Neurology Asia 2006; 11 : 97 – 102

Cognitive evaluation in myasthenia gravis: A P300 and neuropsychological study

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Abstract

Background: Associations between myasthenia gravis (MG) and central nervous system functions have been made for over 80 years, with an increased incidence of sleep and memory disturbance, psychiatric abnormalities, abnormal evoked responses, epilepsy and EEG abnormalities been described, attributed to central cholinergic dysfunction. *Objectives:* To evaluate cognitive dysfunction in patients of MG using various neurophysiology and neuropsychological measurements. *Methods:* Forty patients of myasthenia gravis and 40 age an gender matched controls were evaluated using a P300 and Mini Mental State Examination. In addition all patients were also evaluated with the AIIMS Comprehensive Neuropsychological battery in Hindi (Adult Form). *Results:* No significant difference was found in the P300 latencies and amplitude at Fz, Cz and Pz between patients and controls. However significant impairment in memory (75%) and intellectual processes (68.5%) was found in the patients as compared to normal population.

In *conclusion*, abnormalities were detected in bilateral frontal and temporal lobe functions in patients with MG, unrelated to disease duration and severity thus implicating central nervous system involvement in MG.

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disorder that involves antibody mediated destruction of nicotinic cholinergic receptors. The typical clinical presentation of MG is associated with the prominent role of nicotinic receptors at the motor end plate of striated muscles. The commonest presentation is fatigable weakness of voluntary muscles. However about 60% of patients complain of cognitive difficulties.[1] Several studies have identified central nervous system abnormalities in MG, with abnormalities in both verbal and non-verbal memory[2-5] in MG patients. These have been attributed to dysfunction of central nicotinic receptor systems, though there is limited evidence that central cholinergic receptors are affected.[6]

P300, first described by Sutton *et al*[7] is an endogenous or event related potential, that can be recorded in response to an external stimulus or event. P300 is a composite of the activity arising from different brain generators.[8] A number of studies with intracranial and scalp electrodes have suggested importance of medial temporal lobe structures[9,10] (hippocampus, parahippocampal gyrus and amygdala), posterior and superior parietal cortices[1,12], parietooccipital cortex[13], inferior parietal lobule[14], marginal gyrus[15], sulcus temporalis superior[9,10] and posterior cingulate gyrus[10] as being generators of P300. Also integrity of temporoparietal junction is necessary for P300 generation as reduced amplitudes were found in patients with temporoparietal lesions.[16] In addition cortical EEG also contributes to variability in P300.[17] P300 has found an important utility in providing diagnostic and prognostic information in differentiating between cortical and subcortical dementia[18], pseudodementia and dementia[19] early dementia and normal subjects and study of psychiatric disorders like alcoholism, depression and schizophrenia.[20-22] In a study from India, prolongation of P300 latency was found in patients with sub clinical hepatic encephalopathy as compared to age matched controls thus making it a useful screening test for cognitive dysfunction in this subgroup of patients.[23]

Since its introduction in 1975 the Mini Mental State Examination (MMSE) has become a widely used method both in clinical settings and research.[24] It is a brief standardized method assessing orientation, attention, short-term recall,

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language and the ability to follow simple verbal and written commands. The 160 item AIIMS Comprehensive Neuropsychological battery in Hindi (Adult Form)[25], based upon Luria's functional approach is a useful investigatory procedure in the detection, lateralization and localization of discrete brain lesions typically seen in the neurological settings.

The aim of the present study was to evaluate cognitive function in patients with MG using P300[7], MMSE[24] and Intellectual Processes Scale plus Memory Scale of the AIIMS Comprehensive Neuropsychological Battery in Hindi (Adult form).[25]

METHODS

Forty patients of MG of all stages attending Neurology outpatient departments and admitted in neurology wards between June 2000 to June 2002 were enrolled Inclusion criteria: those above 14 years of age with fatigable weakness of voluntary muscles, a positive Tensilon or Neostigmine test, and a positive decremental response, (patients included even if decrement was not significant if the first two criteria were present), and a minimum of three years of formal schooling.

Patients with evidence of cognitive dysfunction, those with a past history of head injury, and history of alcohol or drug abuse and a psychiatric disorder were excluded. A predesigned proforma about demographic and clinical details was filled for each patient. All patients were evaluated with an MMSE, P300 and IPS plus MS of the AIIMS Comprehensive Neuropsychological Battery in Hindi. Forty healthy age and gender matched attendants of patients with a minimum of 3 years of formal schooling, without any history of cognitive impairment, past history of head injury, alcohol or substance abuse, psychiatric disorder were evaluated with MMSE and P300.

P300

This was conducted using the auditory oddball paradigm in which the subject was presented with a sequence of two distinguishable stimuli, one of which is the frequent stimulus and the other rare stimuli as per standardized techniques of the IFCN guidelines[26] in both patients and controls. Active electrodes were placed over Fz, Cz, and Pz, of the international 10/20 system referenced to bilateral mastoids. A High filter setting of 50 Hz, Low filter setting 0.1Hz, sensitivity of 50μV, time of 1 second was maintained during recording. Presentation of frequent (~80%) tones at 65 db, 1000Hz, 50 ms duration, 10 ms rise and fall time with randomly interspersed rare (~20%) tones at 65 db, 1000Hz, 50 ms duration, 10 ms rise and fall was done. The interstimulus interval was 1500 ms. Patient was mentally asked to count number of rare tones. Cerebral responses to rare and frequent stimuli were recorded and averaged separately. The response to frequent stimulus consists of stimulus related potentials. The first discernable peak in response to the rare auditory stimulus consists of a negative (N1) peak with a frontocentral maximum for both rare and frequent tones. For the targets this is followed by a second negative peak (N2) around 250 ms and a positive peak (P3) peaking between 300 and 370 ms. P3 is maximum at Cz and Pz. In case of a double peak in the P3 range with the first peak P3a showing a more frontal maximum than P3b, the latter was taken. Amplitudes and latency of P300 was averaged and recorded at each site for the rare tones. Recordings were done in a quiet isolated room, under relaxed conditions, in both patients (4.88 ±5.77) after last dose of choline esterase inhibitors and controls.

AIIMS Comprehensive Neuropsychological battery in Hindi (Adult Form)[25]

The memory scale and intellectual processing scale of the above mentioned battery was administered to the patient. There were 12 items in the memory scale and 14 items in the intellectual processing scale. Each item was rated on a 5 point score with 0 being given for all correct answers and 4 for all incorrect responses. Ratings of 1, 2 and 3 suggest intermediate performance. Maximum score for memory scale was 48 and for IPS for 56. Ratings on items with both scales were summed up and a raw score for that scale was generated. Raw scores were converted into T scores, which were developed using means and SD of the scores yielded by a group of normal controls (N=175). Variables like age and education can alter performance in this battery, hence both these variables were considered. An expected T-score using regression analysis was evolved using a population of 175 normal controls. If the T score was more than expected T score the performance was considered abnormal.

MMSE[24] was done in both patients and controls.

Statistical methods

Mean ± SD for P300 latency and amplitude at each site (Fz, Pz and Cz) and for MMSE

was calculated, for both patients and controls. Results were compared using paired t test with a p value of < 0.05 considered as significant. Total number of patients with impairment in memory and intellectual processes as compared to normal population was calculated as a percentage. Since sample size was small, a subgroup analysis was done, using chi square test with Yate's correction, in which the patients were divided into 2 groups: those with a duration of less than 5 years and in stages I and IIA and, those with duration more than 5 years, and in stages IIB and III to evaluate whether duration and staging was associated with impaired neuropsychological performance.

RESULTS

A total of 40 patients were evaluated. Mean age of patients was 38.6 ± 16.5, with 30 males and 10 females. Less than six years of formal school education was present in 4, between 6 to 12 years in 23 patients, while 9 patients had more than 12 years of education. For the severity of MG, 5 patients were in stage I, 20 patients in stage II-A, 7 patients in stage II-B, 8 in stage III and none in stage IV. Disease duration was < 2 years in 30 patients, between 2-5 years in 6 patients and more 5 years in 4 patients. Tensilon and or neostigmine was positive in all patients (100%), with a positive decrement being observed in 30 patients only (75%). A total of twenty patients had undergone thymectomy, 3 had histopathological evidence of thymoma, and 17 patients had thymic follicular hyperplasia.

There were 40 controls. Mean age was 38.2 ±16.8. Males were 29 and females were 11 in number. Less than 6 years formal school education was present in 3 patients, between 6 to 12 years in 20 patients and more than 12 years in 17 patients.

For P300 latency and amplitude, the mean ±SD value at all 3 sites did not reveal any significant difference between patients and controls. For MMSE, there was also no significant difference between patients and controls. The results are shown in the Table 1.

For AIIMS Comprehensive Neuropsychological battery in Hindi (Adult Form), the raw scores, T-scores and expected T scores are shown in Table 2. Memory impairment was seen in 75% and intellectual processes impairment was seen in 68% patients. In a sub group analysis disease duration and staging did not have any correlation with neuropsychological impairment.

DISCUSSION

The present study revealed significant impairment in memory and intellectual processes in 75% and 67.5% patients of MG as compared to normal population, while no significant difference was found for P300 latency and amplitude, and MMSE when compared to controls. This neuropsychological impairment was not related to disease duration and severity.

Associations between MG and central nervous system functions have been made for over 80 years. In increased incidence of psychiatric disorders, epilepsy, EEG abnormalities, abnormal evoked responses, sleep and memory disturbances have been noted in patients with MG in several studies.[2-5,27-32] The inference of many of these studies has been that central cholinergic dysfunction in MG was caused either by anticholinbesterases used to treat MG or by antibodies to muscle nAchRs present in the serum and cerebrospinal fluid of MG

Table 1: P300 and MMSE in patients and controls

	Patient (n=40) Mean (SD)	Control (n=40) Mean (SD)	P Value
Fz latency (ms)	329.0 (36.2)	331.3 (26.2)	0.74
Cz latency (ms)	327.0 (33.2)	329.3 (29.1)	0.73
Pz latency (ms)	335.8 (35.4)	334.0 (27.7)	0.81
Fz amplitude (μV)	10.6 (6.7)	12.5 (7.0)	0.23
Cz amplitude (μV)	11.0 (5.2)	13.2 (7.4)	0.16
Pz amplitude (μV)	10.8 (6.3)	11.8 (6.5)	0.48
MMSE	28.6 (2.2)	29.3 (1.0)	0.08

Table 2: Memory scale and intellectual processing scale in AIIMS Comprehensive Neuropsychological battery in Hindi[25] in patients with myasthenia gravis

	Age (years)	Educations (years)	MS RS	MS TS	MS ETS	IPS RS	IPS TS	IPS ETS
1	15	9	9	47	69.6	18	55	72.7
2	16	10	27	73*	69.1	33	72*	71.9
3	17	14	8	46	66.3	5	40	68.3
4	18	10	25	70*	69.5	34	73*	71.9
5	19	8	26	72*	71.2	35	75*	73.7
6	19	12	28	75*	68.2	32	71*	70.1
7	22	12	26	72*	68.7	32	71*	70.1
8	22	10	30	78*	70.2	34	73*	71.9
9	24	12	26	72*	69.6	35	75*	70.2
10	25	10	31	79*	70.7	33	73*	72.0
11	26	10	27	73*	70.9	37	77*	72.0
12	27	12	35	85*	69.6	36	76*	70.2
13	27	10	29	76*	71.1	33	72*	72.0
14	28	17	19	62	66.0	12	48	65.7
15	30	3	36	86*	76.8	43	84*	78.3
16	31	17	7	44	66.5	8	44	65.7
17	35	4	37	88*	77.0	50	92*	77.5
18	35	9	28	75*	73.2	42	83*	73.0
19	35	10	27	73*	72.4	34	73*	72.1
20	36	15	18	54	68.9	14	51	67.6
21	38	11	32	80*	72.2	34	73*	71.2
22	40	8	35	85*	74.8	35	75*	73.9
23	41	5	37	88*	7.3	40	80*	76.6
24	42	8	30	78*	75.2	37	77*	73.9
25	47	15	26	72*	70.8	29	68*	67.7
26	49	5	2	37	71.1	8	44	67.7
27	50	17	18	59	69.8	8	44	65.9
28	55	3	48	104*	81.2	56	99*	81.3
29	60	10	30	78*	76.8	35	75*	72.3
30	60	12	29	76*	75.3	33	72*	70.5
31	60	17	26	72*	71.5	21	59	66.1
32	60	12	32	80*	75.3	33	72*	70.5
33	65	10	37	88*	7.7	45	86*	72.4
34	71	7	36	86*	81.0	40	80*	75.2
35	22	15	23	67*	66.4	4	39	67.4
36	62	12	29	76*	75.6	9	45	70.6
37	42	17	7	44	68.4	4	39	65.9
38	53	17	4	40	70.3	5	40	66.0
39	66	12	36	86*	76.3	32	71*	70.6
40	55	17	19	47	70.7	0	35	66.0

MS = memory scale, IPS=intellectual processes scale
RS. = Raw Score, TS = T Score, ETS = Expected T score.
* indicates significant impairment in performance.

patients.[33] Nearly 60% patients of MG complain of cognitive difficulty[1], but there are few controlled studies with inconsistent results. Deficits in both verbal and nonverbal memory have been noted as compared to controls in few studies, with cognition improving with plasmapheresis suggesting that circulating antibodies to nicotinic receptors might cognitive dysfunction in MG.[4,34]

The Memory Scale assesses function of both the right and left temporal lobes, while the Intellectual Processes Scale assesses mainly the right and left frontal lobe functions. Thus significant impairment in frontal and temporal lobe function was seen in our study which was unrelated to disease duration and severity, thus this battery is sensitive and is able to detect focal cognitive impairment. The MMSE which is a widely used screening test for simple rapid assessment of cognitive impairment[24] assesses mainly orientation and language and can be totally normal in patients with right hemisphere and frontal lobe damage. Also an abnormal score does not differentiate focal from diffuse cerebral abnormality. Thus it is a useful screening tool for cognitive impairment with sensitivity of 70% and specificity of 60%[35], but is not a diagnostic test for dementia. Also out of the impaired domains detected by the neuropsychological battery only the left temporal is assessed partly by MMSE, while the frontal and right temporal are not assessed by it.

It is well established that increases in P300 amplitudes and sometimes reductions in amplitudes can accompany dementing disorders.[36] Any brain disorder that affects the primary cognitive operations of attention allocation and immediate memory will affect latency and amplitude of P300. As P300 has multiple generators, the clinical utility is essentially restricted to a general measurement of cognitive efficiency, that is how well a person's central nervous system can process and incorporate incoming information. Sensitivities ranging from 13% to 83% for P300 latency prolongation have been reported in various studies for detection of dementia.[19,37] Possible explanations for this variability being the way in which the subject responds to target stimuli (counting or showing), with the former method being more sensitive.[38] Possible explanations for absence of any abnormality in P300 in this study is that it may not be sensitive enough to detect impairment in the areas found to be abnormal by neuropsychological examination.

In conclusion, results from the current study indicate impaired performance in the memory and intellectual processes scale, unrelated to disease duration and severity in patients MG as compared to normal population with no abnormalities detected on MMSE and P300 performance. The etiology of these cognitive disorders remains unresolved, but fatigue, apnea, and indirect immune processes represent important areas of future research.

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