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Cognitive Function Characteristics in Patients with Myasthenia Gravis

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ABSTRACT

Introduction: Myasthenia gravis (MG) is one of the most common neuromuscular junction disorders with various clinical presentations. Several studies showed cognitive function decline in MG patients which affects cognitive domains in memory, attention, executive function, and verbal. The involvement of the central cholinergic system, known as central cholinergic deficits are thought to manifests as impaired cognitive function in patients with MG. The purpose of this study was to evaluate cognitive function characteristic in patients with myasthenia gravis.

Method: This study used a cross-sectional design, involved 33 myasthenia gravis patients in Neurology Outpatient Clinic of Haji Adam Malik Central General Hospital and 33 subjects in healthy control group. Cognitive function tests were performed using the Indonesia version of Montreal Cognitive Assessment (MoCA-Ina). Mann-whitney test was performed to evaluate cognitive performance difference in both groups.

Results: **:** The results were compared between MG and healthy control group. The mean of MoCA-Ina score was significantly lower in MG group compared to healthy control group. The result of this study showed difference in cognitive performance between MG patients and healthy control group ($p<0.001$). This study showed delayed memory, attention, verbal, abstraction, visuospatial and executive function performance was decline in MG patients.

Conclusion: This study concludes significant difference of cognitive performance based on MoCA-Ina scores between myasthenia gravis patients and healthy control group.

Keywords

Myasthenia gravis, Cognitive function, MoCA-Ina

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INTRODUCTION

Myasthenia gravis (MG) is the most common disorder affecting the neuromuscular junction of the skeletal muscle.[1] MG is an autoimmune disease with the classic presentation is fluctuating weakness involves muscles of the eyes, bulbar and proximal muscles.[1,2] Although it is predominantly muscular disease, cognitive impairment in patients with MG has been discussed in the literature.[3] Muscle weakness results from a reduced number of functional nicotinic acethylcoline receptors (nAChRs) at the neuromuscular junction. Some studies showed nAChRs are found in the central nervous system, as well as in the peripheral nervous system, particularly in the hippocampus, hypothalamus, mid brain and cerebral cortex. It has been established that the central colinergic system is important in mediating cognitive processes of learning and memory and it may explain the development of cognitive impairment in MG patients.[4] To date, the studies have produced contradictory results regarding the association between MG and cognitive function. This study aimed to evaluate the cognitive function characteristic in myasthenia gravis patients.

METHOD

This study was a decstriptive-analytic study with a cross-sectional data collection method. The research subjects were taken from myasthenia gravis patients population at Neurology Polyclinic Haji Adam Malik General Hospital and from healthy control group. The inclusion criteria for the present study were a definitive MG diagnosis, patients aged 18-65 years, compos mentis consciousness and cooperative, and agree to participate in the research. All subjects were free of any other neurological, physical or mental disease. A total of 33 patients were selected using a consecutive non-random sampling method and 33 subjects of healthy control subjects were selected using a purposive non-random sampling. The cognitive function was determined through the Indonesia version of Montreal Cognitive Assessment (MoCA-Ina) with a total score is 30. Cognitive impairment defined if the score < 26. Data of demographic, clinical and cognitive domain characteristics were analyzed using univariate descriptive test. Mann-Whitney test was used to evaluate the difference of MoCA-Ina scores between MG and control group.

RESULT

Of all myasthenia gravis patients in Neurology Outpatient Clinic at Haji Adam Malik General Hospital, 33 MG patients and 33 healthy control subjects met the inclusion criteria. MG and controls group were matched for age and education level. The majority of subjects from MG patients were female (69.7%) with a mean age of 42.2 ± 13.2 years, most of the respondents had a high school education level (48.5%), and came from Batak and Javanese ethnic group (36.4%) and most of research subjects married (81.8%). (Table 1).

Table 1. Description of demographic characteristics of research subjects

Demographic characteristics	MG (n = 33)	Control (n = 33)
Age (years), mean ± SD	42.2 ± 13.2	42.09 ± 13.2
Age group, n (%)		
20-30 years	8 (12.1)	8 (12.1)
31-40 years	7 (10.6)	8 (12.1)
41-50 years	7 (10.6)	5 (7.6)
51-60 years	8 (12.1)	9 (13.6)
61-70 years	3 (4.5)	3 (4.5)
Gender		
Male	10 (30.3)	7 (21.2)
Female	23 (69.7)	26 (78.8)
Education level		
Junior high school	2 (6.1)	2 (6.1)
Senior high school	16 (48.5)	16 (48.5)
College	15 (45.5)	15 (45.5)
Ethnic group		
Bataknese	12 (36.4)	8 (24.2)
Javanese	12 (36.4)	21 (63.6)
Melayu	2 (6.1)	1 (3)
Acehnese	3 (9.1)	1 (3)
Mandailing	2 (6.1)	-
Minang	-	2 (6.1)
Tionghoa	1 (3)	-
Nias	1 (3)	-
Marital status		
Married	27 (81.8)	26 (78.7)
Single	6 (18.2)	7 (21.2)

Note: MoCA-Ina: Montreal Cognitive Assessment Score-Indonesia version

The clinical characteristics from MG patiens are shown in Table 2. The majority of patients had early onset MG (69.7%) with mean of onset was 40.27 ± 12.6 years. Most of patients had piridostigmin monotherapy (75.8%), combination therapy of piridostigmin, azatiophrin and steroid (21.2%), piridostigmin and

azatiophrin (3%), with mean of therapy duration 26.06 ± 24.8 months, mean of MG composite score 5.69 ± 2.8. In this study we found only 1 patients (3%) had history of thymoma surgery.

Table 2. Description of clinical charasteristics of MG subjects

Clinical characteristics	n=33
Onset (years), mean ± SD	40.27 ± 12.6
Early onset, < 50 years, n (%)	23 (69.7)
Late onset, ≥ 50 years, n (%)	10 (30.3)
Duration of therapy (months)	26.06 ± 24.8
MG composite score	5.69 ± 2.8
Thymoma history, n (%)	1 (3)

The MoCA-Ina score characteristic are shown in Table 3. It was found the average of MoCA-Ina score was 24.18 ± 3.15 with median score was 25 (minimum 18-maximum 29). The score range lower than control group 27 ± 2.7 with median score was 28 (minimum 21-maximum 30). Mann-whitney test showed significant difference between MG and healthy control group ($p<0.001$).

Table 3. MoCA-Ina score characteristics between MG and control groups

Cognitive characteristics	MG	Control	P value
MoCA-Ina score			
Mean ± SD	24.18 ± 3.15	27 ± 2.7	< 0.001
Median (Min-Max)	25 (18-29)	28 (21-30)	

The description of cognitive domain characteristics are shown in Table 4. Based on cognitive domain characteristics, from the MG group found that 45.5% had decrease performance in the visuospatial and executive function, 9.1% naming, 21.2% immediate memory, 78.8% attention, 78.8% verbal, 81.8% abstraction, 90.9% delayed memory and 9.1% orientation. Whereas in the control group, 18.2% showed decrease performance in the visuospatial and executive function, 1 3% naming, 12.1% immediate memory, 42.4% attention, 39.4% verbal, 63.6% abstraction, 60.6% delayed memory and none of subjects with orientation deficit was found in control group.

Table 4. Cognitive domain characteristics between MG and control groups

Cognitive domain	MG		Control	
	Deficit n (%)	Normal n (%)	Deficit n (%)	Normal n (%)
Visuospatial	15 (45,5)	18 (54,5)	6 (18,2)	27 (81,8)
Naming	3 (9,1)	30 (90,9)	1 (3)	32 (97)
Immediate memory	7 (21,2)	26 (78,7)	4 (12,1)	29 (87,9)
Attention	26 (78,8)	7 (21,2)	14 (42,4)	19 (57,6)
Verbal	26 (78,8)	7 (21,2)	13 (39,4)	20 (60,6)
Abstraction	27 (81,8)	6 (18,2)	21 (63,6)	12 (36,4)
Delayed memory	30 (90,9)	3 (9,0)	20 (60,6)	13 (39,4)
Orientation	3 (9,1)	30 (90,9)	0 (0)	33 (100)

DISCUSSION

In this study all subjects from MG and control groups were matched for age and education. This study found that most of the MG patients were female with the largest age group of 20-30 years and 51-60 years. This result is in line with previous study that female gender mostly found in the age group of 20-40 years with a ratio of men and women of 1 : 3 and men gender mostly found in the age group above 50 years with a ratio of men and women 3 : 2.2 Bimodal distribution of MG incidence has been frequently described suggesting a hormonal or environmental influence on disease onset.5 Most education level in this study was tertiary level and high school that in line with previous study that the average length of formal education is 12-15 years in MG patients.[6]

The average MoCA-Ina score in the MG patients was 24.18 ± 3.15 with minimum score was 18 and maximum score was 29. Meanwhile in the control group the average score was 27.03 ± 2.78 with a minimum score was 21 and maximum score was 30. The mean of MoCA-Ina score was found to be lower in the MG patients than control group which is consistent with previous studies that the mean of MoCA score in MG patients was 22.38 with a minimum score was 10 and maximum score was 29.3 In the other studies the measurement of cognitive function using tools MMSE, SBST, WMS-R also showed a lower range average score in MG group than the control group.[6,7,8]

The early onset MG (EOMG) seems more frequently found in this study than late onset MG (LOMG) and EOMG more frequently among women than men, contrast with LOMG that more frequently among men, which is consistent with previous studies.[9,10] However, in this study only 1 patient was identified with thymoma with 49 years old and male gender which is in line with previous study where the incidence of thymoma increases at onset > 40 years and mostly found in male.[8]

Examination of cognitive function in this study used the MoCA-Ina instrument which included 8 cognitive domains namely visuospatial and executive function, naming, immediate recall, attention, language, abstraction, delayed recall and orientation. In this study, it was found most of research subjects had decrease cognitive domains: delayed recall (90.9%), abstraction (81.8%), attention (78.8%), verbal (78.8%), visuospatial and executive functions (45.5%), immediate recall (21.2%) and naming (9.1%). It was in line with previous study that about 60% MG patients complain of cognitive decline.[11] This result is in accordance with the results of previous studies that in MG group showed decrease cognitive performance after different types of cognitive examinations. This suggests the possibility of central involvement in MG. In addition, it was found that memory function and executive function were most impaired in MG patients. 6 In other studies, a decrease in memory and other cognitive functions was often reported in MG patients and showed significant deficits in the visuospatial domain, memory, verbal learning and spatial orientation.8,12 Other studies showed a decline in cognitive function in MG with cognitive domain that mainly affected was memory, attention, executive function and verbal abilities.[3,6,8]

Several mechanisms have been hypothesized as etiologies of cognitive impairment in MG patients. The central cholinergic deficiency due to the involvement of the central nicotinic Ach receptors (nAChRs) and central cholinergic pathways by the disease process of MG have been suggested as the high likely mechanism.[7] nAChRs are found in the central, as well as in the peripheral nervous systemm particularly in the hippocampus, hypothalamus, mid brain and cerebral cortex. It has been established that the central cholinergic system is important in mediating cognitive procecesses of learning and memory.[4] This assumption has led many studies to support the hypothesis of CNS cholinergic involvement in MG which suggests that MG has central cholinergic involvement in MG. In other studies showed that there are two potential ways in which MG might affect the CNS and thus cognition. Firstly, MG autoantibodies may have central cholinergic effects that result in cognitive dysfunction, especially memory function. The second mechanism is somatosensory deprivation that indicate the somatosensory-enriched environment and intensive training can enhance brain plasticity. The reduced physical activity in MG due to muscle weakness could result in less sensorimotor and affect brain plasticity negatively.[12] The existence of a central cholinergic deficit in MG is supported by the presence of nAChR antibodies found in serum and cerebrospinal fluid and the improvement in cognitive function after plasmapharesis was performed.[11] Other studies demonstrated that MG patients exhibited a decreased cholinergic activity, indicating that MG affects the cholinergic system that leads to reduced cognitive performance.[4]

Some studies did not exclude the possibility that cognitive function may have been affected by other aspects such as sleep apnea, depression and drug use.[4] Also, the pathophysiological and psychological characteristics may have important effects on the cognition of the patients with MG such as differences in antibody type, disease duration, treatment, anxiety and depression.[6] In this study, all of subject had been screened for depression using PHQ-9 questionnaire. Subjects with a tendency to depression based on PHQ-9 scores were excluded from this study.

This study concludes a significant difference of cognitive performance based on MoCA-Ina scores between myasthenia gravis and healthy control group. Most of MG patients had decreased performance on delayed memory, attention, verbal, abstraction and visuospatial and executive function. The further study is needed to analyze the association between myasthenia gravis and cognitive function that may explain the possibility of a central cholinergic deficit in MG.

CONCLUSION

This study concludes significant difference of cognitive performance based on MoCA-Ina scores between myasthenia gravis patients and healthy control group.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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