Benefit from adrenocorticotropic in myasthenia gravis

L. A. LIVERSEDGE, G. M. YUILL, I. M. S. WILKINSON, AND J. A. HUGHES

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SYNOPSIS Twenty-one of 29 patients suffering from myasthenia gravis derived benefit from a short intensive course of adrenocorticotropicin (ACTH). The mean duration of benefit was approximately six months. The best results were obtained in patients with a short history of myasthenia. Transient deterioration during the course of injections was encountered in some cases but necessitated assisted respiration only in patients with severe generalized weakness before treatment.

There have now been several reports of the efficacy of short high dosage ACTH therapy in the management of myasthenia gravis (Soffer et al., 1948; Hellman, 1949; Torda and Wolff, 1951; Grob and Harvey, 1952; Freyberg, 1960; von Reis et al., 1965; Grob and Namba, 1966; Osserman and Genkins, 1966; Cape and Utterbuck, 1969; Gibberd et al., 1971; Liversedge, 1971; Namba et al., 1971; Brunner et al., 1972). It is well known that transient deterioration during the course of therapy may occur. The purposes of this brief communication are (1) to review the results obtained by this form of treatment in one neurological centre; (2) to identify patients in whom benefit might be expected; (3) to identify features associated with deterioration during the course of treatment.

METHODS

The study concerned 29 inpatients with myasthenia gravis whose clinical features are shown in Table 1. Twenty-one patients had a single course of therapy, five patients had two courses, and three patients had multiple courses making a total of 43 courses of treatment. All patients received a five-day course of high dose ACTH therapy (100–200 units daily intramuscularly). (Thirteen patients received ACTH gel, and 16 patients received Synaechen.) The treatment was conducted in a ward with immediately adjacent facilities for respiratory care. Serum electrolytes and 24 hour urinary electrolytes outputs were monitored for three days before and for five days during the course. To counteract the known sodium retaining and potassium losing effects of ACTH, the patients were given a diet containing only 20 mEq sodium daily with potassium supplements during the five days of treatment.

Careful clinical assessment of the patient’s muscular power was carried out before, during, and at intervals after a course of therapy. In view of the widely differing muscular involvement among our cases, the clinical assessment was made firstly on the patient’s degree of inability to follow his normal daily routine, and secondly on the examiner’s overall impression of the patient’s muscular status on examination. The improvement in status relates strictly to a qualitative increase in ability and power, and was not related in any way to the period during which the given improvement was maintained. Thus, good improvement meant that there was a return to normal, or very nearly normal, muscular power and ability to follow normal daily routine. Moderate improvement indicated a substantial increment in

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FEATURES OF THE 29 PATIENTS DURING THE STUDY</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Sex</th>
<th>14–61 years (mean 43 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 female, 14 male</td>
<td></td>
</tr>
<tr>
<td>Severity of myasthenia before treatment*</td>
<td>Grade</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2a</td>
<td>12</td>
</tr>
<tr>
<td>2b</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Duration of myasthenia before treatment</td>
<td>2 months–37 years (mean 7 years)</td>
</tr>
<tr>
<td>Demonstrable thymic enlargement</td>
<td>7 patients</td>
</tr>
</tbody>
</table>

* Grade 1 = ocular myasthenia, grade 2a = mild generalized, grade 2b = moderate generalized, grade 3 = severe generalized myasthenia.
ability and power—falling well short, however, of a return to normal. Slight improvement indicated increment of small but useful degree in ability and power.

With the exception of the patients who deteriorated during the course of ACTH therapy to the extent of requiring assisted respiration, the daily dose of anticholinesterase therapy was left unaltered. In patients requiring assisted respiration, anticholinesterase therapy was conducted on an *ad hoc* basis but was never completely discontinued.

**RESULTS**

In the 43 courses given to 29 patients improvement occurred after 36 courses (84%). The mean duration of improvement was 5.7 months. In the 36 instances of benefit, the improvement was graded as good in 11, moderate in 13, and slight in 12. A really satisfactory response was therefore seen in 11 out of 43 courses of treatment in nine out of 29 patients.

**TABLE 2**

<table>
<thead>
<tr>
<th>Quality of improvement</th>
<th>Good</th>
<th>Moderate</th>
<th>Slight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of myasthenia in months</td>
<td>29</td>
<td>51</td>
<td>81</td>
</tr>
<tr>
<td>Number of cases per group</td>
<td>11</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>Duration of improvement (months)</th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of myasthenia in months</td>
<td>72</td>
<td>65</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Number of cases per group</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

There was an inverse relationship between the duration of the myasthenia gravis at the time of treatment and improvement after ACTH treatment. Thus patients whose myasthenia was of short duration obtained the best improvement both in quality (Table 2) and duration (Table 3). None of the following factors appeared to have any significant influence on the nature of improvement: sex, age, type or severity of myasthenia, presence of thymic pathology or previous thymectomy, or lack of response to a course of high dose ACTH on a previous occasion.

With regard to deterioration during the course of ACTH, the only factor of relevance was the severity of myasthenia before treatment, in that those more severely affected showed a higher incidence of deterioration (Table 4). From Table 4 it can also be seen that types IIB and III were the vulnerable groups for deterioration severe enough to necessitate assisted respiration. No significant influence of the following features was found in relation to the occurrence of deterioration during the course of treatment:

**TABLE 4**

<table>
<thead>
<tr>
<th>Grade of myasthenia*</th>
<th>1</th>
<th>2a</th>
<th>2b</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients deteriorating during treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0</td>
<td>17</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>No.</td>
<td>0/2</td>
<td>3/18</td>
<td>14/21</td>
<td>2/2</td>
</tr>
<tr>
<td>Patients deteriorating during treatment necessitating assisted respiration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>No.</td>
<td>0/2</td>
<td>0/18</td>
<td>4/21</td>
<td>1/2</td>
</tr>
</tbody>
</table>

* Grade 1 = ocular myasthenia, grade 2a = mild generalized, grade 2b = moderate generalized, grade 3 = severe generalized myasthenia.

sex, age, duration of myasthenia, presence of thymic pathology or previous thymectomy, deterioration in a previous course of ACTH, sodium balance or serum potassium during the five days of treatment (potassium balance was not performed).

Particular attention was paid to the state of sodium and potassium metabolism during the course of ACTH. As indicated above, no relationship between improvement after the course or deterioration during the course could be
found with changes in the sodium or potassium metabolism. From Table 5 it can be seen that the
restriction of sodium intake resulted in a virtually neutral sodium balance. The sodium intake of
20 mEq per day almost matched the 24 hour urinary output of sodium. Both the patients who
deteriorated and those who did not, experienced the same very minor degree of negative sodium
balance, −75 and −131 mEq sodium in five days respectively. Potassium balance studies
were not performed, though Table 5 indicates that there was no significant difference in either
the lowest serum potassium or mean serum potassium in patients who deteriorated and in
those who did not. Significant hypokalaemia was never seen in any patient, reflecting the efficiency
of potassium supplementation.

DISCUSSION

Because of the really favourable response to treatment in 11 out of 43 courses of ACTH (nine
out of 29 patients) we feel that this form of treatment has a definite place in the management of
myasthenia gravis. This incidence of good response to treatment is similar to the experience of others. Namba et al. (1971) in their review of
the world literature give a figure of 105 out of 251
courses (54 out of 166 patients), though comparison between patients from different centres
clearly cannot be absolute since the criteria for using ACTH must vary from centre to centre.

There are some minor points of variance between our results and those reviewed by Namba et al. (1971) but the most significant difference is
that the best response in our group was obtained in patients with a short duration of myasthenia,
whereas other workers have found a better response in patients who have had the disease for
over two years. We feel it is important to make
this point after a fruitless search for other features which might help to predict which
patients have a favourable response to ACTH
treatment. The only feature of such significance in our group of patients was a short history of
the disease at the time of treatment.

The occurrence of deterioration during the course of ACTH treatment was rather lower in
our series, 19 out of 43 courses (43%) compared with a figure of 62% in the world series reviewed
by Namba et al. (1971). There are obviously
many possible reasons for this numerical difference—for example, type and grade of
myasthenia, duration, and dosage of ACTH
therapy, etc. For general medical reasons, we
feel that sodium restriction and potassium
supplementation are indicated during the course of high dose ACTH. In this way the chances of
sodium retention with oedema and hypertension and of significant hypokalaemia, are
minimized. We were interested to see if careful control of sodium and potassium metabolism
during the course of treatment in any way
influenced the occurrence of deterioration. As
mentioned our deterioration rate was fairly low.
This could be attributable to the sodium restriction
and potassium supplementation which all our patients received during the course of treatment,
though it must be stated that some patients in our group did deteriorate during the
ACTH therapy without any observed change in
sodium balance or serum potassium levels. We
were unable to detect any significant difference in
sodium and potassium metabolism between
the patients who deteriorated and those who did not.

The only factor we could identify which corre-
lated positively with the occurrence of deteriora-
tion during the course of ACTH therapy was the
severity of the myasthenia at the start of treat-
ment. It is clearly important that respiratory care
facilities should be available when treating
patients with myasthenia by ACTH, especially
when the clinical picture is one of severe affection.

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