Original Article

Assessment of cognitive function in patients with myasthenia gravis

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ABSTRACT

Aim: During the past decade, there has been an increasing interest in the evaluation of cognitive function in myasthenia gravis (MG), neuromuscular transmission disorder caused by acetylcholine receptor auto-antibodies. However, the results of previous studies on cognition and MG are inconsistent and controversial. This study aimed to evaluate cognition in patients with mild/moderate grades of MG. **Methods:** This study included 20 patients with MG with a mean age of 28.45 ± 8.89 years and duration of illness of 3.52 ± 1.15 years. Cognition was tested using a sensitive battery of psychometric testing (Mini-mental State Examination [MMSE], Stanford-Binet Intelligence Scale 4th edition [SBIS] and Wechsler Memory Scale-Revised [WMS-R]) and by recording P300 component of event-related potentials (ERPs), a neurophysiological analog for cognitive function. **Results:** Compared with healthy subjects (n = 20), patients had lower total scores of cognitive testing (MMSE, SBIS and WMS-R) (P = 0.001), higher Beck Depression Inventory 2nd edition scores (P = 0.0001) and prolonged latencies (P = 0.01) and reduced amplitudes (P = 0.001) of P300 component of ERPs. Correlations were identified between total scores of cognitive testing and age (r = -0.470, P = 0.010), duration of illness (r = -0.788, P = 0.001) and depression scores (r = -0.323, P = 0.045). Using linear regression analysis and after controlling for age and depression scores, a significant correlation was identified between total scores of cognitive testing and duration of illness (β = -0.305, P = 0.045). **Conclusion:** Patients with mild/moderate MG may have cognitive dysfunction. This is important to determine prognosis and managing patients.

Key words: Cognition, myasthenia gravis, nicotinic acetylcholine receptors

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease caused mainly by auto-antibodies against skeletal muscle nicotinic acetylcholine receptors (nAChRs) at the postsynaptic membrane resulting in depletion of ACh at the neuromuscular junction.[1] MG is uncommon with a prevalence of (25-125)/10^6. The disease tends to affect women more often than men (3:2) in their second and third decades.[2] The cardinal symptoms of MG are fatigue and weakness of skeletal muscles with repeated or sustained exertion in the course of the day but improved by rest. Ocular muscles are initially involved in about 2/3 of patients then spread to the bulbar and limb muscles. Approximately, 85% of patients develop generalized weakness. Many patients progress from mild to severe disease, and if weakness of respiratory muscles becomes severe enough to require mechanical ventilation, the patient is said to be in crisis.[3] Spontaneous remissions are very rare and last for varying periods that mostly occur during the first 3 years of the disease.[4] In adults, the thymus gland is abnormal in up to 90% of people with MG with approximately 70% of them have thymic hyperplasia while 10-20% have benign thymic tumors or thymoma.[5] The currently used treatment modalities for MG include acetyl choline esterase inhibitors (AChE-Is) (as pyridostigmine),[6] immunopharmacologic drugs (as prednisone,[7] azathioprine,[8] cyclosporine,[9] mycophenolate mofetil,[10] cyclophosphamide,[11] tacrolimus[12] and rituximab[13]) plasmapharesis,[14] intravenous immunoglobulins (IVIGs)[15] and thymectomy.[16]

Access this article online	
Quick Response Code:	Website: www.nnjournal.net
	DOI: 10.4103/2347-8659.143671

Subjective impairments of memory and other cognitive functions are very frequent in patients with MG, however, previous studies, which investigated cognitive

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function in such patients showed contradictory results. Some reported memory difficulties and other cognitive dysfunction[17-21] and electroencephalographic (EEG) abnormalities.[22-24] In contrast, others reported lack of neuropsychological impairments, normal intelligence, attention, memory and motor performance with MG.[25-27]

The exact mechanisms of the co-morbid cognitive dysfunction in patients with MG are unknown. The most likely suggested mechanism is central cholinergic deficiency due to the involvement of central neuronal nAChRs and other cholinergic nervous systems and pathways by the immune-mediated processes of MG.[20,28-30] However, controversial views suggest that the co-morbid nervous system manifestations with MG may result from nonspecific mechanisms as complications of MG, which include respiratory impairment, sleep apnea and hypoxia,[31-33] mental fatigue,[26,27,34] adverse effects from medications used for treatment of MG and mood disorder.[35,36]

This study aimed to investigate cognitive function in adults with mild/moderate MG. Cognitive functions were assessed using a battery of sensitive psychometric testing in addition to recording event-related potentials (ERPs), a neurophysiological analog of cognitive function.

METHODS

Subjects

This study included 20 patients (males = 6, females = 14) diagnosed clinically and electrophysiologically as MG. Their age ranged from 16 to 50 years, and duration of illness ranged from 1 to 4 years. Clinical grading of the patients was done based on the medical, scientific advisory board of MG Foundation of America classification.[37] Patients grading was based on their histories and diagnoses shown in their medical records. Patients reported histories of weakness of ocular muscles (ptosis) (class I), of mild and predominant weakness of the limb muscles (class II a) or oropharyngeal muscles (class II b), or with moderate and predominant weakness of the limb muscles (class III a). Before the presentation, all patients were treated with AChE-Is (pyridostigmine bromide or mestinon in a dose of 60 mg/4 h during the daytime and 60 mg at night time), immunotherapy with prednisolone and/or azathioprine (imuran) or plasmapharesis. Thymectomies were performed to the seven patients with thymoma. Table 1 shows the demographic and clinical characteristics of the studied group. Patients were recruited from the Out-patient Clinic of the Department of Neurology, Assiut University Hospital, Assiut, Egypt during their follow-up visits in which they were free of clinical manifestations (i.e. after resolution of active stage of the disease for at least 3 months) and were on maintenance treatment with low doses of AChE-Is and/or steroids. Twenty healthy subjects matched for age, sex and socioeconomic status were included in this study for statistical comparisons. Control subjects were recruited from the general population. This study was accepted by the regional Ethical Committee. Detailed information on the study was given to all patients, and control subjects, and all gave their written consent to attend the study.

Table 1: Demographic, clinical and laboratory characteristics of the studied groups

Demographic and clinical characteristics	Patients (*n* = 20) (%)	Control subjects (*n* = 20) (%)	*P*
Male/female	4/16	10/10	-
Age (years)	16-50	20-50	-
	28.45 ± 8.89	30.22 ± 5.76	0.380
Duration of illness (years)	1-4	-	-
	3.52 ± 1.15		
Clinical grade			
I	0	-	-
IIa/IIb	2/10	-	-
IIIa/IIIb	8/0	-	-
IVa/IVb	0	-	-
V	0	-	-
Thymic pathology			
Normal	5 (25)	-	-
Hyperplasia	8 (40)	-	-
Thymoma	7 (35)	-	-
Previous treatment (single or combination of the followings)			
Acetyl choline esterase inhibitors	20 (100)	-	-
Prednisolone	20 (100)	-	-
Azathioprine	8 (40)	-	-
Plasmapharesis	9 (45)	-	-
Thymectomy	7 (25)	-	-

Data are expressed as range, mean ± SD, *n* (%). SD: standard deviation

We excluded subjects (patients and controls) with: (1) respiratory involvement or in crisis (i.e. severe stages of the disease); (2) history of other primary neurological (e.g. transient ischemic attacks, cerebrovascular stroke or epilepsy), psychiatric (e.g. major depression) or medical (e.g. diabetes mellitus) diseases which are known to affect cognition; (3) previous serious head injury; (4) any sensory or motor disorder that would preclude psychological testing (as blindness or deafness); and (5) regular treatment with medications (other than those used for treatment of MG) which may alter cognitive testing (e.g. as benzodiazepines, beta-adrenoceptor antagonists, major tranquillizers and antidepressants).

Electroencephalographic recording

Electroencephalographic was done using the eight channels Nihon Kohden machine (4217), employing scalp electrodes placed according to the international 10-20 system with bipolar and referential montages.

Table 2: Comparison between patients and controls in scores of cognitive functions and depression

Variable	Patients (n = 20)	Controls (n = 20)	P
MMSE	23.25 ± 2.35	27.56 ± 1.45	0.036
SBST			
Vocabulary	36.33 ± 5.45	50.45 ± 3.88	0.042
Comprehension	35.46 ± 9.07	49.76 ± 7.56	0.007
Total verbal reasoning score	75.32 ± 8.85	96.82 ± 16.25	0.0001
Visual reasoning	36.63 ± 4.64	48.68 ± 5.04	0.0001
Total visual reasoning score	68.43 ± 8.09	88.33 ± 14.70	0.0001
Quantitative test	36.57 ± 6.54	45.30 ± 5.43	0.0001
Total quantitative reasoning score	75.53 ± 8.67	96.65 ± 9.57	0.0001
Bead memory	45.30 ± 7.28	60.50 ± 10.08	0.0001
Memory for sentences	44.72 ± 6.34	65.56 ± 8.57	0.0001
Total score for short-term memory	85.65 ± 9.66	150.25 ± 25.26	0.0001
Total score of SBST	289.56 ± 55.48	360.34 ± 50.04	0.0001
IQ	78.53 ± 6.46	95.35 ± 8.73	0.0001
WMS-R			
Digit forward	4.56 ± 1.01	6.64 ± 0.88	0.035
Digit backward	2.23 ± 0.25	5.58 ± 0.45	0.010
Mental control	3.57 ± 1.45	5.89 ± 1.06	0.042
Logical memory	10.65 ± 1.30	14.83 ± 2.45	0.007
Associate learning	8.52 ± 2.04	12.06 ± 2.24	0.005
Total scores of cognitive testing (MMSE, SBST and WMS-R)	76.54 ± 8.35	96.54 ± 6.28	0.0001
Depression scores	20.64 ± 6.24	8.65 ± 3.55	0.0001

Data are expressed as mean ± SD. SBST: stanford Binet subtests testing, MMSE: mini-mental state examination, WMS-R: wechsler memory scale-revised, SD: standard deviation, IQ: intelligence quotient

Table 3: Comparison between patients and controls in event-related potentials

Variable	Patients (n = 20)	Controls (n = 20)	P
P_{300} latency (ms)			
Right sided	250.00-450.00	285.00-353.00	-
	350.80 ± 35.88	320.88 ± 25.75	0.010
Left sided	270.00-450.00	250.00-350.00	-
	355.60 ± 33.08	325.45 ± 20.45	0.010
P_{300} amplitude (mv)			
Right sided	2.20-20.25	6.88-20.54	-
	7.55 ± 2.45	12.45 ± 2.84	0.001
Left sided	2.55-18.09	6.80-22.25	-
	6.67 ± 3.23	12.63 ± 2.56	0.001

Data are expressed as range, mean ± SD. SD: standard deviation

Table 4: Pearson's correlation (r and P value) between total scores of cognitive testing and clinical variables, lab variables, depression scores and ERPs variables

Variables	Total scores of cognitive testing (MMSE, SBST and WMS-R)	
	r	P
P_{300} latency	-0.650	0.001
P_{300} amplitude	0.557	0.001
Age	-0.470	0.010
Duration of illness	-0.788	0.0001
Depression scores	-0.323	0.045

ERPs: event-related potentials, MMSE: mini-mental state examination, SBST: stanford Binet subtests testing, WMS-R: wechsler memory scale-revised

total scores of cognitive testing (MMSE, SBIS and WMS-R) and duration of illness (β = -0.305, P = 0.045).

DISCUSSION

The results of this study indicate that patients with mild/moderate MG may experience significant manifestations of cognitive impairment in the absence of disease activity and despite the short duration of illness. Patients with MG may experience poor performance in different cognitive tasks indicating central or brain involvement. These included deficits in verbal relations, comprehension, visual reasoning, pattern analysis, quantitation, bead memory, short-term memory and memory for sentences, digit forward, digit backward, mental control, logical memory, and associate learning. In the agreement with our findings, patients with MG commonly reported subjective cognitive complaints. In patients with MG, several previous studies reported memory difficulties[17,18] and impaired performance on varieties of cognitive tests as MMSE and memory tests,[19] the Boston Naming Test, the Logical Memory and Design Reproduction portions of the WMS, Rey Auditory Verbal Learning Test,[17] and measures of response fluency, information processing and verbal and visual learning.[20,21,47] In additions, the detected abnormalities in P300 component of ERPs also suggest the central or brain involvement in MG. In fact, abnormal evoked potential responses were noted in patients with MG.[48-50] In contrast, several studies reported normal IQ, memory, attention and motor performance and normal ERPs in MG.[25-27] We believe that such discrepancies could be explained by differences in methodologies, small sample size, different lists of inclusion and exclusion criteria and lack of control for potential confounding variables.

Several mechanisms have been hypothesized as etiologies of cognitive impairment in patients with MG. The central cholinergic deficiency due to the involvement of the central nAChRs and central cholinergic pathways by the disease process of MG have been suggested as the high likely mechanisms.[20,28-30] This hypothesis is based on the fact that there are structural identities between different muscle and neuronal nAChRs subunits with the possibility of cross-reactivity between different nAChRs antibodies.[51-53] The hippocampus, a cerebral structure highly involved in learning and memory, has abundant cholinergic innervation and enriched in nAChRs that modulate synaptic plasticity via mechanisms involved in long-term potentiation.[54] Few suggested that cognitive dysfunction co-morbidity may be due to the immune responses driven by muscle and neuronal nAChRs antibodies expressed by cancer (e.g. thymoma) (i.e. paraneoplastic syndrome).[55,56] Others suggested that it might be a nonspecific autoimmune response in presence or absence of tumor.[57] This it further supported by an association of MG with other nonnervous system medical

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Cite this article as: Hamed SA, Youssef AH, Abd ElHameed MA, Mohamed MF, Elattar AM. Assessment of cognitive function in patients with myasthenia gravis. Neuroimmunol Neuroinflammation 2014;1(3):141-6.

Source of Support: Nil. **Conflict of Interest:** No.

Received: *14-07-2014*; **Accepted:** *25-08-2014*