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Diurnal cognitive functioning in patients with myasthenia gravis with the role of chronotype and depression: a pilot study

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Abstract

Purpose: Myasthenia gravis (MG) is an autoimmune disease manifested by fatigue and weakness of the skeletal muscles. Recent research has indicated that MG patients perform significantly worse than healthy controls in cognitive domains such as attention, verbal fluency, visual learning, and memory. This study aimed to investigate the diurnal fluctuations in cognitive performance in patients with myasthenia gravis in relation to selected clinical and socioeconomic parameters of the disease course, along with the role of chronotype and depression.

Methods: The participants were recruited from a neurology outpatient clinic. Patients' cognitive functions were assessed twice: in the morning and the evening of the same day. Neuropsychological diagnosis included attention, memory, executive, verbal, and visuospatial abilities. Mood was measured with the Beck Depression Inventory-II and Positive and Negative Affect Schedule. The Morningness-Eveningness Questionnaire was used to examine chronotype.

Results: The analyses performed showed no significant differences between subjects and within subjects, apart from semantic fluency. Patients receiving antidepressant treatment obtained better results on attention and working memory tasks.

Conclusions: The data obtained show that diurnal neuropsychological performance in MG patients is associated with depression. Routine assessment and treatment of mood disorders could significantly improve cognitive functioning in myasthenia gravis patients.

Key words: myasthenia gravis, cognition, chronotype, depression, circadian rhythm.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease manifested by fatigue and weakness of the skeletal muscles. Its core clinical feature is a fluctuating and fatigable weakness that worsens throughout the day and improves with rest, generally worsening in the evening [1]. MG patients often suffer from nonmotor symptoms, such as headaches, sleep disorders, and cognitive and psychological deficits [2]. Recent research has indicated that MG patients seem to perform significantly worse than healthy controls in cognitive domains such as attention, verbal fluency, visual learning, and memory [3-5]. A meta-analysis, conducted in 2021 by Zhou *et al.* [2], which involved 274 patients and 211 healthy participants, showed that memory functioning is the most common cognitive impairment reported, especially in immediate and delayed recall tasks. Mental processes, including cognition, are significantly associated with circadian rhythms and chronotypes, understood as a phenotype of circadian cycles determined by an endogenous biological clock. Individuals can be classified as having morning/early (ECT), evening/late (LCT), or neutral/intermediate chronotype (ICT) [6] which connects to spontaneous awakening, bedtime and morning wake-up hours, or perceived optimal time of day for well-being and performance. Cognitive functions also tend to be, in general, more efficient at the preferred circadian time compared to the non-favored time of the day [7]. In addition, many MG patients suffer from depression [8], which may affect

their cognitive functioning [9]. Depressive symptoms also show daily fluctuations, with a greater severity in the morning and gradual improvement throughout the day [10], which is opposite to the core MG symptoms.

Although it has been stated that MG patients suffer from cognitive dysfunction, no studies have investigated the role of chronotype and time of day in their cognition. Furthermore, the available studies are based on limited data on the relationship between MG severity or exacerbations and cognitive performance [11]. This study aimed to assess diurnal cognitive performance in patients with myasthenia gravis in the context of selected clinical and socioeconomic parameters of the disease course, along with the role of chronotype and depression.

METHODS

MG patients were recruited from the *Sanitas* Neurology Outpatient Clinic, Bydgoszcz, Poland. The agreement of the Bioethics Committee was obtained. The inclusion criteria involved participants with MG, diagnosed on the basis of clinical presentation (fluctuating weakness of ocular and/or extraocular muscles) and at least one of the following: positive test for acetylcholine receptor or muscle-specific kinase (MuSK) autoantibodies, repetitive stimulation and/or single-fiber electromyography studies confirming postsynaptic neuromuscular junction dysfunction, and clinical improvement after cholinesterase inhibitors. In terms of the disease type, ocular MG (involving only ocular muscle involvement) and generalized MG (confirmed involvement of extraocular muscles) were distinguished [12, 13].

The following tools were used: (1) the Beck Depression Inventory II (BDI-II), to assess the severity of symptoms of depression (with scores exceeding 13 indicating depression) [14]; (2) the Positive and Negative Affect Schedule (PANAS), to examine current emotional states and stable affective characteristics [15]; (3) the Morningness-Eveningness Questionnaire, to assess chronotype [16]; (4) the Rey Auditory Verbal Learning Test (RAVLT), to measure the ability to learn verbal material, and long-term memory learning of new information [17]; (5) forward and backward versions of the Digit Span Test (DST), to assess attention, short-term and working memory [18]; (6) Addenbrooke's Cognitive Examination III (ACE-III), which is a screening tool composed of attention, orientation, memory, language, visual perceptual, and visuospatial skills subscales (with scores lower than 88 indicating cognitive impairment), to provide a comprehensive assessment of general cognitive performance [19]; (7) the Paced Auditory Serial Addition Test (PASAT), to examine auditory information processing speed, flexibility, and sustained and divided attention [20]; (8) the Serial Subtractions Task (SST), to test the speed and flexibility of auditory information processing, attention, and counting [21]; and (9) semantic and phonemic versions of the Verbal Fluency Test (VFT), to examine verbal and executive functions in the search strategy of the semantic memory [22].

The participants were tested for cognitive performance twice: in the morning (8.00 a.m.) and the evening (8.00 p.m.) on the same day, with the set of parallel versions of the cognitive measures in random order. The assessment of mood and chronotype was carried out during a separate meeting. The total testing procedure took approximately 45 minutes each time. Participants were included in the study if they had a confirmed diagnosis of MG and provided informed, voluntary consent. Those with an illness duration of less than 6 months were excluded. Participants could be withdrawn from the study in cases of significant health deterioration or a personal decision to do so.

Statistical analysis

The Shapiro-Wilk test for normality and Levene's test for homogeneity of variance were performed on each variable. The Mauchly sphericity tests were not performed as there were only two time points of measurement. A two-way mixed model repeated measures analysis of variance (ANOVA) was performed to compare the results of cognitive performance between ECT and ICT chronotypes and selected medical variables (thymectomy, use of corticosteroids, duration of the disease, and antidepressant treatment) (2 × 2). The SPSSv26 software was used to perform the statistical analyses.

RESULTS

The study included 33 patients (31 females, 2 males) with MG aged 24-70 years. Table 1 presents the demographic and clinical data of the participants, including type of MG, severity of the disease at the time of the test, type of treatment received, mood disorder treatment, and chronotype. It is worth noting that 18 patients had no antibodies targeting the postsynaptic membrane molecules of the neuro-muscular junction.

None of the analyses conducted showed any significant differences between-subjects and within-subjects effects ($p > 0.05$), apart from that on semantic verbal fluency ($F(1) = 10.445$; $p = 0.009$, $\eta^2 = 0.511$; *Power* = 0.829). For this test, individuals with ICT showed better performance in the morning compared to the evening; in contrast, participants with morning chronotype tended to perform better in the evening. Furthermore, patients receiving antidepressant treatment obtained better results in the evening in PASAT ($U = 61.00$; $Z = -2.604$; $p = 0.009$) and backward DST ($U = 69.00$; $Z = -2.313$; $p = 0.021$) compared to patients who did not receive such treatment. No differences in cognitive functioning

were found between the chronotypes of MG when subgrouped according to thymectomy, use of corticosteroids, and disease duration ($p > 0.05$).

DISCUSSION

The results show that overall chronotype did not affect cognitive performance in patients diagnosed with MG. Furthermore, there were no differences in general cognitive performance in the morning and evening. Recent research has indicated that neuropsychological dysfunctions in MG patients may be associated with perceived fatigue, respiratory impairment, sleep apnea, hypoxia, and adverse effects of the treatment that are known to be more severe during the evening [2, 11, 23]. Neuroendocrinology processes are deeply involved in circadian and homeostatic systems [24], thus chronotype is assumed to affect the cognition in MG, with worse results in the evening, especially in ECT individuals. It can be hypothesized that proper MG treatment plays a protective role in the deterioration of functioning during the day, including in the cognitive domain [16]. In our study, only semantic fluency was affected by chronotype. Surprisingly, ECT achieved better results in the evening, oppositely to ICT. It seems relevant to note that 65% of ECT people suffer from mild to severe depression. Depressive symptoms are more severe in the morning [10]. This could have influenced the results obtained. In addition, verbal functions have been previously found to be most efficient in the evening at around 7.00 p.m. [25].

The groups receiving and not receiving antidepressive treatment significantly differed in cognitive performance in terms of attention, short-term verbal processing, and working memory. Detailed analysis revealed that, overall, 22 patients showed mild to severe depression; 12 did not receive any treatment. Depression is known to deteriorate cognitive performance, especially in executive functioning, working memory, processing speed, and attention [26]. A recent meta-analysis of the effects of antidepressants on cognitive functioning demonstrated their positive effect on cognition, mainly for executive function, short-term and working memory, and attention [27]. MG therapy may protect patients from cognitive decline during the day, and mood disorder therapy may increase cognitive abilities in patients with depression.

The study group included MG individuals with depression, which may have affected the results, as depressive symptoms worsen cognitive performance and vary depending on the time of the day. No relationship between cognitive performance, mood disorder, and severity of MG was observed. However, the prevalence of depression among patients with MG is relatively high and the implementation of complex treatment could improve their quality of life [28]. The limitations of the study include the fact that it used small group with a lack of participants with the evening chronotype, as well as an imbalance in the gender distribution. Furthermore, the potential learning effect from testing the same individuals twice a day could have impacted the results. Therefore, the incidence and clinical significance of the results should not be overestimated.

Table 1. Demographic and clinical data of the sample studied

Factors	
Sex, female/male, *n* (%)	31/2 (94/6)
Age, M (range); SD	46.50; 10.78
Disease duration (years)	7.90; 6.49
Age at onset of symptoms (years)	38.70; 11.61
MG clinical data, *n* (%)	
Ocular type	3 (9.09)
Generalized type	30 (90.91)
AChR antibodies	14 (42.42)
MuSK antibodies	1 (3.030)
Thymectomy	12 (36.36)
Severity of the disease at the time of testing (MGFA), *n* (%)	
Class 0	1 (3.03)
Class I	2 (6.06)
Class II	13 (39.39)
Class III	11 (33.33)
Class IV	6 (18.18)
Type of treatment, *n* (%)	
Acetylcholinesterase inhibitor	31 (93.94)
Corticosteroids	24 (72.73)
Immunosuppressives	19 (57.58)
Immunosuppressives + corticosteroids	15 (45.45)
Antidepressant treatment, *n* (%)	14 (42.42)
Depressive symptoms, *n* (%)	
Minimal range	11 (33.33)
Mild	12 (36.36)
Moderate	5 (15.15)
Severe	5 (15.15)
Chronotype, *n* (%)	
Intermediate	10 (30.30)
Morning	23 (69.70)

Type of MG – Myasthenia gravis type: ocular, generalized, anti-acetylcholine receptor antibodies, anti-muscle-specific kinase antibodies

CLINICAL IMPLICATIONS/FUTURE DIRECTIONS

The data obtained allows us to expand our knowledge of the circadian characteristics of MG and to improve the targeting of future medical interventions to enhance the daily functioning of patients. Furthermore, the study high-

lights the importance of routine evaluation for mood disorders and, if necessary, antidepressant treatment, which could significantly improve patients' cognitive functioning. Further longitudinal research on a larger group, including patients with MG exacerbations and remissions, should be undertaken, also with healthy controls. Investigating factors that protect against reduced cognitive function may help to improve the medical approach to MG.

Conflict of interest

Absent.

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Absent.

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