Absence of central functional cholinergic deficits in myasthenia gravis

Short report

Myasthenia gravis is characterised by abnormal fatiguability of voluntary muscle that results from a reduced number of functional nicotinic acetylcholine receptors (AChRs) at the neuromuscular junction. Receptor loss is caused by IgG anti-AChR autoantibodies, and these antibodies can be detected in serum in 85–90% of cases. Treatment includes the use of acetylcholinesterase-inhibiting drugs which increase the availability of acetylcholine at the receptor, thymectomy and immunosuppressive drugs such as corticosteroids or azathioprine. In refractory cases, plasma exchange brings temporary symptomatic improvement.

Nicotinic AChRs are found in the central, as well as the peripheral, nervous system, particularly in hippocampus, hypothalamus, midbrain and cerebral cortex. Lesion and pharmacological studies in animals and the effects of centrally-acting anticholinergic drugs in man have demonstrated that the central cholinergic system is important in mediating cognitive processes of learning and memory. Further impetus has been given to this research by the discovery in Alzheimer's disease of impaired cortical cholinergic innervation, which has been invoked as the mechanism responsible for the pattern of amnesic deficits seen in this condition. The amnesic effect of anticholinergic agents has been well replicated, but it remains unclear at which stage the primary disruption to information processing occurs.

Central and peripheral nicotinic AChRs while genetically related, are coded for by different genes. Both nicotinic and muscarinic receptors are concentrated in the cerebral cortex, hippocampus and midbrain, often on the same neurons. However, gross disturbances of central function are not evident clinically in myasthenia gravis. Nonetheless, there have been sporadic reports which suggest involvement of the central nervous system. Electroencephalographic abnormalities have been described in myasthenia gravis patients and also in experimental autoimmune myasthenia gravis. Disturbances in REM sleep have also been noted. Lefvert and Pirskanen found raised concentrations of AChR antibodies in the cerebrospinal fluid of myasthenia gravis patients. However, these reports are not well replicated and claims that they provide evidence for immunological involvement of central AChRs in myasthenia gravis have been disputed.

Recently, subtle but unexpected cognitive dysfunction has been uncovered in another supposedly peripheral neurological disorder, motor neuron disease. If central nervous system involvement does occur in myasthenia gravis, it might reasonably be expected to manifest itself in certain abnormalities of cognition in view of the evidence for the role of cholinergic transmission in attention and memory. Moreover, any cognitive impairment present should be reversed by treatment which improves peripheral symptoms. We aimed to test these hypotheses by examining the
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Performance on a vigilance task of symptomatic myasthenia gravis patients before and after treatment.

**Methods**

(a) **Subjects**
The subjects were five female patients (mean age 25 years; range 20–34) with histories of moderately severe myasthenia gravis admitted for inpatient treatment with a course of plasma exchange. In each case, clinical diagnosis was supported by electrophysiological evidence of disordered neuromuscular transmission. Anti-AChR antibodies were present in the serum in four of the cases: clinical details and treatment data are given in the table. It should be noted that although each patient was taking anticholinesterase and/or immunosuppressant medication, all were symptomatic at the time of initial testing and asymptomatic at the time of retesting. Each had undergone plasma exchange to good effect on a previous occasion.

Eight healthy female paramedical staff (mean age 30 years, range 25–38) were used as external controls.

(b) **Tests**
A cognitive test sensitive to impaired central cholinergic function was required which was acceptable to subjects and controls. The starting point for the design of such a test was the increasing experimental evidence that an intact central cholinergic system is crucial to the directing and sustaining of attentional processes.

An increased "fatiguability" of attention in prolonged vigilance tasks has been reported to be the fundamental deficit in hyoscine-drugged subjects and offers a parallel to the accelerated muscular fatiguability seen in myasthenia gravis patients. Thus, a test of selective attention measuring change in performance over time, as well as baseline performance, was chosen.

This test was based on the rapid visual information processing task used by Wesnes and Warburton to demonstrate the facilitating and disrupting effects respectively of nicotine and hyoscine on sustained performance. Since the motor symptoms of myasthenia gravis are often most marked in the ocular muscles, causing diplopia as well as ptosis, the test was adapted to present similar information in the auditory modality. With the help of an electronic metronome, an audiotape was prepared of a series of digits 1–9 spoken at the rate of 75 per minute. Within this series were imbedded "target triads" of three digits in consecutive ascending sequence, such as "2–3–4" or "6–7–8". The series lasted 15 minutes and incorporated 100 target triads at random intervals with the constraint that 20 were presented in each 3-minute period. On hearing a completed target triad, the subject was required to respond by tapping once with a poised index finger on a piece of board. A "hit" was scored if the response was made appropriately within 1–5 seconds of the presentation of the last digit in the triad. Responses made outside this time (false positives) were counted as "errors".

Before each test session, muscular fatiguability was assessed using a grip strength dynamometer in the dominant hand. The subject was asked to squeeze the dynamometer as tightly as possible for four consecutive periods of 10 seconds duration, separated by 5-second rest periods. The maximum force exerted during each period was recorded.

At the initial test session, the Beck depression inventory was administered to screen for the presence of depressive symptoms; the item probing fatigue was omitted. Two further questions were given to probe for the presence of subjective symptoms of impaired concentration over the past week, with answers rated on a 4 point scale: "Have you found it easy to concentrate on reading or watching television?" and "Have you found yourself being absent-minded or forgetful?" (0–3). Symptoms and signs of muscular weakness were also recorded. At the second session, subjects were given the National Adult Reading Test as a measure of verbal IQ.

(c) **Procedure**
The nature of the study was explained to each of the myasthenia gravis patients. The initial test session took place on the day before plasma exchange began and the second test session on the day after the exchange finished, except in one case where the second session took place on the last day of exchange. Each myasthenia gravis subject underwent 2–4 separate plasma exchanges over a 3–5 day period. Accordingly, the period between first and second test sessions varied between 4 and 6 days. In no case was pharmacological treatment altered during this time. Typically, myasthenia gravis patients undergoing plasma exchange report a marked improvement in symptoms which is maximal in the few days following treatment.

The test sessions were given in the afternoon or early evening in a quiet room. Elicitation of physical symptoms and signs was followed by grip strength testing. In the first session, the Beck and cognitive questionnaire was then given; in the second session the NART. The auditory vigilance task was then given, preceded by taped instructions and confirmation that the subject understood the task. In order to control for any practice effects which might contribute to improvement in performance of myasthenia gravis subjects on retesting, control subjects were also retested after a period of 4 days.

**Table Clinical and treatment characteristics of myasthenia gravis patients**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Anti-AChR antibody titre x 10^{-15}M</th>
<th>Anti-cholinesterase drugs at time of testing†</th>
<th>Symptoms at time of test 1</th>
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<tr>
<td>23</td>
<td>1728</td>
<td>-</td>
<td>Dysarthria, dysphagia, limb weakness</td>
<td>None</td>
<td>96</td>
</tr>
<tr>
<td>29</td>
<td>18</td>
<td>+</td>
<td>Diplopia, limb weakness</td>
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<td>99</td>
</tr>
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<td>22</td>
<td>2</td>
<td>+</td>
<td>Ptsis, limb weakness</td>
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<td>112</td>
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<tr>
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<td>-</td>
<td>Diplopia, limb weakness</td>
<td>None</td>
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</tr>
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*Control < 2.0 X10^{-15}M/l
†All patients were taking prednisolone and azathioprine.

**Presented by**

[Signature]

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Results

Demographic, illness and treatment data of the five myasthenia gravis subjects are given in the table. All subjects reported symptoms of muscular fatigability at the first test session; none reported symptoms at the second session. This clinical improvement is borne out by the results of grip strength testing, shown in the fig. Although grip strength at the start of testing was comparable in the first and second test sessions, a greater decrement in power as the test progressed was observed before treatment, such that the grip strength at the end of testing was significantly less before than after treatment ($t$ (df 8) = 3.6, $p < 0.05$).

On pretreatment testing, no myasthenia gravis subject scored significantly on the Beck depression inventory (score range 2-5); neither did any subject at that time report subjective impairments in concentration or memory, as assessed by the probe questions (score range 0-2). Mean verbal IQ of the myasthenia gravis subjects was 105 (SD 8) and that of controls was 113 (SD 9).

Performances of myasthenia gravis subjects and controls on the first and second test sessions were analysed in two ways according to the study’s hypothesis: (a) For the controls, the mean number of correct “hits” in the first test session, out of a possible 100, was 52.3 (SD 9.1), rising to 60.4 (SD 12.7) at the second session 3 days later. This improvement in performance between sessions was presumably due to a practice effect, and was significant on a $t$ test of mean within-subject differences ($t = 4.2$ (df = 7); $p < 0.01$).

For the myasthenia gravis subjects, the mean number of correct hits was 45.8 (SD 6.5) at the first session and 58.8 (SD 16.6) at the second, post-treatment session. This mean improvement was not significant ($t = 1.7$ (df = 4); NS). This improvement in performance between sessions was more variable in the myasthenia gravis subjects (range of improvement +0 to +42) than in the controls (range of improvement +2 to +17).

The mean number of “errors” (responses in the absence of a target triad) was similarly small for all test sessions, not exceeding 6 for myasthenia gravis subjects or controls.

(b) The main hypothesis of the study was that any reversible impairment in central cholinergic function in myasthenia gravis would be reflected in an inability to sustain attention over time, itself reversible by treatment. To obtain a measure of the degree to which subjects were able to sustain attention, the proportion of correct hits during the first 40% (6 minutes) of the test session was compared to that in the last 40%, before and after treatment.

Significant decline in mean performance during

![Diagram](image_url)

**Figure** Fatiguability of grip strength before and after plasma exchange.

testing was not shown by the pretreatment myasthenia gravis subjects (-4%), either in comparison with themselves after treatment (+1%) or in comparison with controls (-1%).

Discussion

This study of cognitive function in myasthenia gravis failed to demonstrate deficits suggestive of impaired central cholinergic transmission. The ability to direct and sustain attention was measured using an auditory vigilance task in five young patients with moderately severe myasthenia gravis before and after treatment with plasma exchange. Despite clinical evidence of impaired peripheral cholinergic transmission, reversed by treatment, the myasthenia gravis subjects showed no absolute performance deficit, nor a decline in performance over time, when compared with either their own performance after treatment, or with that of healthy controls.

In view of the negative results, the validity of the test chosen to assess central cholinergic function merits discussion. Much experimental work has concerned the role of cholinergic pathways in human cognition. However, a clear consensus of opinion has been slow
to emerge. It is well replicated that anticholinergic agents such as hyoscine have amnesic effects, but the cognitive mechanism by which these are brought about is disputed. Frith et al\textsuperscript{19} concluded that their work “suggests a cholinergic mechanism in the encoding of new information into long-term storage”, supporting the interpretation that cholinergic activity is crucial in the transfer of information from primary into secondary memory.\textsuperscript{20} However, diazepam with little anticholinergic activity similarly disrupts the acquisition (rather than the retention or recall) phase of learning, and differences between the cognitive effects of the two types of drugs have not been shown.\textsuperscript{19}

The alternative view, increasingly supported by experimental data, is that cholinergic mechanisms are primarily involved in processes of attention rather than memory. Studies using search and vigilance tasks suggest that anticholinergic drugs specifically impair the direction\textsuperscript{15} and maintenance\textsuperscript{14} of selective attention. Thus, the detrimental effect of such drugs on memory is secondary to an attentional deficit which allows the intrusion of irrelevant, usually unattended stimuli. The choice of test in the present study was made on the basis of this evidence as well as the pattern of the peripheral impairment due to cholinergic deficits seen clinically in myasthenia gravis: that of “fatiguability”. These considerations suggested that a dynamic test of attention over time was the most valid measure of central cholinergic activity, directly analogous to that used by Wesnes and Warburton.\textsuperscript{14}

It is important to note (table) that all myasthenia gravis subjects were taking maintenance medication at the time of testing. In particular, anticholinesterase agents such as physostigmine can enhance certain cognitive, mnemonic processes\textsuperscript{21} just as anticholinergic agents disrupt them, and would presumably act to offset any cognitive deficit in myasthenia gravis. However, the myasthenia gravis subjects in this study displayed peripheral signs of cholinergic impairment, muscular fatiguability, despite this medication. Moreover, these signs improved significantly after plasma exchange without alteration of medication. If the putative central cholinergic impairment in myasthenia gravis parallels the peripheral impairment, the anticholinesterase agents taken by the myasthenia gravis subjects are therefore unlikely to have prevented its detection.

In conclusion, this study offers no functional evidence to support the sporadic reports of central nervous system cholinergic involvement in myasthenia gravis. Attentional processes presumed to reflect central cholinergic activity were not found significantly to be impaired, in accord with general clinical impressions and with the common practice of using these patients as controls for neuropsychological studies in other neurological disorders. The results are also consistent with the evidence that immunological cross-reactivity between peripheral and central AChRs is very limited.

We thank Ms Eve Goodger and Ms Margaret Callanan for their help and advice.

References

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S W Lewis, M A Ron and J Newsom-Davis

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