International Journal of Research in Medical Sciences
Wardhana IBGW et al. Int J Res Med Sci. 2019 Aug;7(8):3230-3234
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20193426

Review Article

Psychopharmacology in myasthenia gravis patients with focus on depression

Ida Bagus Gede Wisnu Wardhana[1]*, Anak Ayu Sri Wahyuni[1], Komang Arimbawa[2]

[1]Department of Psychiatry, [2]Department of Neurology, Udayana University Medical School/Sanglah Hospital, Denpasar, Bali, Indonesia

Received: 26 June 2019
Accepted: 17 July 2019

***Correspondence:**
Dr. Ida Bagus Gede Wisnu Wardhana,
E-mail: barong666punyah@yahoo.com

ABSTRACT

Myasthenia gravis is an autoimmune disease with a potential to disrupt brain function and cause depression as a result of the disease itself or treatment side effect. Some biological and psychological mechanisms have been proposed for the correlations between myasthenia gravis and depression. Depression might present in patients myasthenia gravis, and it might complicate the course of the disease. Adequate treatment might not only improve the depression but might also impact the myasthenia gravis in general.

Keywords: Contraindication, Depression, Myasthenia gravis, Psychopharmacology, Side effect, Treatment

INTRODUCTION

Myasthenia gravis (MG) is a relatively rare autoimmune condition in which the formation of antibodies to the post-synaptic nicotinic acetylcholine receptors in the neuromuscular junction in the skeletal muscle.[1] Although the progress of the medical world makes the mortality of this disease relatively low, this disease has a significant impact on the quality of life. In addition, the fluctuating course of the disease and its clinical heterogeneity often make it difficult for clinicians to make optimal approaches in determining clinical profiles, effects, and outcomes of therapy.[1,2] Until now there has been no clear consensus for the therapeutic strategy of MG.[1]

Beside clinical impact, MG also has a significant psychosocial impact. Chronicity of the disease, the frequent need for long-term therapy and psychiatric symptoms such as anxiety and depression have been reported in patients with MG, but so far only a few are known about their frequency and their relation to disease pathogenesis.[3] The fluctuating course can be very confusing because at one time the patient can function normally, but at other times he experiences a heavy loss of strength. Other people can see the patient as lazy people. This can cause frustration, so that finally up to 51% of MG patients can experience psychiatric disorders.[4] In these patients, the prevalence of anxiety disorders is estimated at 50% and depression has a prevalence range of 26-33%.[5]

Among the various psychopathology, depression is a disorder that needs special attention, because in depression an inflammatory dysregulation occurs which is also part of the pathophysiology of MG.[6] Clinical manifestations (e.g. fatigue) can also be similar between depression and MG.[5]

Therefore, when depression arises in patients with MG, it becomes ambiguous whether these two conditions have one or two-way relationships, overlapping conditions, or a single condition with various manifestations that seem representative for other conditions. Due to this complexity, the authors are interested in discussing about psychopharmacology in MG patients with focus on depression.

PSYCHIATRIC COMORBIDITY IN MYASTHENIA GRAVIS

Type and prevalence

Comorbid nervous system manifestations and syndromes in MG can present as problems with memory, sleep abnormalities, autonomic dysfunction, peripheral neuropathy, epilepsy, psychiatric disorders (depression), etc.[7] It is estimated that 51% of MG patients experience psychiatric disorders.[5] Patients with more severe disease are reported to have a higher level of psychopathology than patients with milder MG.[8] In MG patients who showed psychopathology, the prevalence of anxiety disorders was estimated at 50% and depression had a prevalence range of 26-33%.[5]

Another study obtained a prevalence of depression in patients with MG of 26.1%, of which 7.3% had suicidal ideas, while 46.3% of patients also experienced anxiety disorders.[7] This is in line with research which states that there is a relationship between depression, anxiety, and self-efficacy, and shows a higher level of distress, anxiety, and depression in patients with MG than healthy controls.[8]

Pathophysiology of psychiatric symptoms in myasthenia gravis

The most opinion nowadays states that MG psychopathology tends to be caused by psychological reactions to chronic and unpredictable course of the diseases and not due to involvement of the central nervous system. However, MG is an autoimmune disease and therefore has the potential to interfere with brain function that determines the occurrence of behavioral changes, both due to the course of the disease itself and as a side effect of MG treatment. Psychopathology can appear in the form of depression, suicidal behavior, and sleep disorders, or psychotic symptoms because of pyridostigmine bromide and corticosteroids therapy.[9-11]

Some studies has been done to examine the possibility of involvement of the central cholinergic process and they obtain supportive findings, such as the presence of abnormal electroencephalography (EEG) and elevated levels of MG-related antibodies in cerebrospinal fluid in MG patients, in which anti-AChR antibodies are estimated interact with nicotinic receptors in the central nervous system.[10,11]

Another opinion states that patients with MG are prone to psychiatric disorders as a result of psychological reactions to their illness. Fluctuating respiratory symptoms make patients prone to panic disorder and / or agoraphobia. Although anxiety and depression may be more common in MG patients with respiratory failure, this psychiatric disorder is also found in patients without any complaints of respiration. Bulbar disorders can also explain the occurrence of social anxiety due to dysfonia, dysarthria, and dysphagia.[9]

DEPRESSION IN MYASTHENIA GRAVIS

General overview of depression

Depression is a form of mood disorder that has significant morbidity and mortality, is associated with a poor incidence and outcome if it occurs together with medical illnesses, interpersonal relationship disorders, drug abuse, and loss of time that should be used for work. The lifetime prevalence of this disorder is estimated at 20% in women and 12% in men.[12] Although the exact etiology of depression is unknown, a number of findings indicate that predisposing factors include the genetic structure of a person interacting with stress-causing life events.[13] Depression diagnoses are determined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM V) or International Classification of Disease (ICD-10) mental and behavioral disorders block.

Depression in MG has a high prevalence but tends to be less recognizable because the weakness symptoms of MG can overlap with somatic symptoms in depression, thus potentially worsening prognosis due to delayed management of depression.[8]

The neurobiological mechanism of depression in myasthenia gravis

Biologically, depression is a neuropsychiatric syndrome characterized by relatively mild cellular and molecular changes associated with abnormalities in brain function, brain structure, and pharmacology of receptors. Depressed patients show impaired activation of the HPA axis where cortisol fails to provide physiological effects, including fails to provide negative feedback on the HPA axis and anti-inflammatory effects at the peripheral level due to impaired sensitivity of glucocorticoid receptors.[14] Other studies have also documented about the possibility that depression is associated with systemic inflammation, where in depressed patients there is a decrease in mitogen stimulated lymphocyte proliferation and a decrease in natural killer cell (NK) activity in depression, which has led to studies of cytokine levels.[15] Plasma concentrations for IL-1-rA, IL-6, sIL-6R, sIL-2R, TfR, C reactive protein (CRP) were significantly higher in depressed patients compared to control subjects.[16]

One significant support for the possibility of a link between depression and MG is that both conditions are more common in women, and both are found to have immune dysregulation.[17] This prevalence difference in men and women is thought to be due to genetic differences that affect phenotypic expression in MG, for example the type of anti AChR antibody.[18]

Another similarity between MG and depression is the presence of immune dysregulation in both conditions. Cytokines can cause mood swings and depression. Down-regulation of the HPA axis is associated with neurophysiological changes involved in depression.[19]

There are three proposed pathways about how inflammatory activation can reach the brain to give effect to the mood. First, cytokine molecules can cross the blood brain barrier in some areas using specific transport proteins, as well as nonspecific transport of organs around the ventricles. Second, afferent nerve fibers can also carry inflammatory signals to the brain when inflammatory cytokines bind to cytokine receptors and transmit these signals to the central nervous system. Third, there are cellular pathways where active immune cells can reach the brain with the help of CC-chemokine ligand 2 (CCL2) and CXC-chemokine ligand 1 (CXCL1).[20] In addition, the presence of cerebro-reactive autoantibodies in cerebrospinal liquor, such as anti-NMDA and anti-ribosomal P, can cause significant disturbances in neurons. These inflammatory processes can then induce behavioral changes by reducing brain plasticity, reducing the availability of neurotransmitters, and increasing neurotoxicity.[20]

Other studies mention the involvement of acetylcholine (ACh) signaling in MG and depression. An imaging study shows that acetylcholine levels increase in depressed patients, and that depressive symptoms can be induced through acetylcholinesterase blockade (AChE). In addition, similar effects of antidepressants can be induced in animal models and several clinical studies by limiting acetylcholine receptor activity (ACh). This finding leads to the hypothesis of cholinergic-adrenergic equilibrium, where high cholinergic and low adrenergic activity can cause depression.[13]

Psychosocial aspects of depression in myasthenia gravis

The psychological aspects of MG can be categorized into: (1) the patient's psychological health effects on the expression of his illness; (2) the effect of the disease on the psychological health of the patient. Depression often arises in connection with the occurrence of the following in patients:

- Frustration and anger when the body cannot do what the patient wants to do
- Constantly worried that new symptoms will appear and that the drug has side effects
- Dissatisfaction with physical appearance (for example, due to weakness of facial muscles causes inability to smile and speak unclearly)
- Significant changes in the lifestyle of patients, for example when they have to leave work, school and others.
- Tension can occur in interpersonal relationships as patients and their families try to deal with the limitations that occur due to the disease
- Fear of being stigmatized
- When family members and friends have difficulty understanding why weaknesses can vary daily or even within hours, so patients can feel betrayed and resentment.

Myasthenia gravis patient can experience depression because of their illness, changes in lifestyle from those who previously productive as people who can only stay at home, financial burdens, and dependence on other family members that they did not experience before.[4]

Life events that because stress seem to be related to anxiety and depression in patients with MG. These events can be very difficult to overcome by MG patients who also struggle to overcome the burden of MG's unpredictable, chronic, and life-threatening diseases.[8] The patient's perception of quality of life was also related to the level of depression of the patient, where this perception was influenced by the type of dominant MG symptoms, the number of myasthenic crises and the treatment given.[21] This can cause a decrease in physical capacity and psychological well-being, which in turn can affect the actual quality of life and the patient's MG course.[3,22]

Psychopharmacology related to depression in myasthenia gravis

Immunotherapy has become an important revolution for the treatment of several diseases but has a profile of side effects that often involve psychological symptoms, especially depression. These drug-induced depressive symptoms are generally dominated by somatic or neurovegetative symptoms that can be treated with antidepressants.[20] Treatment with corticosteroids, for example, has been known to precipitate dose-dependent psychiatric disorders, especially affective disorders, so it must be considered in the etiology of psychopathology in MG.[3] However, depression is a heterogeneous disorder, and a subgroup of patients who are depressed tends to show low-grade chronic inflammation and is often resistant to traditional antidepressant therapy, so this group might benefit from drugs that work through inflammatory pathways.[20]

Inflammatory effects on behavior can vary between patients. Knowledge of depression risk factors in patients makes us able to prevent unwanted effects. One important risk factor is the presence of psychiatric disorders, especially history of depression. Genetic risk factors considered to play a role include the polymorphisms of serotonin gene transporter functional promoter (5-HTTLPR) or other serotonin (e.g. HTR1A) or inflammation (e.g. IL-6, COX-2, TNF-alpha). In addition, several genetic variants along the interferon a / b signaling pathway and genetic variants in the IL-6, IL-1b or nitric oxide synthase-1 (NOS1) gene increase symptomatology of depression and anxiety, especially in the presence of psychosocial stressors in the general population. Another risk factor is psychosocial stressors as a potential inflammatory inductor. Stress that occurs in early life, such as childhood trauma, permanently increases proinflammatory cytokines, possibly through epigenetic changes, so that it has a significant stress response than those without risk factors.[20]

Some studies suggest avoiding the use of psychotropic drugs such as chlorpromazine, haloperidol, clobazam and amitriptyline in MG because of the risk of worsening muscle weakness. Antipsychotics work very selectively on muscarinic and nicotinic receptors. Nicotinic receptors have a direct effect on MG.[23] Antipsychotics will inhibit the performance of acetylcholine in nicotinic receptors α7 and α4β2 and muscarinic receptors M1, M2, M3 and M4.[24] Acetylcholine is a neurotransmitter that works in the neuromuscular junction of the sympathetic and parasympathetic nervous system for muscle activation.

The use of typical antipsychotic (haloperidol) causes a decrease in cell proliferation and neurogenesis in the hippocampal dentate gyrus, then a downregulation of the HPA axis in the form of impaired negative feedback of cortisol and cortisol increases. This increase in cortisol induces an increase in expression of gene coding for serotonin transporters which is associated with an increase in serotonin reuptake so that serotonin levels leading to receptors drop and trigger depression. Atypical antipsychotics (clozapine) causes an increase in cell proliferation and neurogenesis in the hippocampal dentate gyrus which regulates the HPA axis.[25]

Clobazam is a benzodiazepine derivative which is a long acting GABA-A receptor agonist with anxiolytic, sedative and anticonvulsant activity. Clobazam can cause muscle weakness and is contraindicated in patients with MG.[26]

Recommendations

Recommendations for clinical practice

Screening and evaluation of risk factors such as psychiatric history, genetic polymorphism, increased inflammatory cytokines, or social support can help initiate personalized preventive therapy for those who are likely to experience psychiatric side effects. Prophylactic therapy and concurrent therapy with selective serotonin reuptake inhibitors (SSRIs) have been successful in reducing the incidence and severity of depression. However, an increase in the biological inflammatory markers predicts a poor response to SSRIs and can be more responsive to tricyclic antidepressant groups, therefore the therapy must be adjusted. Drugs targeting biological inflammatory pathways can be a future alternative for subgroups of patients who do not respond to standard antidepressant therapy.[20] The use of atypical antipsychotics (Clozapine) for depressed patients causes an increase in cell proliferation and neurogenesis in the hippocampal dentate gyrus which regulates the HPA axis but requires routine evaluation because antipsychotic drugs cause disturbances in nerve and muscle nicotinic and muscarinic receptors.[25]

Recommendations for research

Future research can be directed at clarifying the causal relationship between psychopathology and disease severity, as well as therapeutic efforts for comorbid depression conditions. Some variables that can be considered for research include emotional status and coping mechanism, inadequate psychiatric evaluation or psychological support, social stressors, evaluation of the use of antipsychotics as psychopharmaceuticals on MG depression and their effects on the central nervous system.[8]

CONCLUSION

- Myasthenia gravis (MG) is a relatively rare autoimmune condition that can affect various aspects of a person's life.
- Psychiatric problems frequently occur in MG patients and one of the most is depression.
- Depression in MG patients can be mediated by inflammation, induced by drug use, or as psychosocial consequences of MG.
- Screening and evaluation of risk factors can help initiate personalized preventive therapy for patients who are likely to experience psychiatric side effects.
- The use of antipsychotics for depression in MG will worsen depressive symptoms and MG symptoms.
- Future research can be directed at clarifying the causal relationship between psychopathology, disease severity, and depression.

ACKNOWLEDGEMENTS

Authors would like to thank appreciate Cindy Gautama for her assistance in writing and translating.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Shah AK, Goldenberg WD. Myasthenia gravis New York: MedScape; 2016. Available at: http://emedicine.medscape.com/article/1. Accessed 24 March 2019.
2. Mourao AM, Gomez RS, Barbosa LSM, Freitas DdS, Comini-Frota ER, Kummer A, et al. Determinants of quality of life in Brazilian patients with myasthenia gravis. Clinics. 2016;71(7):370-4.
3. Freeman C, Lewis I, Heckmann JM. Neuropsychiatric symptoms in patients with thymoma-associated and non-thymoma myasthenia gravis. S Afr J Psych. 2014;20(2):50-3.
4. Aguinaldo JL, de Guzman R. The Effectiveness of Logo-Bibliotherapy on the Depression of Selected Filipino Suffering from Myasthenia Gravis. Asian J Natural Appl Sci. 2014;3(2):31-9.
5. Jones SM, Gwathmey KG, Burns TM. Quality of life measures for myasthenia gravis and evaluation of non-motor symptoms. Clin Exp Neuroimmunol. 2015;6(1):32-9.

6. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So, depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013;11(200):1-16.
7. Hamed SA. Comorbid nervous system manifestations and disorders with myasthenia gravis: Evidences and possible mechanisms. J Neurol Neuro Sci. 2012;3(1):1-17.
8. Aysal F, Karamustafalioglu O, Ozcelik B, Yilmaz M, Karamustafalioglu N. The Relationship of Symptoms of Anxiety and Depression with Disease Severity and Treatment Modality in Myasthenia Gravis: A Cross-sectional Study. Noro Psikiyatr Ars. 2013;50(4):295-300.
9. Ybarra MI, Kummer A, Frota ERC, de Oliveira JT, Gomez RS, Teixeira AL. Psychiatric disorders in myasthenia gravis. Arq Neuropsiquiatr. 2011;69(2-A):176-9.
10. Leon-Sarmiento FE, Bayona EA, Bayona-Prieto J, Osman A, Doty RL. Profound Olfactory Dysfunction in Myasthenia Gravis. Plos One. 2012;7(10):1-5.
11. Ouanes S, Hizem Y, Djebara MB, Kacem I, Gargouri A, Gouider R. Differential Diagnosis of Hallucinations in a Patient with Myasthenia Gravis. Innov Clin Neurosci. 2013;10(9-10):23-5.
12. Halverson JL. Available at: http://www.medscape.com/ 2015. Accessed 18 June 2015.
13. Mineur YS, Obayemi A, Wigestrand MB, Fote GM, Calarco CA, Li AM, et al. Cholinergic signaling in the hippocampus regulates social stress resilience and anxiety-and depression-like behavior. Proc Natl Acad Sci U S A. 2013;110(9):3573-8.
14. Nikkheslat N, Zunszain PA, Horowitz MA, Barbosa IG, Parker JA, Myint, et al. Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. Brain, Behav, Immun. 2015;48:8-18.
15. Duivis HE, Vogelzangs N, Kupper N, de Jonge P, Penninx BWJH. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of Depression and Anxiety (NESDA). Psychoneuroendocrinol. 2013;38(9):1573-85.
16. Pandey GN, Dwivedi Y. Peripheral Biological Markers for Mood Disorders. In: Ritsner MS, editor. The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes Volume III. Berlin: Springer; 2009: 121-149.
17. Vogelzangs N, Duivis H, Beekman A, Kluft C, Neuteboom J, Hoogendijk W, et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry. 2012;2(2):e79.
18. Abukhalil F, Mehta B, Saito E, Mehta S, McMurtray A. Gender and Ethnicity Based Differences in Clinical and Laboratory Features of Myasthenia Gravis. Autoimmune Dis. 2015;1-4.
19. Vaillant AAJ, Mohammed W, Vuma S, Anderson N. Autoimmunity in Neurological and Psychiatric Disorders: Participation of Antibodies and Cytokines in the Immunopathogenesis of these Diseases. Immunome Res. 2015;11(1):1-4.
20. Kovacs D, Kovacs P, Eszlari N, Gonda X, Juhasz G. Psychological side effects of immune therapies: symptoms and pathomechanism. Curr Opinion Pharmacol. 2016;29:97-103.
21. Mourão AM, Araújo CM, Barbosa LSM, Gomez RS, Burns TM, Lemos SMA, et al. Brazilian cross-cultural translation and adaptation of the Questionnaire of Life Quality Specific for Myasthenia Gravis - 15 items. Arq Neuropsiquiatr. 2013;71(12):955-8.
22. Boldingh MI, Dekker L, Maniaol AH, Brunborg C, Lipka AF, Niks EH, et al. An up-date on health-related quality of life in myasthenia gravis -results from population-based cohorts. Health Quality Life Outcomes. 2015;13(115):1-14.
23. Ahmed A, Simmons A. Drugs Which MAy Exacerbate or Induce Myasthenia Gravis: A Clinician's Guide. Internet J Neurol. 2009;10(2).
24. Levin ED, Rezvani AH. Nicotinic Interactions with Antipsychotic Drugs, Models of Schizophrenia and Impacts on Cognitive Function. Bioch Pharmacol. 2009;74(8):1182-91.
25. Morais M, Pinheiro A, Patricio P, Alves N, Pinto L, Sousa N, et al. The Impact of Antipsychotic Drugs in Depression: A Role for Adult Neurogenesis? Neurosciences Res. 2014;24:448.
26. National Center for Biotechnology Information. PubChem Compound Database. 2019. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/2789. Accessed 14 March 2019.

Cite this article as: Wardhana IBGW, Wahyuni AAS, Arimbawa K. Psychopharmacology in myasthenia gravis patients with focus on depression. Int J Res Med Sci 2019;7:3230-4.