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A Cross-Sectional Study on Characteristics of Adult Myastenia Gravis Patients in Hospital Seberang Jaya

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Abstract
Background and Purpose: Myasthenia gravis (MG) is an autoimmune disease that impacts an affected individual's control of the skeletal muscles. To understand the common characteristics and comorbidities of MG patients who attended the adult neurology clinic at Hospital Seberang Jaya (HSJ), Penang from January-December 2016. **Methods:** This cross-sectional study reviewed sixty medical records of MG patients. The retrieved data was analyzed descriptively using SPSS version 23. **Results:** The mean age was 55 years, ranging from 16 to 81years old. Late Onset Myasthenia Gravis (LOMG) was more common, compared to Early Onset Myasthenia Gravis (EOMG), 34(56%) vs. 26(43%). Chinese predominated by 55%. Class I Myasthenia Gravis Foundation of America Clinical Classification (MGFAC) was the commonest. Ptosis noted in 80% of clinical manifestations. Comorbidities were associated in 40 (66.7%) of the MG patients, commonest being hypertension and diabetes. Ocular MG was more commonly seen in LOMG, compared to EOMG. **Conclusion:** Data from HSJ revealed, most MG patients were females, Chinese and of Class 1 type of MGFAC. LOMG was more common among the Chinese local population and among the ocular MG. Even though MG was seen more among the Chinese local population but myasthenia crises were least in them. Notable was an association between ocular MG and thyroid disease. More comorbid were seen in the LOMG. Our study did not show any association of comorbidities with worse outcome. The findings will aid primary health care to screen, formulate strategies and also improve quality of life (QoL).

Keywords: Myasthenia gravis, Ocular Myasthenia, type of myasthenia, characteristic of myasthenia, Early onset Myasthenia Gravis (EOMG), Late onset Myasthenia Gravis (LOMG).

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease that impacts an affected individual's control of the skeletal. Patients often present with ptosis, diplopia, facial weakness, dysarthria, and unstable gait.[1] The underlying cause is due muscles namely, the eyes, face, and the process of deglutition to the presence of antibodies which blocks the action of neurotransmitter; acetylcholine that binds to the nicotinic acetylcholine receptors (AChR) at the neuromuscular junction.[2] These antibodies interrupt the transmission of nerve impulses at the neuromuscular junction.[1] In normal circumstances, the binding of the chemical neurotransmitter will allow transmission of impulses and trigger muscles into action.[3] When there is a decrease in quantity of receptor sites, the muscles do not get sufficient signals to trigger the actions, resulting in weaknesses.[2] It was observed that the thymus gland either triggers or sustains antibodies produced.[2] The prevalence of MG is about 150 per million.[4] The annual incidence is 10 per million.[4] In our country MG was not explored in wider perspective. The purpose of the study is to understand the common characteristics and comorbidities of MG patients who attended the adult neurology clinic at Hospital Seberang Jaya, Penang from January - December 2016.

2. Materials and methods

2.1 Study Design & Setting.

This cross-sectional study utilized medical records of sixty MG patients who attended the neurology clinic of Hospital Seberang between January to December 2016. These 393

bedded hospital is considered as the second largest hospital in the state of Penang. [5] Cluster group hospitals facilitate patient registration and transfers between hospitals using a single registration number throughout the duration of treatment.

The records' unit of HSJ had facilitated the retrieval of patients' records. All information obtained from their initial presentation, including information from referrals were translated into the data collection form. (Table 1) We categorized the characteristics according to early onset Myasthenia Gravis (EOMG) as those whose onset is at age 50 years old and below and the remaining are those whose onset is beyond 50 years of age referred as late onset Myasthenia Gravis (LOMG), consistent with previous studies. [6,7] HSJ is a cluster, lead hospital for four major district hospitals, centered within an urban setting of mainland Penang.

2.2 Descriptive Covariates

Covariates explored in this study were demographics (age, gender, source of referral); risk factors (comorbidities, family history, underlying thyroid disease); clinical characteristics (date of onset, myasthenia type, fatigue, ptosis, diplopia, dysphagia, dysarthria, facial weakness, body weakness, initial and worst MG presentation); complications (thymoma, thymectomy, MG crisis); treatment (Immunosuppressant, intravenous immunoglobulins, plasmapheresis), diagnostics (acetyl choline antibodies), MGFAC classification and outcomes.

2.3 Ethics statement

The ethical approval for this study was obtained from the Medical Research Ethics Committee (MREC), registered with the National Medical Research Register (NMRR 17-110-33970). Informed consent was waived.

2.4 Sampling Frame

The list of confirmed MG patients that attended the neurology clinic of HSJ was obtained via the hospital neurology clinic registry. Using this list, the medical records of the MG patients were traced from the hospital record's department. A total of 60 medical records were traced.

2.5 Procedure

The required information were retrieved after critical review from the patients' medical records and subsequently translated into a data collection form (refer appendix). The retrieved data was then tabulated and cleaned in a structured database which each has serial subject identity number and linked on a password accessible to the author only. The data was then analyzed quantitatively to describe the sample characteristics. Subject anonymity was assured.

2.6 Statistical analysis

Descriptive analysis was conducted for all covariates retrieved. Frequencies and relative frequencies were reported for categorical variables, while continuous variables were expressed as mean and standard deviations (SD). Statistical package for social sciences (SPSS) version 23 was used.

3 Results and Discussion

Data from HSJ was analyzed and tabulated (Fig 1). The age demarcation for EOMG and LOMG were as mentioned above with literature reference. There is other reviews [8,9,10] where the onset age demarcation differs slightly in which the age demarcation cut off were taken at 40 years or the LOMG and very LOMG demarcation at 65 or demarcation of elderly onset at 69 years (Fig 2).

In our study, the Chinese predominated the majority of the subjects by 33 (55%) followed by Malays 25 (41.7%) and Indians 2 (3.3%). Our results showed Chinese predominance in LOMG is comparable to another study.[7] The demography according to ethnic in Penang in the year 2016 were; Chinese constitute 43.8%, Malays 45.3% and Indians 10.5%.[11] Our study showed MG were more common among the Chinese ethnic in comparison with the local population in Penang in year 2016.

In our study, EOMG was seen more in females; male: female ratio of 5:8, compared to LOMG which was seen more in males, ratio of 6.3:5, consistent with previous literature. [1,3,7,9,12] In a local study [13], the reverse was seen, EOMG was more common in males.

Our study also showed LOMG had more anti Acetyl Choline receptor (AChR) antibodies (Table 1). [9] The LOMG are associated with AchR antibodies [9] 22(36.7%) vs. EOMG; 12 (20%) compared to EOMG. Other studies had found EOMG showed more associations with AChR.[6]

The most common clinical presentation was of class 1 of MGFAC (Fig 3) and ptosis [13] constituted 80 % of presentation (Fig 4). In comparison between ocular and generalized MG, ocular was more common to generalized type, consistent with a previous study [14] ; 32 (53.3%) vs. 21(35%). Comparatively, ocular was also more common in LOMG [9] to EOMG; 16 (47%) vs 6 (23%) (Table1). Other reviews had suggested of the probability of MG missed in the older age group due to sagging facial muscles. [6,13] Total of 8 ocular MG at initial presentation had progressed to generalized MG; 5 (19.2%) EOMG vs. 3(8.8%) LOMG.

Our results showed, 40 (66.7%) of our MG patients had comorbidities (Table 1). This figure is lower compared to a study.[8] We found more comorbid conditions in the ocular MG to generalized;20 (62.5%) vs 15(53.6%).[4,8] Our comorbidities are more among the LOMG; 31 (51.7%) vs. EOMG; 9 (15%).[8] Only 2 deaths among our MG patients which are MGFAC class 1 and class 4 and following complications of multiple comorbidities. Myasthenia crisis also seen more in those with comorbid; 6 (10%) vs. those without comorbid; 2 (3.3%). Both are LOMG and have multiple comorbid.[8] In a review it was alluded having more comorbidities is related to comparative poorer outcome and also seen more in LOMG.[8] Our study did not show any association of comorbidities with worse outcome. The commonest comorbid in our study are hypertension and diabetes.[8] The presence of comorbidities especially in the LOMG can pose intricacy in the therapeutic management but with institution of appropriate treatment can contribute to the overall QoL [4,9].

All our Indian subjects experienced myasthenia crisis; 2(100%). This was seen among 2(6%) of Chinese and 6 (24%) of Malay population (Table 1).

Majority of our patients were treated with two or more immunosuppressant with favorable outcome (Table 1). [15] Our study compared the usage of 1 drug vs. 2 drugs in EOMG and LOMG; EOMG has more single drug usage; 9(37.5%) vs. LOMG 10 (27.8%). EOMG also has more 2 drug usage; EOMG 13(54.2%) vs LOMG 17(47.2%). Treatment with 2 immunosuppressant were most among the Malays; 16(64%); followed by 1(50%) among the Indians and least among the Chinese; 13(39.4%). Myasthenia crises was also seen more in those receiving two immunosuppressant vs.1 immunosuppressant; 6(10%) vs. 3 (5 %).

In our study, almost one third, (19) 31.7% had associated thyroid disease; 6 (10 %) EOMG vs. 13 (21.7%) LOMG. Out of 19 subjects with thyroid disease, 10 were on 2 immunosuppressant. Only 2 subjects died; both were LOMG, Chinese females and both did not have myasthenia crisis; 1 died of septicaemia; had multiple comorbid and was on 2 drug immunosuppressant; while the other was not on any drugs and devoid of myasthenia crisis, but died due to complications of advanced lung cancer. We found an association between our ocular MG and thyroid disease.[8] 11(18.3%) were ocular MG vs. 8 (13.3%) generalized MG.

The possible link between ocular MG and autoimmune disorder namely, thyroid and the susceptibility towards neuromuscular blockage in comparison to generalized MG was reviewed in other studies (Table 1). [8,16,17]

In our study, thymoma was seen in 11(18.3%) of our patients which was slightly higher than other studies [1,4,6] Thymoma was seen more in EOMG; 7(11.6%) vs. LOMG 4 (6.6%) but only 8 (13.3%) had thymectomy. The remaining 3 opted for conservative treatment. In other reviews it was more common in the LOMG. [6,7]

None of our patients had family history of MG.

Source of referrals were majority from government district hospitals and health centers; 38 (63.3%) vs. private hospitals and general practitioners; 22(36.7%). More EOMG; 9 (15%) vs. LOMG; 5 (8.3%) were employed at time of interview being of comparatively younger age.

The repetitive nerve stimulation carried out in 5 showed 3 were positive. All 3 were ocular MG with no myasthenia crisis; 2 of whom are EOMG. Only 1 subject with dysphagia tested negative for anti-muscle-specific tyrosine kinase.

In our study the different characteristics and the associations of EOMG vs LOMG were delineated. This cross-sectional study could not establish the causality of MG. This single center study could not be generalizable too.

More studies on the immunological aspect may lead to newer therapies and further understanding of Ocular MG. Further studies are also needed on the outcome of hospitalization comparing those with and without co morbid, the precipitating factors of myasthenia crises, drugs such as anti-hypertensive and statins and complications of MG as it will give a more comprehensive picture of the presentation of MG to Hospital Seberang Jaya.

3.1 Comparison of comorbidities and other characteristics in early onsets vs. late onset myasthenia gravis with (n=60)

Table 1 shows sample characteristics. The mean (SD) age of the sample in this study was 55(16.7) years, and the majority were aged between 16 to 81 years old. The mean (SD) age of EOMG was 31(11.5) and for LOMG 60 (6.8). The median duration of follow up of the patients at neurology clinic in 2016 is four years. LOMG was more common than EOMG; 34 (56%)) versus (vs.) 26 (43%). There were 2 new cases in our study; Both belong to EOMG. In comparison between ocular vs. generalized MG; generalized MG is seen more in EOMG;15 (57.7%). Ocular MG was seen more in LOMG;16 (47%). 8 ocular MG had progressed to generalized MG; EOMG 5(19.2%) vs. LOMG; 3 (8.8%).

Table 1: Comparison of comorbidities and other characteristics in early onsets vs. late onset myasthenia gravis with (n=60).

Characteristics	**EOMG (n=26)**	**LOMG (n=34)**	***P*** value [+]
AGE	Mean 42years; SD 13.5; minimum 16, maximum 66	Mean 67years; SD 7.3; minimum 53, maximum 81	
Age of onset	Mean 31years; SD 11.5; minimum 15, maximum 50	Mean 60years; SD 6.8, minimum 51, maximum 78	
Duration of follow up at HSJ	Median is 4 years; IQR (7.7)		
RACE			0.076
Chinese	10	23	
Malays	15	10	
Indians	1	1	
GENDER			0.181
Male	10	19	
Female	16	15	
Co Morbids			<0.001
	17	3	
	2	11	
	7	20*	
Thymectomy	4	4	0.683
Thymoma	7	4	0.133
Thyroid Disease	6	13	0.211
Myasthenic crisis	5	5	0.641
Anti AChR Antibody positive	12	22	0.150
Class of Mgfac			0.950
Class I	10	13	
Class II	1	1	
Class IIa	6	7	
Class IIb	5	9	
Class III	2	3	
Class IV	2	1	
Ocular	6 (23%)	16 (47%)	
Generalised	15 (57.7%)	15(44.1%)	

Ocular onset to Generalized	5 (19.2%)	3 (8.8%)	
Treatment			
IVIG	5	4	0.422
Plasmapheresis	2	2	0.781
Immunosuppressant (Mycophenolate Mofetil, Prednisolone, Azathioprine)			0.842
Nil (n=11)	4	7	
One drug (n=19)	9	10	
Two drugs (n=30)	13	17	

* 2 died due to comorbid are LOMG; + P value was computed using Chi-square test ;

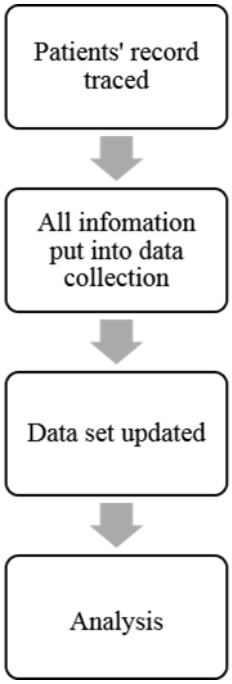


Fig. 1: Study Flow Chart.

3.2 Cases of MG by age grouped in decades.

In the gender distribution our results showed slight female preponderance 31 (51.7%) vs. 29 (48.3%) males (figure 2).

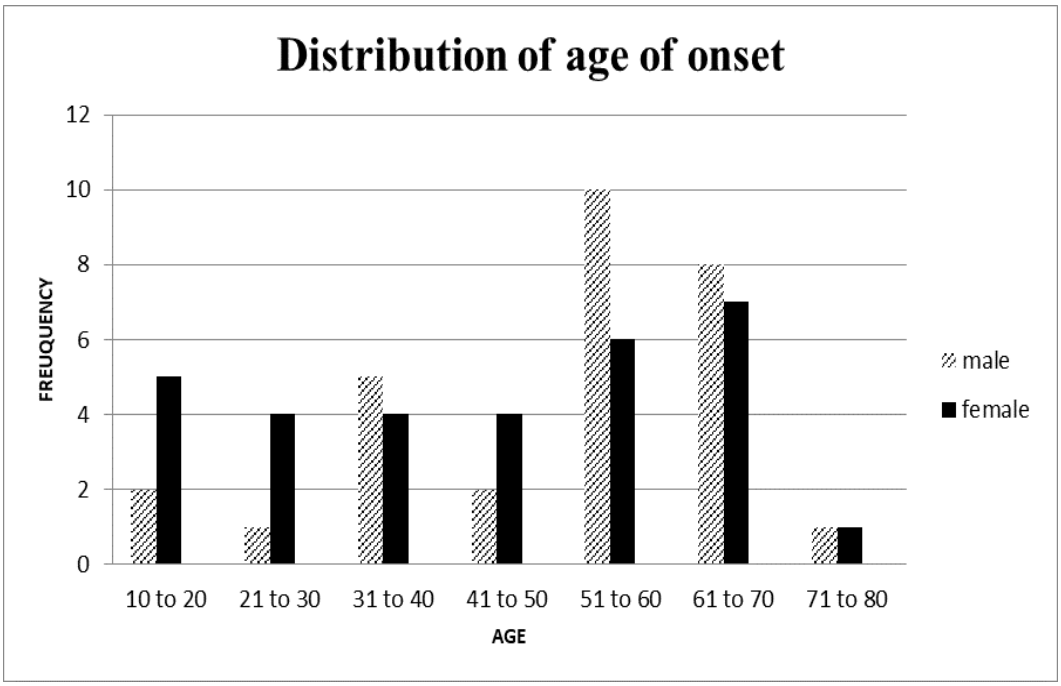
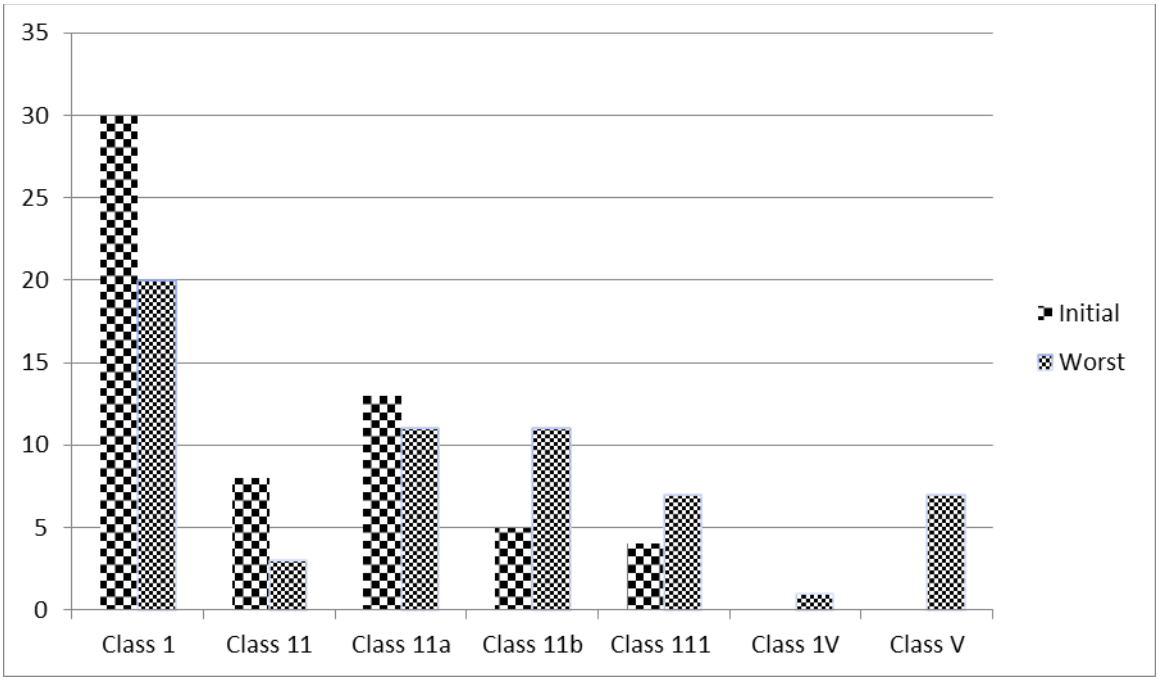


Fig. 2; Cases of MG by age grouped in decades.

3.3 Comparison of Initial and Worst presentation of Myasthenia Gravis Foundation of America Clinical Classification (MGFAC)

The MGFAC Classification shows Class I being the commonest at initial and worst presentation of MG patients; 30 (50 %) vs. 20 (33.3%). The least is Class 111 for initial presentation; 4 (6.7%) and worst presentation; Class IV; 1(1.7%) (Figure 3).

Fig. 3; Comparison of Initial and Worst presentation of Myasthenia Gravis Foundation of America Clinical Classification (MGFAC).



3.4 Clinical presentation of Myasthenia Gravis

Ptosis constitute 80% of clinical presentation in MG; 20(33.3%) from EOMG and 28(46.7 %) from LOMG (P = 0.600); followed by diplopia 38.3%; EOMG 10(16.7%) and LOMG 13 (21.7%) with *P* = 0.980 and Dysphagia 35%; EOMG 8(13.3%) and LOMG 13(21.7%) with *P* = 0.550 (Figure 4).

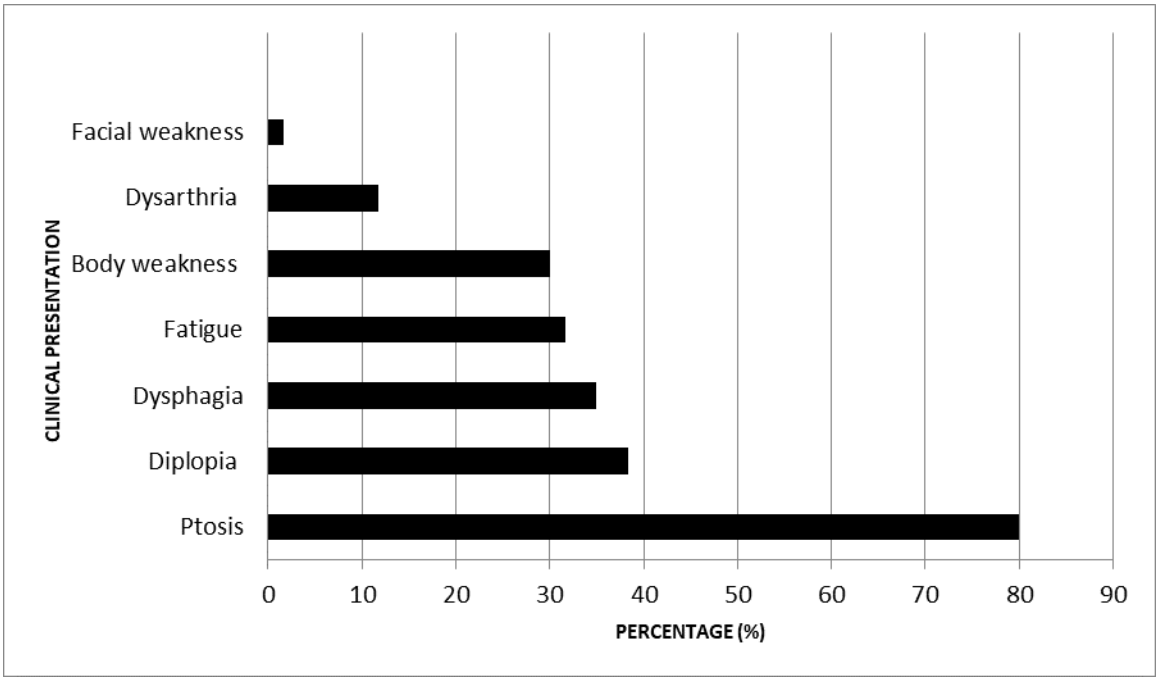


Fig. 4; Clinical presentation of Myasthenia Gravis.

4 Conclusion

Data from HSJ showed that most MG patients were females, Chinese and of Class 1 type MGFAC. LOMG was more common among the Chinese local population. Even though MG was seen more among the Chinese local population but myasthenia crises were least in them. Ptosis constituted the most common manifestation. Ocular MG was seen more in the LOMG. Our study also showed an association between ocular MG and thyroid disease. The usages of 1 and more immunosuppressant were seen more among EOMG. The usage of 2 immunosuppressants were the least among the Chinese too. More comorbids were

seen in the LOMG and our study did not show any association of comorbidities with worse outcome. The commonest comorbid were hypertension and diabetes. Understanding the characteristics in EOMG vs. LOMG will aid in clinical management, enable to screen, formulate strategies and improve QoL.

Instruments (Tools)

Subject ID: _____ Version 2

Data Collection Form: A cross sectional study on characteristics Of Adult Myastenia Gravis Patients in Hospital Seberang Jaya

Appendix

1. Demographics			
1.1 Case No:			
1.2 Age:		1.3 Race:	
1.4 Gender:	○ Male ○ Female		
1.5 Employment	○ Yes, please specify: ○ No ○ No information available ○ Retired		
1.6 Home address	○ Penang Island ○ Mainland- SPU/SPT/SPS ○ Others		
2. Clinical Presentation (At Onset)			
2.1 Date of onset:			
2.2 Age of onset			
2.3 Clinical symptoms	○ Fatigue ○ Ptosis Unilateral / bilateral ○ Double vision/diplopia ○ Dysarthria ○ Dysphagia ○ Body weakness ○ Facial weakness ○ Initial MG presentation ○ Worst MG presentation ○ Others: Please specify _____		
2.4 MG crisis (if any)	○ Date: ○ Type: Myasthenic / Cholinergic		
2.5 Thymoma present: 2.6 Thymectomy done:	○ Yes ○ No ○ Yes Findings: _____ ○ No		
3. Co- Morbid	○ Specify		
4. Diagnosis			
4.1 Date of Diagnosis			
4.2 Duration interval of presentation to diagnosis:			
4.3 Source of referral	○ Health Clinic ○ GP clinic ○ Hospital admission ○ Others: _____		
4.4 Pre-Diagnosis Management (If any):	○ Traditional/Complementary Medicine If yes, details: _____ ○ Other non-neurologist/ophthalmologist referral and investigations If yes, details: _____ ○ No		
4.5 Family History of similar disease	○ Yes Details: _____ ○ No		
4.6 Type	○ Ocular ○ Generalized ○ Ocular to generalized		
5. Diagnostic Investigation			
5.1. MRI Imaging of Brain ○ Yes, **DATE**: Details of report: ○ No			
5.2 Acetyl cholinesterase antibody ○ Yes			

○ No	
5.3 Anti MuSK antibody ○ Yes Details of report: ○ No	
5.4 Repetitive Nerve Stimulation test (RNS-EMG)	○ Yes ○ No
6.Diagnostic Criteria	
6.1 MGFA (Myasthenia Gravis Federation of America) ○ Yes *Type:* ○ No	
7. Differential Diagnosis (If ruled out; Thyroid, Motor Neuron Disease, Eaton Lambert)	
8.Treatment	
8.1 Medications / Procedures: (e.g statins, B blockers, pyridostigmine) 8.2 Immunosuppressant (Mycophenolate Mofetil, Prednisolone, Azathioprine) 8.3 Plasmapheresis: Yes No 8.4 IVIG: Yes No	
9. Outcome	
9.1 Alive ○ Follow up ○ Default - no. of times - possible cause(s)	9.2 Death ○ Date: ○ Cause of death:
9.3 Remission No remission- symptoms - No symptoms	9.4 Last observation compared to baseline & Other details

Financial interest: The authors declare they have no financial interest.

Abbreviation: Myasthenia Gravis (MG), HSJ (Hospital Seberang Jaya), vs. (Versus), SPT (Seberang Perai Tengah), EOMG (early onset myasthenia gravis), LOMG (Late onset myasthenia gravis), Acetyl Choline receptor (AChR), Not available (NA). Intravenous Immunoglobulins (IVIG), Myasthenia Gravis Foundation of America Clinical Classification (MGFAC). QoL (quality of life).

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