BirEx JOURNAL
Budapest International Research in Exact Sciences
Medical, Biological, Argiculture, Engineering
Science and other related areas
e-ISSN : 2655-7827
p-ISSN : 2655-7835
http://www.bircu-journal.com/index.php/birex

Clinical Characteristic Myasthenia Gravis among Indonesians

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Abstract: *Myasthenia gravis (MG) is a relatively rare autoimmune disorder on peripheral nerves where an antibody of nicotinic acetylcholine postsynaptic receptor is formed on neuromuscular junction (NMJ). MG is clinically characterized with a fluctuating muscle weakness. The incidence rate is 0.25 to 2.0 per 1,000,000 among population. 10% of the population is children and adolescents. Over the past forty years, a mortality rate has improved in the myasthenic crisis from 75% to less than 5%. Moreover, in Indonesia, this is still considered a rare disease. This study applied a retrospective cross-sectional study design. Data were gathered from patients diagnosed and treated for myasthenia gravis admitted in the neurological emergencies in the hospital during January to November 2019. Afterwards, the follow-up clinical information was also being analyzed. 12 cases of myasthenia gravis were collected with females predominated (75%), and one male (25%) with the average age of 30-40 years. The majority (75%) had the onset of < 35 years. The patients were from various districts, with 75% referral from the district and 58% housewives. Clinically, 8% patients had the ocular myasthenia and 92% was the generalized one. The ocular myasthenia had a relatively earlier onset. As MG symptomatology bears a wide range of variability and severity, it was graded based on Osserman's and Myasthenia Gravis Foundation of America's (MGFA) classification. Out of all patients, 13.7% belonged to Osserman's class 1-3 (33%) and class 4-5 (67%). Myasthenia Gravis Foundation of America (MGFA) grading calibrated the severity of each crisis. The findings were 17% crisis of milder degree and 83% of moderate to severe nature. The thyroid disorder was evident in one of the patients (8.3%). Laboratory findings were 75% patients with the increase in leukocyte count. The treatment was only 25% anticholinesterase, 50% anticholinesterase and steroid, in addition to 25% anticholinesterase and therapeutic plasma exchange (TPE). The hospital stay was (the average in days) 83% with >7 days. The myasthenia gravis reported was 12 cases. Patients' outcome depended on the clinical condition when they first arrived in the hospital. These findings will be useful for the resource allocation and planning in health services. Many regions worldwide have few or no epidemiological data on the myasthenia gravis, and more studies are required to yield more estimates that are accurate.*
Keywords: *demographic; clinical characteristics; myasthenia gravis*

I. Introduction

Murthy (2020) states that Myasthenia Gravis (MG) is a group of disorders on neuromuscular junction (NMJ) caused by a postsynaptic autoimmune. The autoimmune targets on the acetylcholine receptor (AChR), muscle – specific kinase (MuSK), lipoprotein - related protein 4 (LRP4) and agrin. The clinical indication of MG is with a fluctuating muscular weakness. According to Gilhus (2015) myasthenia gravis characterized by an abnormal and progressive weakness on skeletal muscle continuously used, accompanied with fatigue during activity and after resting, afterwards, the muscle strength recovers. The disease is a result of the impaired synaptic transmission or the neuromuscular junction (Melzer, 2016).

Myasthenia Gravis is a rarely found autoimmune disease. More cases are evident in women than men (Melzer, 2016). The peak of the onset is at the age of the second and third decades (in women) and fifth and sixth decades (men). Myasthenia Gravis is neither a hereditary disease nor a type of infectious disease. (Carr, 2010) states that the incidence of MG

is 0.25 - 2.0 cases per 1,000,000 population per year with an increase in annual prevalence of 72: 1,000,000 (range 15–179). 10% of patients are children and adolescents. Family risk increases for MG. Patients' siblings or close relatives may risk by 4,5% for the onset of MG (Hemminki, 2006).

MG is classified based on serum antibodies and clinical features. The identification of specific subtypes determines the therapeutic approach as well as the prognosis (Dalkas, 2019). Clinical subtypes include ocular MG, general onset of generalized MG and general slow onset. Subtypes by antibodies include MG with AChR antibodies, MG with anti-MuSK antibodies, MG with anti-LRP4 antibodies, seronegative myasthenia and myasthenia with coexisting autoimmune diseases. Another subtype is adult-onset MG with thymoma and ryanodine receptor antibodies. The relative prevalence of subtypes by antibodies are: MG with 80% AChR antibody, MG with 4% MuSK antibody, MG with 2% LRP4 antibody and seronegative myasthenia (Romi, 2011).

The clinical features of MG consist of fluctuating lethargy and weakness affecting the ocular, bulbar, and extremity (proximal) skeletal muscle groups. Pragmatic clinical classification distinguishes pure ocular myasthenia from common myasthenia with mild, moderate, and severe manifestations. Ocular myasthenia exclusively affects the outer ocular muscles including the M. levator palpebrae and the presence of ptosis and double vision complaints. Ptosis and double vision may be temporary, fluctuating or progressive during the day. Only 10-20% of patients show fatigue and weakness of the muscles that are constantly confined to the outer eye muscles. Most patients proceed to general muscle fatigue and weakness, occurring within 24 months after the onset of the disease. Myasthenia is generally defined as the clinical affection of muscle groups in addition to ocular muscles aside from their severity (Robertson, 1998).

The most common cause of MG is an abnormal development of immunological parts (epitopes). This occurs in or around nicotinic AChR in the postsynaptic endplate region of the neuromuscular junction. AChR antibodies trigger immune degradation from AChR and postsynaptic membranes. The loss of functional AchRs in large quantities can cause a reduction for muscle fibers depolarizing during motor nerve terminal activation, resulting in a decrease in muscle action potential and important muscle fiber contractions. The presence of obstacles to neuromuscular transmission can cause clinical weakness if the amount of damaged fiber is large (Burns, 2012).

Drachman (2012) states that patients, negative for anti-ACHR antibodies may be seropositive for antibodies against MuSK (Muscle-Specific Kinase). Muscle biopsy in these patients indicated signs of myopathy with prominent mitochondrial abnormalities as opposed to neurogenic features and atrophy. This often found in patients positive for MG for anti-ACHR. Mitochondrial decline may explain the involvement of anti-MuSK positive oculobulbar MG (Statland, 2013).

A number of findings have been linked to MG, such as women and people with certain human antigen leukocytes (HLA) with a genetic predisposition to autoimmune diseases. Histocompatibility profiles of the complex include HLA-B8, HLA-DRw3, and HLA-DQw2 (although the correlation to ocular MG forms has not proven yet). SLE and RA may be associated with MG Drachman (2012). Sensitization of foreign antigens with cross reactivity with nicotinic AcH receptors has been suggested as a cause of myasthenia gravis, but trigger antigens have not yet been identified (Statland, 2013).

II. Methods

This study applied a retrospective cross-sectional study design. Data were gathered from patients diagnosed and treated for myasthenia gravis admitted in the neurological emergency in the hospital during January to November 2019. Information on the clinical follow-up was also analyzed.

Budapest International Research in Exact Sciences (BirEx) Journal
Volume 2, No 2, April 2020, Page: 257-263
e-ISSN: 2655-7827 (Online), p-ISSN: 2655-7835 (Print)
www.bircu-journal.com/index.php/birex
emails: birex.journal@gmail.com

III. Discussion

The myasthenia gravis gathered was 12 cases and females predominated (75%), only one male (25%) with the average age of 30-40 years. The majority (75%) was with the onset < 35 years. The patients were from various districts, namely, 75 % referral from the district and 58% was housewives. Clinically, 8% patients had the ocular myasthenia and 92% was the generalized one. The ocular myasthenia had a relatively earlier onset. As MG symptomatology bears a wide range of variability and severity, it was graded based on Osserman's classification and Myasthenia Gravis Foundation of America's (MGFA) classification. Out of all patients, 13.7% belonged to Osserman's class 1-3 (33%) and class 4-5 (67%). The severity of each crisis was calibrated in terms of MGFA grading. The findings were 17% crisis of milder degree and 83% of moderate to severe nature. The presence of thyroid disorder was found in one of the patients (8.3%). Laboratory findings were 75% patients with the increase in leukocyte count. The treatment was only 25% anticholinesterase, 50% anticholinesterase and steroid, in addition to 25% anticholinesterase and therapeutic plasma exchange (TPE). The hospital stay was (the average in days) 83% with >7 days.

Table 1. Clinical Characteristic of Myasthenia Gravis

NO	Variable	Classification	Total (n)	Percentage (%)
1	Gender	Male Female	3 9	25 75
2	Age (Year) study	<35 years >35 years	6 6	50 50
3	Age (Year) onset	<35 years >35 years	9 3	75 25
4	Occupation	Housewives Employee Students	7 2 3	58 17 25
5	Residence	West Aceh Aceh Besar Middle Aceh Aceh Jaya Bireun Banda aceh Pidie Subulussalam	1 1 1 1 1 3 3 1	8.3 25 25
6	Education			
7	Types of MG	Ocular General	1 11	8 92
8	Osserman's class	1-3 4-5	4 8	33 67
9	Clinical Distribution	-Ocular Symptoms -Bulbar Symptoms -Motor Symptoms -Respiratory Symptoms -ICU Care/ MV -MG Crisis	12 11 11 4 3 3	100 92 92 33 25 25
10	MGFA grade of worst crisis	I/IIa/Iib IIIa/IIIb/IVa/IVb/V	2 10	17 83

11	Treatments	- mestinon - mestinon + metil - mestinon + TPE	3 6 3	25 50 25
12	Hospital stay (Average in days)	<7 >7	2 10	17 83
13	Risk Factors	Thyroid disease Neoplasm	1 1	
14	Complications	Pneumonia Kidney Disease		
15	EKG Findings Thorax Findings	Atrial Fibrillose STEMI Normal Cardiomegaly Pneumonia Normal	- - 12 - - 12	 100 100
16	Brain Imaging	normal	12	100
17	CT scan Thorax Thymic Pathology	normal	12	100

Discussions

In January to November 2019 period, 12 cases of myasthenia gravis were gathered with females predominantly (75%), and one male (25%) with the average age of 30-40 years. Myasthenia Gravis is a rarely found autoimmune disease. More cases are found in women than men with the onset of peaks on second and third decade (for women), while the fifth and sixth (for men) (Melzer, 2016). Myasthenia Gravis is neither a hereditary nor infectious disease. The incidence rate is 0.25 - 2.0 cases per 1,000,000 population per year with an increasing prevalence by 72:1,000,000 (range 15–179). 10% patients are children and adolescents. Family risk increases for MG. Patients' siblings or close relatives may risk by 4, 5% for the onset of MG (Carr, 2010).

Clinically, 8% patients suffered from the ocular myasthenia and 92% with the generalized one (Li KK, 2017). The former had a relatively earlier onset. As MG symptomatology bears a wide range of variability and severity, it was graded based on Osserman's classification and Myasthenia Gravis Foundation of America's (MGFA) classification. Out of all patients, 13.7% belonged to Osserman's class 1-3 (33%) and class 4-5 (67%). Myasthenia Gravis Foundation of America (MGFA) grading calibrated the severity of each crisis. The findings were 17% crisis of milder degree and 83% of moderate to severe nature. The thyroid disorder was evident in one of the patients (8.3%). MGFA classification dissimilates to Osserman's classification in the evaluation of severity. Moreover, it is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to the therapy. This is more objective and precise than Osserman's classification. In addition, the QMG score is prone to be affected by clinical classification and post intervention status and should not be employed to compare severity among patients. In this study, MGFA classification, rather than Osserman's classification and QMG score, was the independent factor of DMV in PTMC, demonstrating that preoperative MGFA classification can be used to predict PTMC (Jaretzki, 2000).

Clinical characteristics of MG include fluctuating fatigue and weakness with an impact on the group of ocular, bulbar, and extremity (proximity) of skeletal muscles The classification of pragmatic clinical differentiate pure ocular from generalized myasthenia low, moderate and severe manifestations. The ocular myasthenia exclusively affects the outer ocular muscles including M. levator palpebrae and the presence of ptosis and double vision complaint. Such Ptosis and double vision may have temporal effect, fluctuating or progressively during the day.

Only 10-20% patients demonstrate muscles' fatigue and weakness continuously, limited on the outer. Most patients proceeded with general muscle fatigue and weakness for the following 24 months after the onset of the disease. Myasthenia is commonly defined as clinical affection on muscle group apart from independent ocular muscle aside from their severity (Robertson, 1998).

The laboratory findings were 75% patients with the increase in leukocyte count. The treatment was only 25% anticholinesterase, 50% anticholinesterase and steroid, in addition to 25% anticholinesterase and therapeutic plasma exchange (TPE). The hospital stay was (the average in days) 83% with > 7 days. Anticholinesterase, Pyridostigmine works on smooth muscles, the central nervous system (CNS), and secretory glands to block the AChE. The intermediate-acting agent is more preferable in the clinical use than the short acting one, bromide neostigmine, and the long acting, chloride ambenonium. Acetylcholinesterase inhibitors are the first-line treatment in patients with MG. The response to treatment varies from marked improvement in some patients to little or no improvement in others. Acetylcholinesterase inhibitors acts as a symptomatic therapy by increasing the amount of available acetylcholine at the NMJ. They do not alter disease progression or outcome. Pyridostigmine is the most commonly used drug. It has a rapid onset of action within 15 to 30 minutes reaching peak activity in about two hours. The effect lasts for about three to four hours. The initial oral dose is 15–30 mg every 4–6 hours titrated upwards depending on the patient's response. Adverse side effects of Pyridostigmine are mostly due to the cholinergic properties of the drug such as abdominal cramping, diarrhea, increased salivation and bronchial secretions, nausea, sweating, and bradycardia. Nicotinic side effects also frequently occurred including muscle fasciculation and cramping. High doses of pyridostigmine exceeding 450 mg daily, administered to patients with renal failure, have been reported to cause worsening of muscle weakness Steroid (Proudfoot, 2006).

Farmakidis (2018) states that corticosteroid is an anti-inflammation and immunomodulation agent applied to treat idiopathic and autoimmune disorders. Until recently, this drug has been among the first immunomodulation agents use to treat MG, which are effective and frequently used. The drug is administered in moderate or severe cases that is irresponsive to AChE inhibitors and thymectomy. The long-term usage with the corticosteroid proves to be effective allowing remission or improvement on most patients (Benatar, 2016). Initially, worsening may occur, yet, in 2-4 weeks clinical improvement is shown. This agent is usually employed in more than 1 or 2 years. The remission is 30% and the improvement is by 40%. Corticosteroid works well in both Ocular and generalized MG (Sanders, 2016). They can be combined with other immunosuppressive drugs for better effects with lower dosage and shorter duration (Achiron, 2000).

IVIG is recommended for MG crisis, on patients with severe weakness that is less controlled by other agents or as the plasma exchange at a dose of 1 g/kg. IVIG is also effective in moderate and severe MG worsening into crisis (Jacob, 2020). A high dose of IVIG succeeds in MG, in spite of the unknown work mechanism. The crisis management implements this (such as myasthenic crisis and perioperative period) not combined with the plasmapheresis. Like plasmapheresis, this drug is also with a rapid onset, yet, the effect works in short term (Wolfe, 2002).

Plasmaparesis (plasma exchange) is believed to work by eliminating humoral factors (ie, anti-ACHR antibodies and immune complexes) from the circulation in order to add other immunomodulatory therapies and as a tool for crisis management. Like IVIG, plasmapheresis is commonly used for myasthenia crises and refractory cases. Improvement occurs within a few days, but not lasting for more than 2 months (Gajdos, 2002). Plasmapheresis is an effective therapy for MG, especially in preparation for surgery or short-term management of exacerbations. Long-term regular or weekly plasmapheresis can be employed when other treatments cannot control the disease. Complications are mainly limited to intravenous (IV) access complications (for example, the centerline placement), yet may also include

hypotension and coagulation disorders, though it is rarely the case. Every day plasma replacements are carried out 3-8 times at a dose of 50 ml/kg BW. This method will provide clear improvements in a short amount of time. Plasmapheresis, when combined with the administration of immunosuppressive drugs, will be very beneficial for severe cases. However, there is no clear evidence that this therapy can provide good results allowing patients to live or stay at home. Plasmapheresis may be effective in myasthenia activity due to its ability to remove antibodies to the acetylcholine receptor; nevertheless, it is not useful in the treatment of chronic cases (Patwa, 2012).

Thymectomy is a selected important medication in myasthenia gravis (MG), especially when thymoma is found. This has been proposed as the first line therapy on most patients with generalized myasthenia gravis (MG). Thymectomy results in remissions (Liew, 2014). American Association of Neurology recommends thymectomy for the non-thymomatous patients of myasthenia gravis (MG) autoimmune. This is suggested as an option to increase the possibility for remissions or improvements (Leuzzi, 2014).

Advancement in our understanding and treatment of MG has transformed this once debilitating disease into one of the most treatable neuromuscular disorders. The majority of patients can achieve symptomatic remission with immunosuppressive drugs and cholinesterase inhibitors. Immunomodulatory therapies like PLEX and IVIg have reduced morbidity and mortality during myasthenic crisis, shortening time on ventilator support and hospital stays. The role of thymectomy is still being elucidated, but this is the first-line treatment for patients with thymoma-associated MG, and may be a viable option for non-thymomatous MG. New investigational drugs like rituximab hold promise for future treatment of refractory disease. As our understanding of the neuromuscular junction advances, so does our rational choice of targets for both therapy and diagnostic testing, making MG one of the best-understood and treatable autoimmune neuromuscular disorders.

IV. Conclusion

The myasthenia gravis reported was 12 cases. . Patients' reported outcome depended on the clinical condition when they first arrived in the hospital. These findings will be useful for the resource allocation and planning in health services. Many regions worldwide have few or no epidemiological data on the myasthenia gravis, and more studies are required to yield more accurate estimates.

References

Achiron A, Barak Y, Miron S, et al. Immunoglobulin treatment in refractory myasthenia gravis. Muscle Nerve 2000;23(4):551–5.

Burns et al. Myasthenia Gravis. In Netter`s Neurology2nd Edition. 2012; 73: 684-702.

Benatar M, McDermott MP, Sanders DB, et al. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): a randomized, controlled trial. Muscle Nerve 2016;53(3):363–9.

Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurol. 2010;10:46.

Dalkas MC. Immunotherapy in myasthenia gravies in the era of biologics. Nat Rev Neurol. 2019;15:113–24.

Drachman DB. Myasthenia Gravis and Other Diseases of The Neuromuscular Junction Kasper. In: Braunwald, Fauci, Hauser, Longo, Jameson. Harrison's : Principle of Internal Medicine 18th ed. McGraw Hill. 2012; 366: 2523-2518.

Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of Myasthenia Gravis. Neurol Clin. 2018;36(2):311-337. doi:10.1016/j.ncl.2018.01.011

Gajdos P, Chevret S, Toyka K. Plasma exchange for myasthenia gravis. Cochrane Database Syst Rev 2002;(4):CD002275.

Gilhus NE, Verschuuren JJ. Myasthenia gravis: Subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14:1023–36

Hemminki K, Li X, Sundquist K. Familial risks for diseases of myoneural junction and muscle in siblings based on hospitalizations and deaths in sweden. Twin Res Hum Genet. 2006;9:573–579. doi: 10.1375/twin.9.4.573

International MG/COVID-19 Working Group, Jacob S, Muppidi S, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci. 2020;412:116803.

Jaretzki AR, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg. 2000;70:327–334. doi: 10.1016/S0003-4975(00)01595-2.

Kupersmith MJ, Ying G. Ocular motor dysfunction and ptosis in ocular myasthenia gravis: effects of treatment. Br J Ophthalmol 2005;89(10):1330–4.

Li KK, Qian K, Feng YG, Guo W, Tan QY, Deng B. Predictive factors of prolonged mechanical ventilation, overall survival, and quality of life in patients with post-thymectomy myasthenic crisis. World J Surg Oncol. 2017;15(1):150. Published 2017 Aug 8. doi:10.1186/s12957-017-1209-1

Liew WK, Powell CA, Sloan SR, et al. Comparison of plasmapheresis and intravenous immunoglobulin as maintenance therapies for juvenile myasthenia gravis. JAMA Neurol 2014;71(5):575–80.

Leuzzi G, Meacci E, Cusumano G, Cesario A, Chiappetta M, Dall'Armi V, Evoli A, Costa R, Lococo F, Primieri P, et al. Thymectomy in myasthenia gravis: proposal for a predictive score of postoperative myasthenic crisis. Eur J Cardiothorac Surg 2014; 45:e76-88, e88.

Murthy JMK. Myasthenia Gravis: Do the Subtypes Matter? Ann Indian Acad Neurol. 2020 Jan-Feb;23(1):2. doi: 10.4103/aian.AIAN_595_19. Epub 2020 Jan 21. PMID: 32055109;

Melzer N, Ruck T, Fuhr P, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol. 2016;263(8):1473-1494. doi:10.1007/s00415-016-8045-z

Mittal MK, Barohn RJ, Pasnoor M, et al. Ocular myasthenia gravis in an academic neuro-ophthalmology clinic: clinical features and therapeutic response. J Clin Neuromuscul Dis 2011;13(1):46–52.

Romi F. Thymoma in myasthenia gravis: From diagnosis to treatment. Autoimmune Dis. 2011;2011:474512.

Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2012;78(13):1009–15.

Proudfoot A The early toxicology of physostigmine: a tale of beans, great men and egos. Toxicol Rev 2006;25(2):99–138.

Robertson NP, Deans J, Compston DA. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. J Neurol Neurosurg Psychiatry. 1998;65:492–496. doi: 10.1136/jnnp.65.4.492.

Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology 2016; 87(4):419–25.

Statland JM, Ciafaloni E. Myasthenia gravis: Five new things. Neurol Clin Pract. 2013;3(2):126-133. doi:10.1212/CPJ.0b013e31828d9fec

Wolfe GI, Barohn RJ, Foster BM, et al. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. Muscle Nerve 2002;26(4):549–52.