natural and synthetic substances can bind with high affinity. However, each type of transmitter can activate more than one type of receptor.[13]

2. Effect of Oxygen Saturation due to Respiratory Distress

Another possible etiologic mechanism that has been suggested in previous studies concerns the diaphragm, which, like various other striated muscles, is also affected by the binding of MG antibodies to nicotinic receptors. In MG, many patients experience shortness of breath during sleep, when the diaphragm is directly involved in the regulation of airflow. Although cognitive impairment is a common consequence of decreased oxygen saturation during the sleep phase, only one study has assessed the relationship between sleep and cognition in MG cases.[10]

The pathophysiology of cognitive decline in sleep apnea patients begins with intermittent hypoxia which induces an increase in sympathetic nervous system activity. Increased activity of the sympathetic nervous system will induce a series of processes, which include vasoconstriction of blood vessels, endothelial dysfunction of these vessels, exaggerated inflammatory response, and breakdown of the blood-brain barrier. Damage to the blood-brain barrier causes structural and functional changes in brain tissue, including brain tissue that carries cognitive functions, which leads to the process of neurodegeneration. The parts of the brain that are important for the formation of cognitive function that are prone to decrease in volume and function due to this process are the Hippocampus, frontal, parietal, and temporal lobes. The population of neurons in these three parts of the brain is sensitive to hypoxic conditions, so that intermittent hypoxic conditions that last a long time will cause damage to these neuronal populations[14,15]. Another mechanism of cognitive decline in hypoxic conditions is that hypoxia will increase the formation of ROS that have the potential to damage cells in the brain. In addition, excessive daytime sleepness or excessive sleepiness experienced by patients with sleep apnea causes a slowdown in information processing in the brain. According to previous research, sleep apnea causes hypoxia so that oxygen to the brain, especially the frontal lobes, decreases. Decreased oxygen to the frontal lobes results in a decrease in cognitive function, especially executive function.[16–18]

3. Effect of Nonspecific Immunological Process

A third possibility that could explain the cause of cognitive dysfunction in MG relates to the effects of nonspecific immunological processes (ie cytokines) triggered by antibody influx into the central nervous system. This hypothesis emerges as a possible etiologic cause of the electrical abnormalities that are consistently found in the brains of MG patients and animals with MG. It has not been determined with certainty whether

this immunological response plays role in cognitive impairment in MG. Further research should be carried out to assess this possibility.[10]

Research on cytokines is carried out by various disciplines, including research looking for the relationship between cytokines and the CNS. From these studies, two basic questions emerged, namely 1. How do cytokines modulate the CNS? And 2. What is the role of cytokines in the pathogenesis of nervous system diseases?. Research has shown that cytokines can affect CNS function, for example influencing CNS-controlled autonomic nervous function, neuroendocrine and behavioral responses. Two proinflammatory cytokines, TNF-α and IL-1 play role in modulating the brain-behavior of normal organisms. These two cytokines are also involved in synaptic plasticity, neural transmission and Ca21 signaling.[19]

It is known that cytokines can affect central nervous function in various ways and cytokine expression is also found in cases of infection and brain injury. Also found some evidence of the involvement of cytokines in the induction and modulation of neurological diseases ranging from Alzheimer's disease to chronic fatigue syndrome. Initially, cytokines were identified as intracellular signaling molecules and function as mediators between the immune system and the central nervous system. Immunological activity in the host is often associated with changes in behavior, body temperature and neuroendocrine activity, all of which are regulated by the CNS. It is concluded that cytokines induced during the immune response will modulate CNS function to elicit physiological, behavioral and endocrine mechanisms to fight infection. Systemic or direct injection of various cytokines into the cerebral ventricles activates the hypothalamic-pituitary adrenal (HPA) axis, causing fever and prolonged slow wave sleep, reduced food/beverage intake, and decreased motility. The most frequently tested cytokine here is IL-.[19]

4. Effects of Fatigue

The main symptom of MG is the fluctuatif fatigue in the striated muscles. Physiologically, this symptom manifests in a decreased ability to maintain muscle activity, but behaviorally the patient describes this experience as an increase in physical fatigue. It is important to note that patients also report experiencing feelings of mental exhaustion in addition to symptoms of physical exhaustion. This complaint is not commonly found, considering the level of physical and mental fatigue felt by each person is different, where an increase in one dimension can be followed by an increase in other dimensions.[10]

Taking into account that the level of perceived mental and physical fatigue increases in MG and these two dimensions of fatigue vary widely from one another. To assess this relationship, a study took data on levels of mental and physical exhaustion before and after performing a series of cognitive examinations. The examination includes measurements of the parameters of attention, memory, visuospatial function, and information processing speed. Fatigue was assessed using the Multicomponent Fatigue Inventory (MFI), which is a self-assessed assessment instrument to measure changes in cognitive and physical fatigue (before and after the examination). Examples of items found in MFI include: "Is your attention span now lower than usual?" and "Have you been feeling weak lately?" Prior to completing the series of cognitive checks, subjects had to rate their level of fatigue using a scale ranging from 1 ("not tired at all") to 5 ("very tired"). Then, the subject will undergo a series of cognitive examinations, and are given some time off to rest during the examination. After performing a cognitive examination for about 1.5 hours, the subjects were asked to rate the change in their level of fatigue compared to the value of the level of fatigue before the examination.[10]

Baseline scores for levels of mental and physical exhaustion were compared with healthy control subjects. The post-examination level of fatigue scores showed a significant increase in both mental and physical fatigue levels for the MG patient group, but not in healthy control subjects. Where patients reported significantly greater fatigue after completing the cognitive examination session, whereas healthy control subjects did not report any changes in fatigue levels after completing the cognitive examination session. When the correlation between performance on cognitive examination and fatigue level was computed, it was found that there was a significant relationship between changes in mental fatigue level and performance for the parameters of fluency response ($r = -0.50$), speed of information processing ($r = 0.51$), verbal learning ability ($r = -0.39$), and visual retention ($r = -0.46$). In each of these parameters, cognitive performance decreases as perceived fatigue increases. No significant relationship was found

between the level of physical fatigue and cognitive performance.[10]

These results provide strong evidence that factors related to fatigue can affect cognitive performance. It is known that a causative relationship cannot be deduced from correlation analysis. However, the fact that changes in mental fatigue levels are closely related to cognitive parameters that clearly distinguish MG patients from healthy controls suggests that the association is more than coincidental. In future studies, it will be important to determine whether cognitive performance actually decreases with increasing fatigue in MG. These findings have recently been demonstrated in a number of samples of patients with multiple sclerosis. Since fatigue in multiple sclerosis is the result of CNS involvement, it is interesting to determine whether fatigue originating from the periphery (as in the case of MG) also produces deleterious effects on cognitive function.[10]

Conclusion:

Impaired memory function in patients with myasthenia gravis is thought to occur through several mechanisms, including central cholinergic activity, which supports the fact that nicotinic AChR shows the action of neurotransmitter functions in the central nervous system, hypoxia, inflammatory processes, and the influence of physical and psychological fatigue. Karena sebagaian besar penelitian menggunakan sampel yang kecil dan jenis studi belum beragam, however, this still requires further research.

References:

[1] Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: A review. Autoimmune Dis. 2012;1(1).

[2] Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis : Epidemiology , Pathophysiology and Clinical Manifestations. 2021;

[3] Grob D, Brunner N, Namba T. Invited review. 2008;(February):141–9.

[4] Ochs CW,Bradley RJ, Katholi CR, Byl NN, Brown VM, Jones LL SJ. No Title. J Med. 29(1–2):1–12.

[5] Mao Z, Yin J, Lu Z, Hu X. Association between myasthenia gravis and cognitive function: A systematic review and meta-analysis. Ann Indian Acad Neurol. 2015;18(2):131–7.

[6] Klaus B, Müller P, van Wickeren N, Dordevic M, Schmicker M, Zdunczyk Y, et al. Structural and functional brain alterations in patients with myasthenia gravis. Brain Commun. 2022;4(1):1–12.

[7] L S. Human physiology. In: Brooks. 7th ed. Philadephia; 2010. p. 157–65.

[8] Roesler R, McGaugh JL. Memory consolidation. Encycl Behav Neurosci Second Ed. 2021;2–3:462–9.

[9] Zhou X, Zhou Y, Hua J, Xue Q. Association Between Myasthenia Gravis and Memory : A Systematic Review and Meta-Analysis. 2021;12(November):1–11.

[10] Paul RH, Mullins LL GJ. Myasthenia Gravis and Related Disorders. In: HJ K, editor. Second Edi. Saint Louis University, St.Louis: Humana Press;

[11] Kaltsatou A, Fotiou D, Tsiptsios D, Orologas A. Cognitive impairment as a central cholinergic deficit in patients with Myasthenia Gravis. BBA Clin [Internet]. 2015;3:299–303. Available from: http://dx.doi.org/10.1016/j.bbacli.2015.04.003

[12] Hamed S, Mohamed M, Youssef A, Abd ElHameed M, Elattar A. Assessment of cognitive function in patients with myasthenia gravis. Neuroimmunol Neuroinflammation. 2014;1(3):141.

[13] A S. Neuropharmacology-Acetylcholine and Nor Epinephrine. Lampung University; 2014.

[14] Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest [Internet]. 2012;141(6):1601–10. Available from: http://dx.doi.org/10.1378/chest.11-2214

[15] Lim DC, Pack AI. Obstructive sleep apnea and cognitive impairment: Addressing the blood-brain barrier. Sleep Med Rev [Internet]. 2014;18(1):35–48. Available from: http://dx.doi.org/10.1016/j.smrv.2012.12.003

[16] Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome : A critical review. 2004;772–85.

[17] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: Towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11(1):1–16.

[18] Kim SJ, Lee JH, Lee DY, Jhoo JH, Woo JI. Neurocognitive dysfunction associated with sleep quality and sleep apnea in patients with mild cognitive impairment. Am J Geriatr Psychiatry [Internet]. 2011;19(4):374–81. Available from: http://dx.doi.org/10.1097/JGP.0b013e3181e9b976

[19] Rambe A. Changes in Serum TNF-α, Interleukin-1, and Interleukin-6 Levels After Amitriptyline or Dexketoprofen Administration and Their Correlation With Pain Intensity Levels in Patients with Chronic Tension-Type Headache. Medical Faculty North Sumatera university; 2015.