EFFECTS OF ADRENOCORTICOTROPHIC HORMONE ON NEUROMUSCULAR FUNCTION IN PATIENTS WITH MYASTHENIA GRAVIS [1]

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(Received for publication June 2, 1949)

The adrenocorticotrophic hormone of the pituitary gland has been administered to patients with myasthenia gravis mainly on the basis of the following observations and inferences: (*1*) the immediate cause of the symptoms of myasthenia gravis is a decrease of acetylcholine synthesis (1–4); (*2*) administration of the adrenocorticotrophic hormone increases acetylcholine synthesis *in vivo* (5); (*3*) increase of the lymphatic tissue (round-cell infiltration of various organs, mainly striated muscle [6]) and "hyperfunctioning" thymus (*7*) have been found in patients with myasthenia gravis. Tissue fractionation studies (8, 9) have shown that one of the sources of the substances that inhibit acetylcholine synthesis is the thymus. Administration of the adrenocorticotrophic hormone induces reduction in the mass of the thymus and the lymphatic tissue (10, 11); (*4*) removal of the pituitary gland in rats induces changes in the electromyogram (12) that closely resemble the abnormalities noted in patients with myasthenia gravis (13, 14); (*5*) the pituitary gland of several patients who died of myasthenia gravis showed accumulation of an eosinophilic colloid material suggesting altered function of the gland (15–19).

This report aims to illuminate the nature of myasthenia gravis by a further analysis of its phenomenology. Therapeutic implications are outside its scope.

MATERIAL

The effect of the administration of adrenocorticotrophic hormone of the pituitary gland was studied in five patients moderately to severely ill with myasthenia gravis.[2]

Patient R. G., a 45 year old woman, had had myasthenia gravis for ten years. She received a total of 180 mg. of neostigmine bromide a day, distributed over the waking hours, taken in three hourly intervals, 25 mg. of ephedrine sulfate once a day, and 1 gram of potassium chloride three times a day. While on this medication, she was able to rise from her bed and to sit by it in an armchair. She was barely able to walk very short distances when aided by an attendant. She had ptosis of the left eye-lid; her extraocular movements were limited in all directions. She also exhibited marked weakness and easy fatigability of the muscles of the palate, tongue, deglutition, chewing, face, and extremities. In addition, she had severe anorexia.

Patient H. L., a 24 year old woman, had had myasthenia gravis for four years. She received a total of 300 mg. of neostigmine bromide a day, distributed over the waking hours, taken in three hourly intervals, 25 mg. of ephedrine sulfate three times a day, 1 gram of potassium chloride three times a day, and 0.13 gram of guanidine hydrochloride three times a day. When on this medication, she was able to walk but showed severe general weakness, ptosis of the right eye-lid, and serious difficulty in swallowing. She had marked muscle weakness and easy fatigability of the muscles of the palate, tongue, deglutition, chewing, face, and extremities. There were periods when general weakness was much intensified and walking became almost impossible. She had anorexia.

Patient M. Y., a 31 year old woman, had had myasthenia gravis for nine years. Removal of the thymus in 1942 was followed by only a temporary remission. The patient received the total amount of 150 mg. of neostigmine bromide a day, distributed over the waking hours, taken in three hourly intervals. No other medication was taken. When on this medication, she was able to walk and do light housework. She exhibited general muscle weakness and easy fatigability, ptosis of one eyelid, marked weakness of the muscles of the tongue, deglutition, chewing, palate, face, and arms. When speaking she held up her chin with her hand. She had anorexia.

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[2] Since the completion of this manuscript three additional patients with myasthenia gravis have been given adrenocorticotrophic hormone in the manner described above. The results support in general the inferences of this study.

Patient A. S., a 37 year old woman, had had myasthenia gravis for 13 years. She received a total of 112 mg. of neostigmine bromide a day, distributed over the waking hours, taken in three hourly intervals. No other medication was taken. When on this medication she was able to walk and to do light housework. She exhibited marked general muscle weakness and easy fatigability. She had ptosis of the left eye-lid. She also exhibited weakness of the muscles of the palate, tongue, deglutition, face, arms, and mainly the legs. She had moderate anorexia.

Patient J. R., a 29 year old woman, had had myasthenia gravis for 17 years. She received a total of 45 mg. of neostigmine bromide a day, distributed over the waking hours, taken in six hourly intervals, and 25 mg. of ephedrine sulfate. When on this medication she was able to walk and to do light housework. She exhibited weakness of her leg muscles, moderate weakness of the muscles of the face, and ptosis of the left eye-lid.

During the three years before this special study began the patients experienced minor transient fluctuations but no long lasting or significant changes in their clinical states.

METHOD

The five patients were permitted to take known amounts of neostigmine bromide, and, if already receiving it, other medications. Throughout the study the patients were encouraged in any spontaneous attempts to reduce the amounts of the medications taken. The patients were warned against expecting improvement of their symptoms as a result of the injections received.

Upon admission to the hospital, electromyographic and myographic studies were performed once a day approximately at the same time of the day. After a one week period of observation each patient received by intramuscular injections 20 mg. of the adrenocorticotrophic hormone (Armour) every six hours for five days. Tests were performed during the administration of the hormone and afterwards until the writing of this report (approximately three months).

Controls. Ten healthy women aged from 27 to 44 years served as controls.

Electromyography

Records of muscle action potential were taken from healthy women and from patients with myasthenia gravis by the following method (6, 7): The forearm was firmly fixed in the supine position onto a padded board by means of broad straps placed across the arm near the elbow and the wrist. Of the two silver recording electrodes (0.5 sq. cm.), one was fixed with adhesive tape to the skin over the ventral surface of the first phalanx of the fifth finger and the other over the surface of the hypothenar eminence at a distance of about 5 cm. from the first electrode. The electrodes were connected to the grid terminals of an amplifier feeding into an oscilloscope. The stimulating electrodes consisted of two silver plates, the larger being affixed to the skin over the triceps muscle and the smaller, a movable electrode 0.5 cm. in diameter, being pressed firmly against the skin over the ulnar nerve just above the elbow. Good contact was established by the use of electrode jelly over the skin, which was partially deprived of its superficial epidermis. Ten and 30 pulses per second, each of 100 microseconds' duration and of "supramaximal" intensity, were administered for two minutes. The sweep circuit of the oscilloscope was synchronized with the stimulator so that successive stimuli and muscle action potentials were superimposed on the screen of the cathode ray tube. The action potential was recorded photographically.

Electromyograms were recorded for seven days before administration of the hormone, the five days during administration of the hormone, four days after completion of the series of administrations of the hormone, and at biweekly intervals thereafter. The records were taken at the same time of the day, three hours after the administration of neostigmine bromide before and during administration of the hormone, and from six to 15 hours after administration of neostigmine bromide after completion of the series of administrations of the hormone.

Myography

Muscle function was also tested by an ergograph. The ergograph consisted of a heavy spring attached to an isotonic lever writing on a kymograph. The spring was stretched 2.5 cm. once a second by the index and middle finger of the right hand exerting a tension of 15 kg. until fatigue occurred. The patients with myasthenia gravis performed the test once a day for a week before the period of administration of the adrenocorticotrophic hormone, during the five days of administration, and for four days after completion of administration of the hormone. Thereafter, the test was performed biweekly. The myograms were recorded immediately after completion of the electromyograms.

Biochemical studies (Acetylcholine Synthesis)

Acetylcholine synthesis in the presence of serum was studied following the method described by Torda and Wolff (2) before the injection period of the hormone, the third day after completion of the injection period, and biweekly thereafter. The method consists of incubation of a tissue containing choline acetylase with blood serum and determination of the amount of acetylcholine formed during the period of incubation.

RESULTS

General observations

During the five days of administration of the adrenocorticotrophic hormone the patients experienced a gradually increasing disability lasting until the second day after the end of the series of injections. This disability consisted of malaise, headache or "heaviness of the head," disturbance

in the menstrual cycle (bleeding), slightly increased fatigability, occasional diarrhea, abdominal cramps, and complaints of hot feet and hands.

On the second or third day after the last injection of the adrenocorticotrophic hormone the situation changed: the patients exhibited and described increasing well being and began to reduce the daily intake of neostigmine bromide and the other agents. Patient H. L. reduced the total of 300 mg. of neostigmine bromide a day to 45 mg. and omitted the other medications; patient M. Y. reduced the total daily intake of neostigmine bromide from 150 mg. to 15 mg.; patient A. S. reduced the total daily intake of neostigmine bromide from 112 mg. to 22.5 mg.; patient R. G. reduced the total daily intake of neostigmine bromide from 180 mg. to 90 mg.; and patient J. R. reduced the total daily intake of neostigmine bromide from 45 mg. to 15 mg. Also, more visible and measurable changes occurred in the patients that might indicate the beginnings of a partial remission. Thus, there was a clearly evident improvement of the facial muscle strength, the general muscle weakness and easy fatigability diminished, and the ptosis of the eye-lids was less evident. Difficulty in swallowing diminished significantly and the patients were able to hold heavy objects in their hands for a period of time. The appetite for food increased. However, in all instances the remission was incomplete. The muscle groups most severely involved (*i.e.* extraocular muscles and leg muscles in patient R. G., muscles of the forearm and foot in patient H. L., some muscles involved in chewing in patient M. Y., leg muscles in patients A. S. and J. R.) showed only partial recovery of function. This improved neuro-muscular function persisted from the completion of administration of the adrenocorticotrophic hormone to the writing of this report (approximately three months).

Electromyography

Healthy subjects maintained the muscle action potential during indirect stimulation with ten pulses per second for two minutes unaltered (13, 14) (Figure 1A). The action potential decreased on the average 12 per cent during indirect stimulation with 30 pulses per second for two minutes.

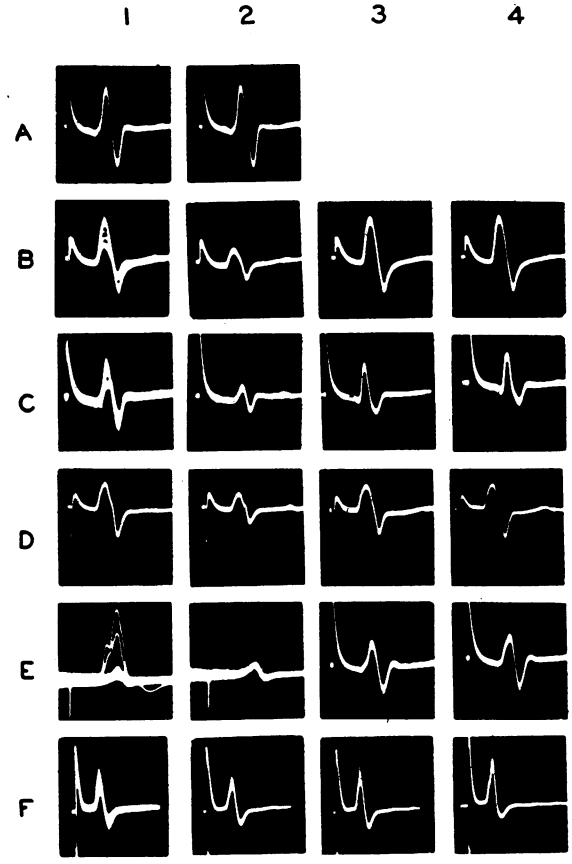

FIG. 1. EFFECT OF ADRENOCORTICOTROPHIC HORMONE ON MUSCLE ACTION POTENTIAL DURING REPETITIVE INDIRECT STIMULATION WITH TEN PULSES PER SECOND (PERCUTANEOUS STIMULATION OF THE ULNAR NERVE)

A. Muscle action potential of a control subject:
   1. Taken during the first few pulses of a 30 second stimulation period;
   2. Taken at the end of the 30 second stimulation period; the action potential was maintained unchanged.

B. Muscle action potential of patient H. L.:
   1. Taken during the first few pulses of a 30 second stimulation period before administration of the hormone;
   2. Taken at the end of the 30 second stimulation period; the action potential decreased during the first few pulses of stimulation and was maintained at the new level thereafter;
   3. Taken during the first few pulses of a 30 second stimulation period the third day after completion of the series of administrations of the hormone;
   4. Taken at the end of the 30 second stimulation period; the action potential was maintained unaltered.

C. Muscle action potential of patient M. Y.:
   1. Taken during the first few pulses of a 30 second

stimulation period before administration of the hormone;
2. Taken at the end of the 30 second stimulation period; the action potential decreased during the first few pulses of stimulation and was maintained at the new level thereafter;
3. Taken during the first few pulses of a 30 second stimulation period the third day after completion of the series of administrations of the hormone;
4. Taken at the end of the 30 second stimulation period; the action potential was maintained unaltered.

D. Muscle action potential of patient A. S.:
1. Taken during the first pulse of a 30 second stimulation period before administration of the hormone;
2. Taken at the end of the 30 second stimulation period; the action potential decreased during the first few pulses of stimulation and was maintained at the new level thereafter;
3. Taken during the first pulse of a 30 second stimulation period the third day after completion of the series of administrations of the hormone;
4. Taken at the end of the 30 second stimulation period; the action potential was maintained unaltered.

E. Muscle action potential of patient R. G.:
1. Taken during the first few pulses of a 30 second stimulation period before administration of the hormone;
2. Taken at the end of the 30 second stimulation period; the action potential decreased during the first few pulses of stimulation and was maintained at the new level thereafter;
3. Taken during the first few pulses of a 30 second stimulation period three months after completion of the series of administrations of the hormone;
4. Taken at the end of the 30 second stimulation period; the action potential remained unaltered.

F. Muscle action potential of patient J. R.:
1. Taken during the first few pulses of a 30 second stimulation period before administration of the hormone;
2. Taken at the end of the 30 second stimulation period; the action potential was maintained within normal limits.
3. Taken during the first few pulses of a 30 second stimulation period the third day after completion of the series of administrations of the hormone;
4. Taken at the end of the 30 second stimulation period; the action potential remained unaltered.

Since the recording electrodes were not moved during the 30 second stimulation period the action potentials of columns 1 and 2 and columns 3 and 4 are comparable. Since the recording electrodes could not be placed in exactly the same position on successive days the action potentials in column 1 are not comparable with those in column 3.

In all records the sweep circuit of the oscilloscope was synchronized with the stimulator so that successive stimuli and muscle action potentials were superimposed on the screen of the cathode ray tube.

In patients severely ill with myasthenia gravis the muscle action potential in affected muscles rapidly decreased during repetitive indirect stimulation (13, 14). Thus, before administration of the adrenocorticotrophic hormone, the action potential of patients H. L., M. Y., R. G., and A. S. decreased during the first few seconds of stimulation and was maintained at the new amplitude during continuation of the stimulation for two minutes. There was a considerable daily variation in the decrease in the amplitude of the muscle action potential. The decrease of the action potential was, however, in all instances over 35 per cent with 10 pulses per second and over 55 per cent with 30 pulses per second (Figure 1B–1F). The muscle action potential in patient J. R. was similar to the action potential of healthy controls, as is always the case in patients moderately or mildly ill with myasthenia gravis (13).

After completion of administration of the adrenocorticotrophic hormone and while on reduced medication the patients maintained the action potential during repetitive indirect stimulation with 10 and 30 pulses per second in a manner approximating that of healthy subjects (Figure 1B–1F). At the time of writing this report, approximately three months after completion of the administration of the hormone, the action potential was still maintained in a manner approximating that of healthy subjects.

Myography

The patients were trained for a few days in the use of the ergograph during the preliminary period of observation. The amount of work performed varied daily. The average number of contractions were, however, far below the average number of contractions of control subjects, except with patient J. R. The average number of contractions before occurrence of fatigue was 31 in patient R. G., 44 in patient A. S., 47 in patient M. Y., 75 in patient H. L. and 110 in patient J. R. The average of the ten healthy controls was 150.

During the period of administration of the adrenocorticotrophic hormone the number of contractions slightly and gradually increased. After completion of administration of the adrenocorticotrophic hormone the work performance continued to increase. The number of contractions increased from the first to the fifth day after completion of the series of administrations of the hormone. The average number of contractions during the first four days after completion of administration of the hormone was 98 in patient R. G., 120 in patient A. S., 165 in patient M. Y., 233 in patient H. L., and 160 in patient J. R. The increase in performance was maintained at the time of writing of the present report (approximately three months) (Table I). Although this test involves motivation, a sudden and dramatic increase in performance suggests an improvement of the function of the neuro-muscular system per se.

TABLE I

Effect of adrenocorticotrophic hormone on work performance (ergograph)

Treatment	Time	Number of contractions before occurrence of fatigue					
		Patients with myasthenia gravis					Healthy women
		R. G.	A. S.	M. Y.	H. L.	J. R.	
Before administration of the hormone		28 23 26 34 39 35 33 31	49 40 35 34 32 56 54 40 38	30 53 56 43 53	58 77 74 83 79	126 100 102 86 92	130 150 170 184 120 110 170 130 173 167
During administration of the hormone	First day	42 50	58 42	53 46	99	92 104	
	Second day	53 57	55 45	60 67	103 101	108 110	
	Third day	72 76			109 111	120	
	Fourth day	73 70	63 60	74 80			
	Fifth day	90 100	61 54	93 50	120 120	140 150	
After administration of the hormone	First day	89 80	80 80	90	200	141	
	Second day	90 98	120 128	165 170	232	150	
	Third day	105 100	140 130	186 180	245	174	
	Fourth day	124 98	138 130	190 180	255	170	
	Two weeks	103 108	137	185	250	180	
	Four weeks	110		192	240		
	Eight weeks	112		190	245		
	12 weeks	106		187	240		

Biochemical studies (Acetylcholine synthesis)

The synthesis of acetylcholine in the presence of body fluids (1–3) from patients with myasthenia gravis is decreased, suggesting that the body fluids contain in excess substances that inhibit the activity of choline acetylase. The more severe the myasthenia gravis the less well the blood serum supports the activity of choline acetylase.

In the presence of blood serum from patients with myasthenia gravis before administration of the adrenocorticotrophic hormone the synthesis of acetylcholine decreased 25 to 55 per cent (Table II). In the presence of blood serum taken the third day following completion of the series of administrations of the hormone and biweekly thereafter until writing of the present report (approximately three months) the synthesis of acetylcholine greatly increased and became similar to that occurring in the presence of serum from healthy subjects (Table II). The amount of acetylcholine synthesized in the presence of serum from the controls averaged 2.08 $\mu g \pm 7$ per cent per 100 mg. tissue containing choline acetylase.

GENERAL COMMENT

Administration of the adrenocorticotrophic hormone of the pituitary gland to patients with myasthenia gravis was first begun in 1944 by Torda and Wolff (5, 20). A partial remission consisting essentially in the ability to perform more work while taking significantly reduced amounts of medication occurred in the two patients with myasthenia gravis treated with the hormone. Because satisfactory objective procedures testing neuro-muscular function per se had not been elaborated in this laboratory at the time and since spontaneous remissions and improved motivation make evaluation of clinical changes difficult, inferences concerning the effect of the adrenocorticotrophic hormone in patients with myasthenia gravis were deferred.

In 1948 Soffer and collaborators (21) using no objective testing procedures of the neuro-muscular function reported a remission of the symptoms of

myasthenia gravis in a moderately ill woman after administration of the adrenocorticotrophic hormone.

Hellman (22) reported an augmentation of the symptoms of patients with myasthenia gravis as a result of administration of the adrenocorticotrophic hormone. However, this impairment seems to have occurred during the period of injection with the hormone, an effect also noticed in the patients of the present study. Decrease in symptoms in the latter patients was evident only after the second day following the last injection of the hormone.

Increased general disability during the period of administration of the adrenocorticotrophic hormone may result from the sudden changes in many phases of metabolism. Some of these are a decrease of the glutathione content of blood (23, 24), a sudden increase of the secretion of many steroid hormones (23–28), an adverse effect on carbohydrate metabolism, and disturbances in the electrolyte balance within the body (26). All of these changes impede the synthesis of acetylcholine (20, 29–31) and augment the symptoms of patients with myasthenia gravis (20). A decrease of symptoms in patients with myasthenia gravis studied at the New York Hospital in 1945 followed an experimentally induced (20) increase of the "reduced-glutathione" content of the body.

TABLE II

Effect of adrenocorticotrophic hormone on the ability of blood serum to support acetylcholine synthesis

Experiment	Amount of acetylcholine synthesized in per cent of control				
	Patients				
	R. G.	H. L.	M. Y.	A. S.	J. R.
Before administration of the hormone	45	50	58	60	75
Third day after administration of the hormone	92	98	97	100	99
Two weeks after administration of the hormone	94	96	98	97	96
Three months after administration of the hormone	92	95	96		

The remission observed after administration of the adrenocorticotrophic hormone began a few days after the completion of the injections. The remission, although incomplete, was sudden in onset, was significant and long lasting, encouraging the inference that administration of the hormone and the occurrence of the remission were causally related. Remission must be, by the nature of the disorder, incomplete, since after patients with myasthenia gravis have had muscle dysfunction for some years, as was the case in the patients of this study, irreversible structural changes in muscle probably occur. Even assuming that regeneration under suitable conditions may ultimately take place, such regeneration would not exhibit itself in a short time.

If the view suggested by this laboratory be valid, *i.e.*, that the immediate cause of the symptoms of patients with myasthenia gravis is a decrease in the synthesis of acetylcholine (1–4) then the observation that administration of the adrenocorticotrophic hormone increases the synthesis of acetylcholine (5) becomes extremely pertinent to an understanding of the apparent remission of symptoms observed in patients with myasthenia gravis after administration of the adrenocorticotrophic hormone.

SUMMARY

1. The adrenocorticotrophic hormone of the pituitary gland has been administered to five patients moderately to severely ill with myasthenia gravis.

2. Before administration of the adrenocorticotrophic hormone the patients exhibited the known decline of the amplitude of muscle action potential during repetitive indirect stimulation. Also, the amount of work performance on an ergograph averaged only 30 per cent of that performed by healthy subjects selected from the same sex and from similar age group as were the patients. The amount of acetylcholine synthesized in the presence of blood serum of the patients was below normal.

3. Four hundred mg. of the adrenocorticotrophic hormone were administered in 20 mg. amounts every six hours. During the period of administration the patients experienced an increase in disability. The second day after completion of the series of injections the patients experienced changes suggesting the beginnings of

an incomplete remission of the disorder. This consisted of marked improvement of muscle function while on appreciably reduced neostigmine bromide. The much reduced ability of blood serum to support acetylcholine synthesis returned to normal. Furthermore, the electromyogram and myogram became similar to those of healthy subjects. This incomplete remission precipitated by the adrenocorticotrophic hormone persisted for an, as yet, undefined period.

ACKNOWLEDGMENT

The authors wish to express their gratitude to Dr. John R. Mote, Medical Director, Armour Laboratories, Inc., for the generous supply of the adrenocorticotrophic hormone.

The electrical equipment was constructed by Grass Instrument Company.

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