Diagnostic difficulties encountered in the myasthenic syndrome sometimes associated with carcinoma

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SYNOPSIS Six patients with the physiological features of the myasthenic syndrome associated with carcinoma are presented. The clinical features encountered in this group, including age, mode of onset, and duration of symptom indicate that it may escape detection owing to its resemblance to other neuromuscular disorders. Conventional concentric needle electromyography may lead to the disorder being confused with a myopathy. The association with carcinoma is by no means constant. Clinical and physiological improvement with guanidine is described in each case.

The occurrence of myasthenic features among the non-metastatic neurological complications of carcinoma was noted by Henson *et al.* (1954). The physiological features of this syndrome were differentiated from myasthenia gravis by Lambert *et al.* (1956). The block in neuromuscular transmission appears to be caused principally by a defect in the acetylcholine release mechanism at the nerve ending (Hofmann *et al.*, 1967). Guanidine ($\text{NHC}(\text{NH}_2)_2$), which enhances acetylcholine release (Otsuka and Endo, 1960), is more effective than anticholinesterase preparations in treatment (Lambert, 1966).

The chance finding of the physiological features of this disorder in a 20 year old girl with muscle weakness (Johns and Brown, 1967) led to a study of neuromuscular transmission in any subject with unexplained weakness over a two year period at the Johns Hopkins Hospital and subsequently for two years at the Royal Victoria Infirmary, Newcastle upon Tyne. Five additional cases have been found. The protean clinical features were in many instances outside the range of cases previously reported and illustrate how the syndrome may evade diagnosis and mimic a myopathy. They also provide experience in treatment with guanidine.

METHODS OF INVESTIGATION

NEUROMUSCULAR TRANSMISSION The technique was similar to that described by Grob *et al.* (1956). Supramaximal stimuli (the intensity being 150% of that required to evoke the entire muscle action potential) of 0.2 ms duration were delivered to the ulnar nerve at the wrist through surface electrodes from a Device Stimulator (type 3072) triggered by a Digitimer through a gated pulse generator.

Recordings of the evoked muscle action potential (MAP) from the abductor digiti minimi muscle were made between surface electrodes of 10 mm diameter, one situated over the belly of the muscle and the other as a reference over the base of the fifth finger. These sites were marked on the skin enabling subsequent recordings to be made from exactly the same position. The potentials were amplified through Medelec parametric (type 2A3) and Tektronix (type 3A74) amplifiers and displayed on a storage oscilloscope. 'Grounding' was effected by an electrode encircling the wrist distal to the stimulating electrodes. Isometric contraction was ensured by mechanical fixation of the hand to a board.

In most studies, the duration of the stimulus train was 10 seconds. The frequencies of stimulation were 1, 3, 10, and 30 per second.

ELECTROMYOGRAPHY Concentric needle electrode studies were made on the deltoid and quadriceps femoris muscles. The mean duration and amplitude of the muscle action potentials and the percentage of polyphasic potentials recorded during voluntary

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TABLE
CLINICAL DETAILS

	G.M.	M.T.	M.H.	E.G.	F.P.	J.R.
<i>Clinical</i>						
Sex	F	F	F	M	F	M
Age when seen (yr)	20	47	57	57	68	55
Duration of symptoms when seen (yr)	1	2/12	2/12	2/12	25	5/12
Pain in legs	At onset	At onset	—	Throughout	Throughout	At onset
Transient oculomotor features	—	Slight ptosis	Slight ptosis	—	—	Slight ptosis
Presence of carcinoma	—	Died, cause unknown	Found 3 months later	Found 8 months later	—	—
<i>Electromyogram</i>						
<i>Deltoid</i>						
Mean MAP amplitude (μ V)	140	82	116	132	109	74
Duration* (ms)	9.8 (10.7)	13.2 (13.8)	10.8 (11.9)	8.6 (10.2)	8.4 (12.5)	9.0 (11.8)
% polyphasic potentials	14	6	2	8	2	9
<i>Quadriceps femoris</i>						
Mean MAP amplitude (μ V)	190	102	1,212	172	178	129
Duration* (ms)	9.5 (9.8)	11.9 (12.5)	13.8 (13.4)	11.8 (13.4)	9.1 (13.6)	8.8 (13)
% polyphasic potentials	10	8	—	12	3	11
<i>Neuromuscular transmission</i>						
Initial evoked MAP (mV)	1.2	2	6	4.6	4.5	1.6
% after 1/s nerve stimulation for 10 s	68	62	66	72	78	71
% after 30/s nerve stimulation for 10 s	600	150	420	600	420	1,700
<i>Effect of guanidine</i>						
Clinical response	Excellent	Partial	Good	Good	Partial	Good
% increase in single evoked MAP	1,000	300	400	300	300	300
Side-effects	Peripheral paraesthesiae, anxiety	Vomiting	—	Vomiting	Vomiting	Rash
Dosage at which encountered (mg/kgBW/day)	45	45	—	42	26	28
Dosage ultimately used	37	35	40	35	22	—

* Normal values for age ($\pm 20\%$) in parentheses (after Buchthal, 1968).

contraction were estimated from a total of nine recording sites in each muscle.

OTHER INVESTIGATIONS In each patient, the following studies were also made: motor and sensory conduction velocity in the forearm segment of the ulnar nerve; blood urea and electrolytes including magnesium, haemoglobin, full blood count, and erythrocyte sedimentation rate; liver function tests and serum creatine phosphokinase; examination of cerebrospinal fluid.

Other relevant investigations in a search for carcinoma, including barium meal and enema, were also performed in each patient except case 5. Muscle biopsies were performed in patients 1 and 2 only. No patient had received antibiotics or—with the exception of a general anaesthetic in patient 2—any other drug known to impair neuromuscular transmission during the month before study.

CASE 1

G.M., a 20 year old girl, presented in May 1966 with a one year history of progressive weakness of the legs and arms. She had noticed that her knees would 'give way' and that her calf and thigh muscles were transiently painful and tender. The weakness gradually progressed with no relapses or remissions. Soreness and 'grittiness' of the eyes was a persistent complaint. In October 1965 she was given pyridostigmine (Mestinon) without significant improvement.

On examination, she had a waddling gait. There was symmetrical weakness of the proximal muscles, particularly the hip flexors. Distal strength was good. There was slight wasting of the quadriceps femoris muscles. Tendon reflexes were all depressed and the knee jerks were absent. She could rise from the floor only by Gowers' manoeuvre, could not get up from a chair without using her hands, and was unable to

climb stairs. On objective strength testing she was not as weak as this degree of disability would have suggested. There were no sensory signs.

Routine electromyography was compatible with a mild myopathy (Table). Biopsy of the quadriceps femoris muscle showed only minimal fibre atrophy and slight variation in fibre size with haematoxylin and eosin staining, though subsequent electron microscopic studies of this material have shown significant changes (Bergman and Johns, 1971). Other investigations were normal.

FIG. 1. Case 1. Superimposed hypothenar muscle action potentials evoked by 10 second trains of supramaximal stimuli delivered to the ulnar nerve. Stimulation at one per second (A) caused decline, while stimulation at 30 per second (B) caused facilitation. Vertical division A: 0.2 mV. B: 1.5 mV. Horizontal divisions 2 ms.

NEUROMUSCULAR TRANSMISSION The initial evoked MAP was abnormally small (Table). At a stimulus rate of one per second this became depressed still further. However, at a stimulus rate of 30 per second the potential increased six-fold within 10 seconds (Fig. 1). A single MAP was recorded in response to a nerve stimulus. The muscle was then contracted voluntarily for 10 seconds and a second MAP was

similarly recorded. This was $2\frac{1}{2}$ times as large as the first potential (Fig. 2).

That the disorder was caused by a defect of neuromuscular transmission was confirmed by two studies using the method described by McQuillen and Johns (1967). In the first, trains of stimuli were delivered to the ulnar nerve at the wrist and the nerve action potential recorded at the elbow. The size of the nerve action potential did not alter at stimulation rates of 1, 3, 10, and 30 per second, thus showing that the defect was not in nerve conduction. In the second, trains of stimuli were delivered through a bipolar needle electrode inserted in the biceps brachii

FIG. 2. Case 1. Hypothenar muscle action potential response to a single supramaximal stimulus delivered to the ulnar nerve, before (1) and after (2) a 10 second voluntary muscular contraction. Vertical division 0.5 mV. Horizontal division 2 ms.

muscle and the MAP was recorded from concentric needle electrodes at proximal sites in the same muscle fibre. The size of the MAP did not alter to stimulus rates of 1, 3, 10, and 30 per second. This excluded muscle as the site of the defect.

PROGRESS Guanidine was given initially four-hourly as four doses per day. There was prompt clinical improvement. She became able to rise from a chair and climb stairs with ease. Guanidine dosage was gradually increased (Fig. 3). When this was raised from 37 to 45 mg per kg body weight per day, she developed peripheral paraesthesiae and complained of insomnia. The dose was therefore reduced again to 37 mg per kg body weight per day, whereupon both these side effects disappeared. By August 1966 she was able to return to work and lead an active life. The size of the initial evoked MAP had increased from 1.2 to 12 mV and showed virtually no alteration

FIG. 3. Case 1. Course.

in size to trains of stimuli delivered to the nerve at slow or fast rates.

In June 1966, despite the improvement in strength of her arms and legs, she developed breathlessness on exertion caused by weakness of respiratory muscles. Her vital capacity at this time was 2.03 litres (predicted normal 3.34 litres). This symptom became gradually worse over the next four months until her vital capacity had fallen to 1.34 litres. Her chest expansion was poor and fluoroscopic studies showed that the diaphragm did not move on inspiration. Her guanidine dose always caused some improvement in her exercise tolerance. The dose was adjusted so that she received it more frequently with resulting clinical and spirometric improvement.

In May 1973 she underwent a normal, full term, spontaneous delivery. Her disease and medication did not affect her pregnancy, nor did the pregnancy or delivery affect her disease. The child was perfectly normal and has exhibited no weakness.

COMMENT This appears to be the youngest case reported. After eight years the possibility of an underlying neoplasm must be remote. The temporary impairment of respiratory muscles which responded to adjustment of guanidine dosage is an unusual feature in this syndrome. It is noteworthy that the

disease and medication did not complicate a normal pregnancy and delivery.

CASE 2

M.T., a 47 year old female, had a feverish illness with malaise, sore throat, and aching limbs in August 1966. On waking the following morning she had profound muscle weakness; she could barely get out of bed and was unable to rise from a chair. Her condition did not alter until October 1966 when a muscle biopsy was performed under general anaesthesia. After this she had prolonged apnoea and developed an inhalation bronchopneumonia. Her muscle weakness became worse.

On examination in October 1966 the patient had profound weakness, worse in the proximal muscles. Movement appeared slow and clumsy. She could stand only if supported. Muscle tone was flaccid. There was moderate muscle wasting. Tendon reflexes were all depressed or absent. There were no sensory signs.

Electromyography was compatible with a mild myopathy (Table). On maximum voluntary contraction a full interference pattern was obtained but its amplitude was reduced. Other investigations including biopsy taken from the quadriceps femoris muscle were normal.

NEUROMUSCULAR TRANSMISSION STUDIES The initial evoked MAP was depressed (Table). During a train of stimuli to the nerve at one per second this became depressed still further. During stimulation at 30 per second there was only a slight increase in the size of the MAP towards the end of the 10 seconds (Fig. 4, upper panel). After a 10 second period of voluntary muscular contraction, the evoked MAP was increased four-fold.

Wide fluctuations in the size of the evoked MAP occurred through the day (Fig. 5, left). This was not

related to her treatment time. If either arm were immobilized in a splint for an hour there was a significant rise in the size of the evoked MAP (Fig. 5, right). This suggested that the fatiguing effect of the slight movements permitted when the arm was not splinted were enough to contribute to keeping neuromuscular transmission constantly depressed.

PROGRESS She was treated with guanidine in increasing dosage with moderate clinical improvement. On 35 mg per kg body weight per day she was able to walk unaided and could get up from a chair, but she was still disabled. The initial evoked MAP rose to 5.5 mV. At the onset of treatment with guanidine, the potentiation of the evoked MAP at rapid stimulus rates became more striking and started earlier in the course of the train although it was still not completed within 10 seconds (Fig. 4, middle panel), though on higher doses the potentiation was nearly completed within three seconds (Fig. 4, lower panel).

In view of her persisting disability the guanidine was increased to 45 mg per kg body weight per day. This caused no further improvement and resulted in intractable vomiting. She was therefore maintained on 35 mg per kg body weight per day.

In December 1966 the patient's muscle weakness suddenly increased and she became unable to turn over in bed. Her voice became weak and attempts to swallow fluid resulted in nasal regurgitation. She became nauseated and vomited. She had no ocular signs but developed palatal weakness. The initial evoked MAP was then 1.2 mV. When her vomiting ceased she was given guanidine 28 mg per kg body weight per day. Her strength once more improved so that she was able to walk about and the evoked MAP rose to 4.5 mV. A similar relapse in her condition occurred in February 1967. At this time her initial MAP fell to 0.2 mV. Again when her vomiting ceased, gradual increasing doses of guanidine resulted in improvement.

Relapses in strength had been accompanied by profound constipation at which stage the barium studies showed that, though deglutition was satisfactorily initiated, oesophageal peristalsis was defective and intestinal motility was sluggish. In January 1968 her weakness became suddenly worse and she developed marked weakness of bulbar and respiratory muscles. This responded slightly to the addition of neostigmine 1.5 mg intramuscularly three-hourly. However, she did not recover from a state of profound generalized weakness which was unresponsive to either neostigmine or guanidine. Postmortem examination showed no gross abnormality of the central or peripheral nervous system or of the muscles. There was slight wasting of the quadriceps femoris but histological examination of this muscle

FIG. 4. Case 2. Hypothenar MAP evoked by trains of supramaximal nerve stimulation at 30 per second, on no treatment (upper panel), on guanidine 0.625 g daily (middle panel), and on guanidine 1.25 g daily (lower panel). Vertical divisions, 4 mV. Horizontal division, one second.

FIG. 5. Case 2. Left, MAP amplitude recorded from the same site on the hypothenar eminence evoked by single supramaximal nerve stimuli at different times of day. Right: MAP amplitude plotted while hand was immobilized in splint.

and the deltoid were again within normal limits. There was no postmortem evidence of malignant disease.

COMMENT The strikingly rapid and severe onset of weakness with subsequent incapacitating relapses differs from the features of cases previously reported. The initial studies of neuromuscular transmission did not seem to confirm the diagnosis in that there was only negligible growth of the MAP evoked by rapid repetitive nerve stimulation. Nevertheless, the more obvious increment during such stimulation after introduction of guanidine suggests that the defect in the acetylcholine release mechanism was so marked that it required the combination of guanidine and such stimulation to overcome it even temporarily.

The defective oesophageal and intestinal motility raises the possibility that, in this case, disordered neuromuscular transmission to smooth muscle might also have been present. While there was a profound block of neuromuscular transmission at the time of her death, this had been more severe at earlier stages in her illness and the precise cause of death remains obscure.

CASE 3

M.H., a 57 year old female, was first seen in April 1968 with a two month history of difficulty in rising from the sitting position and in climbing stairs. For six weeks she had also noticed increasing unsteadiness so that she could no longer stand unaided, clumsiness of her arms and legs, and difficulty in speaking.

On examination she had a marked cerebellar dysarthria and truncal ataxia with incoordination in all limbs. There was also slight weakness of the pelvic and shoulder girdle muscles and tendon reflexes were either markedly depressed or absent. There was a slight intermittent ptosis.

Electromyography was normal and the initial investigations had failed to show any evidence of a tumour.

NEUROMUSCULAR TRANSMISSION STUDIES The initial evoked MAP was 6 mV. During one per second stimulation this decreased to 4 mV. During 30 per second stimulation, however, the amplitude increased to 25 mV.

PROGRESS Guanidine was given three-hourly through the day in increasing dosage up to 40 mg per kg body weight per day. The amplitude of the initial evoked MAP rose from 5 to 20 mV. Before this treatment she was unable to feed or wash herself and could not stand, even with support. When taking guanidine she was able to look after herself and could walk with a frame, previously impossible because of the weakness in her arms. Her truncal ataxia was unaltered.

Two months after her first assessment, a radiograph of the chest showed that a rounded soft tissue density had appeared between the trachea and the right main stem bronchus and biopsy of a small scalene lymph node showed undifferentiated metastatic oat cell carcinoma.

COMMENT This combination of the myasthenic syndrome and a cerebellar disturbance occurred in one patient in the series of Lambert *et al.* (1961) and has also been reported by Satoyoshi *et al.* (1973). Each is a remote effect of the same carcinoma. The myasthenic syndrome may be masked by the cerebellar deficit yet the diagnosis is important for, as shown here, the overall disability may be helped by guanidine.

CASE 4

E.G., a 57 year old man, was seen in November 1970 with a two month history of increasing walking difficulty preceded by severe cramp-like pain in the calves. The disability had progressed from a feeling of unsteadiness when carrying heavy loads to inability to climb stairs without assistance.

On examination there was symmetrical weakness in both pelvic and shoulder girdle muscles and attempted movement caused pain. Tendon reflexes were absent and there were no sensory signs.

The electromyographic findings were suggestive of a myopathy but other investigations were initially normal.

NEUROMUSCULAR TRANSMISSION STUDIES The evoked MAP was 4.6 mV. During one per second stimulation this declined and during stimulation at 30 per second the amplitude increased to 27.6 mV within 10 seconds.

PROGRESS Guanidine was given three-hourly through the day in increasing dosage with improvement in strength. After two months his walking was almost normal, though he still tired easily and could not carry heavy loads. Although chest radiographs and bronchoscopy had been normal initially, eight months after his first visit he developed a dry cough and investigations revealed an inoperable anaplastic

carcinoma between the right and left main bronchi. Radiotherapy did not improve his weakness, and he died after a further six months.

COMMENT The dominant symptoms of this patient's presentation were in fact muscular pain and stiffness. Initially his disability was more due to these than to weakness. Both pain and weakness improved during

FIG. 6. Case 5. Hypothenar MAP responses to 10 second trains of nerve stimulation. Frequencies of one per second (upper), three and 10 per second (middle), and 30 per second (lower). On the left, 2 ms per horizontal division. Right: one second per horizontal division. Vertical scale: 1 mV per division, upper three panels. 5 mV per division, lower panel.

treatment with guanidine. This case also shows how the syndrome may precede the appearance of carcinoma.

CASE 5

F.P., a 68 year old housewife, was seen in 1971 with

a 25 year history of walking difficulty accompanied by severe cramp-like pains in the calves. The onset had been gradual but fluctuation had occurred: at times she could walk up to half a mile supported with a stick; at other times she could barely stand. She volunteered that, after a few paces, her walking seemed to improve though after this she would tire easily.

On examination there was symmetrical weakness of the proximal muscles of both pelvic and shoulder girdles. Tendon reflexes were depressed at the knees but brisk elsewhere. Sensory signs were absent.

Electromyography showed a reduced mean MAP amplitude and duration with a full interference pattern on voluntary contraction. Investigations were otherwise normal.

NEUROMUSCULAR TRANSMISSION STUDIES The amplitude of a single evoked MAP was 4.5 mV. During stimulation at one per second this declined to 3.5 mV. After a 10 second train of stimuli at 30 per second, this increased to 15 mV, but, as in case 2, it was evident that this facilitation was still occurring after this time (Fig. 6).

COURSE There was modest improvement when guanidine was given. Her walking remained laboured but she became able to manage without a stick. However, nausea and vomiting occurred on a moderate dosage and, ultimately, she was unable to tolerate more than 22 mg per kg body weight per day.

COMMENT The 25 year history is of particular interest. To our knowledge this is the longest reported in this syndrome and can be taken as evidence against the existence of carcinoma. The preservation of tendon reflexes in the upper limbs is an unusual feature.

CASE 6

J.R., a 55 year old man, was first seen in September 1971. That April he noticed marked soreness of both calves which persisted for two to three days only. In May pain occurred in the thigh muscles. This was followed by weakness which persisted. From that time he had been able to walk only a few paces and that with difficulty. He felt unsteady and was subject to sudden falls when his knees would give way. He tired easily. Since July he had had occasional transient diplopia.

On examination his gait was ungainly and difficult. He walked swinging his hips and trailing his feet, holding onto the wall for support. He was unable to rise from chair or bed unaided. There was slight symmetrical weakness of the shoulder girdle muscles and moderate weakness of the trunk and pelvic

girdle muscles. Tendon reflexes were absent, there were no sensory signs.

Electromyography showed a modest reduction in the mean MAP duration. The amplitude was initially small but, in this instance, facilitation could be observed during voluntary effort. Other investigations were normal.

NEUROMUSCULAR TRANSMISSION STUDIES A single evoked MAP was considerably reduced at 1.6 mV. After voluntary effort for 10 seconds, this increased to 9 mV. During one per second nerve stimulation the MAP declined from one to 0.8 mV and at 30 per second it rose to 25 mV in 20 seconds.

PROGRESS Guanidine was given in increasing dosage over a two week period; on 21 mg per kg body weight per day he became able to get out of a chair fairly briskly and to walk rapidly without support. Although still clumsy in his movements, he had lost all evidence of muscle weakness. The amplitude of a single evoked MAP rose to 3 mV. However, he developed a severe dermatitis which subsided when guanidine was stopped. Reinstitution of guanidine caused re-appearance of the rash and it was once again discontinued. He was tried a third time on guanidine, this time with steroids in an attempt to suppress the dermatitis. This failed and he has not been on guanidine since.

COMMENT This case shows the profound disability which may result from this disorder while strength is only slightly reduced. It is clear that his dermatitis was caused by guanidine, preventing its long-term use.

DISCUSSION

The clinical features of these patients suggest that this syndrome may encompass a broader clinical spectrum than was previously thought and may thus evade detection. The characteristic facilitation of strength during voluntary effort was not always clearly evident on examination. The patients merely appeared weak or clumsy. Furthermore, the occurrence of muscular pain (a presenting symptom in five of our patients) does not immediately suggest a myasthenic defect.

The apparent discrepancy between severe disability and relatively slight weakness on strength testing (noted also by Lambert *et al.*, 1965) in some instances led to doubt about the genuineness of these symptoms before it was realized that the disability was due to difficulty in initiating

ing movement. Finally, the known association of this syndrome with carcinoma may lead to its possibility being discounted where no carcinoma can be shown.

The electromyographic aspects show that the standard conventional techniques practised in most centres may not be enough to establish the diagnosis. The increase in MAP amplitude during voluntary effort may easily be overlooked if the diagnosis is not suspected and, even when the disorder is considered, this feature may not be apparent using concentric needle electrodes. Furthermore, using such recording methods in this series, we noted an excess of short duration and of polyphasic potentials. Their amplitude was generally low while the number of potentials evoked by a maximal contraction was not reduced (Table). Such findings could be interpreted as indicative of myopathy and this might appear to confirm the clinical impression of polymyositis or muscular dystrophy. Hence, when the incremental response is noted in a patient with electromyographic features suggesting a myopathy, it may in the past have been considered to be merely an accompaniment of the myopathy rather than a feature of defective neuromuscular

transmission (Stanton and Strong, 1967). It may be suggested that in such instances there is a co-existing myopathy and myasthenic syndrome. However, since correction of the myasthenic block with guanidine can lead not only to full return of strength but to disappearance of these 'myopathic' electromyographic abnormalities (Oh, 1972 and personal observation). It is more likely that they are changes secondary to the block of neuromuscular transmission.

The simplest screening test for this syndrome consists of evoking a single MAP before and after voluntary effort. The characteristic growth between 220 and 1,700% (Lambert *et al.*, 1961), occurred in all our subjects. This distinguishes the disorder from myasthenia gravis.

It is fortunate that this disorder can be identified at an accessible peripheral site in all cases, although, on clinical grounds, features are evident only in proximal muscles. In this respect it differs from myasthenia gravis where no such disturbance may be found in clinically unaffected muscles (Botelho *et al.*, 1952). The amplitude of a single evoked MAP fell between 1.2 and 6 mV, showing that the defect was greatest in rested muscle. The response to repeated

FIG. 7. Case 3. Effect of edrophonium (Tensilon). The amplitude of the MAP evoked by continuous three per second stimulation is plotted against time. Insets, vertical scale: 1 mV per division. Horizontal scale: 2 ms per division.

tive nerve stimulation is also characteristic, with the exception of case 2 where facilitation occurred only at rapid stimulation rates after the introduction of guanidine. In certain of our cases, MAP facilitation was not complete even after 10 seconds stimulation at 30 per second. Thus, longer stimulus trains may at times be required before a full assessment could be made of these physiological changes.

The features bear a superficial resemblance to the changes occasionally seen in myasthenia gravis where the facilitation of the MAP at rapid stimulus rates leads to the conclusion that there is a transient defect in the acetylcholine release mechanism (Takamori and Gutmann, 1971). However, the clinical distinction between these disorders is clear and the facilitation in these instances does not exceed 50% of the original MAP. Furthermore, administration of guanidine to one such patient resulted in only transient improvement followed by significant worsening in her condition (Brown and Johns, 1969).

Clinical improvement followed the introduction of guanidine in all our patients. In each, a three-hourly regime through the day brought about the best result. Side-effects were less troublesome when it was introduced in low dosage which was increased at intervals of not less than two weeks. A peculiar feature noted by Lambert (1966) and seen in our series is that, after an increment to the guanidine dosage has been made, there is usually further gradual clinical and physiological improvement for many weeks, without further adjustment in this dosage.

The most noticeable change in clinical status was in the ability to initiate movement; the previous clumsiness and slowness gave way to ability to perform rapid incisive movements. With the exception of cases 5 and 6, all were able to tolerate up to 35 mg per kg body weight per day, though the appearance of side-effects above 40 mg per kg body weight per day (Table) shows that the optimal therapeutic dose is close to the toxic dose.

A test dose of edrophonium (Tensilon) 10 mg given to each subject before their taking guanidine had a negligible clinical effect, though neuromuscular transmission studies did show a transient decrease in the degree of block. Figure 7 shows an example. However, the addition of

either pyridostigmine (Mestinon) or neostigmine (Prostigmin) to treatment with optimal dosage of guanidine did not induce any additional clinical improvement in our patients (with the exception of transient benefit during the terminal relapse with bulbar weakness in case 2). Hence, our experience does not suggest that such combined therapy will be of help.

The successful treatment of these patients (most of whom appear not to have carcinoma) with guanidine highlights the importance of diagnosis. Either the acute or gradual appearance of proximal weakness and muscular pains with an electromyogram which is 'myopathic' appears to be compatible with the myasthenic syndrome. The lack of variability in strength and the paucity of oculobulbar features at times provide little evidence to suggest that a myasthenic disorder is present and depression of lower limb reflexes may be the only clinical feature to distinguish this syndrome from a myopathy.

SUMMARY

Many of the clinical and electromyographic features of six patients with the myasthenic defect of Eaton-Lambert type would have led to the syndrome being confused with myopathic or neuropathic disorders but for the performance of neuromuscular transmission studies. The satisfactory response to guanidine and the appearance of carcinoma in only two of the cases emphasizes the importance of diagnosis.

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REFERENCES

- Bergman, R. A., Johns, R. J., and Afifi, A. K. (1971). Ultrastructural alterations in muscle from patients with myasthenia gravis and Eaton-Lambert syndrome. *Annals of the New York Academy of Sciences*, **183**, 88-122.

- Botelho, S. Y., Deaterly, C. F., Austin, S., and Comroe, J. H., Jr (1952). Evaluation of the electromyogram of patients with myasthenia gravis. *Archives of Neurology and Psychiatry*, **67**, 441-450.
- Brown, J. C., and Johns, R. J. (1969). Clinical and physiological studies of the effect of guanidine on patients with myasthenia gravis. *Johns Hopkins Medical Journal*, **124**, 1-8.
- Grob, D., Johns, R. J., and Harvey, A. M. (1956). Studies in neuromuscular function. 1. Introduction and methods. *Bulletin of the Johns Hopkins Hospital*, **99**, 115-124.
- Henson, R. A., Russell, D. S., and Wilkinson, M. (1954). Carcinomatous neuropathy and myopathy. A clinical and pathological study. *Brain*, **77**, 82-121.
- Hofmann, W. W., Kundin, J. E., and Farrell, D. F. (1967). The pseudomyasthenic syndrome of Eaton and Lambert: an electrophysiological study. *Electroencephalography and Clinical Neurophysiology*, **23**, 214-224.
- Johns, R. J., and Brown, J. C. (1967). The Eaton-Lambert syndrome (myasthenic syndrome of bronchogenic carcinoma) in a 20-year-old girl. (Abstract.) *Neurology (Minneapolis)*, **17**, 286-287.
- Lambert, E. H., Eaton, L. M., and Rooke, E. D. (1956). Defect of neuromuscular conduction associated with malignant neoplasms. (Abstract.) *American Journal of Physiology*, **187**, 612-613.
- Lambert, E. H., Rooke, E. D., Eaton, L. M., and Hodgson, C. H. (1961). Myasthenic syndrome occasionally associated with bronchial neoplasm: neurophysiologic studies. In *Myasthenia Gravis*, pp. 362-410. Edited by H. R. Viets. Thomas: Springfield, Ill.
- Lambert, E. M., Okihiro, M., and Rooke, E. D. (1965). Clinical physiology of the neuromuscular junction. In *Muscle*, pp. 487-499. Edited by W. M. Paul, E. E. Daniel, C. M. Kay, and G. Monckton. Pergamon Press: New York.
- Lambert, E. H. (1966). Defects of neuromuscular transmission in syndromes other than myasthenia gravis. *Annals of the New York Academy of Sciences*, **135**, 367-384.
- McQuillen, M. P., and Johns, R. J. (1967). The nature of the defect in the Eaton-Lambert syndrome. *Neurology (Minneapolis)*, **17**, 527-536.
- Oh, S. J. (1972). The Eaton-Lambert syndrome. Report of a case. *Archives of Neurology*, **27**, 91-94.
- Otsuka, M., and Endo, M. (1960). The effect of guanidine on neuromuscular transmission. *Journal of Pharmacology and Experimental Therapeutics*, **128**, 273-282.
- Satoyoshi, E., Kowa, H., and Fukunaga, N. (1973). Subacute cerebellar degeneration and Eaton-Lambert syndrome with bronchogenic carcinoma. A case report. *Neurology (Minneapolis)*, **23**, 764-768.
- Stanton, J. B., and Strong, J. A. (1967). Myopathy remitting in pregnancy and responding to high-dosage oestrogen and progestogen therapy. *Lancet*, **2**, 275-277.
- Takamori, M., and Gutmann, L. (1971). Intermittent defect of acetylcholine release in myasthenia gravis. *Neurology (Minneapolis)*, **21**, 47-54.