THE TREATMENT OF DYSTROPHIA MYOTONICA WITH A.C.T.H.

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Following the reports of Reese and Peters (1952) and of Shy and McEachern (1951) that A.C.T.H. was of benefit in the relief of dystrophia myotonica by increasing muscle strength, it was decided to try the effect of A.C.T.H. on a further group of patients. The results obtained form the basis of the present report. Case 1 is reported in detail, the remainder briefly.

Case Reports

Case 1.—Mr. S. is aged 35. In 1943, when serving in the Royal Marines, he noticed an inability to relax his grip. He was admitted to hospital where the diagnosis of dystrophia myotonica was made, and his discharge from the Marines followed. Since 1943 he has become bald and has experienced progressive difficulty in eating owing to stiffness of the muscles of mastication and of the tongue. At times there is such difficulty in moving the tongue and muscles of deglutition that he is unable to prevent a bolus of food lodging in the pharynx with consequent choking. This has been severe enough on at least three occasions for him to be admitted to various hospitals as an emergency. Saliva is difficult to swallow and speech has become monotonous so that people complain of difficulty in understanding him. Increasing weakness of the muscles of the neck makes it difficult for him to raise his head from a pillow and he has noticed that the neck has become much thinner in recent years.

The difficulty in relaxing his grip has become more marked and he complains that when shaking hands he frequently hurts himself on jewelled rings. On walking, the left leg may suddenly stiffen from the hip to the toes causing him to fall over. The right leg has been similarly affected but less frequently. He has noticed that the left calf seems bigger than the right. There are no visual symptoms and respiration has never been interfered with. In spite of his disabilities he has been able to continue at his work as an artificial limb maker. There has been no decrease in libido and no impotence. He is married and has two daughters aged 7 and 6 years.

He gave a past history of an appendicectomy in 1944.

Both parents were of normal physique, but his paternal uncle was a very big, muscular man. Two brothers, aged 28 and 20, were killed in the war; both were of

exceptional muscular development and very tall, one being 6 ft. 2 in. and the other 6 ft. 9 in. There were no other siblings.

On examination the essential features were as follows. The patient was of normal intelligence, but he was worried about his condition. Frontal baldness extended to the occiput, the remaining hair being thin and fine. The skin of the face was slightly greasy. The poverty of facial movement and the absence of wrinkling of the forehead were noteworthy in spite of moderate ptosis. The stance was lordotic. The patient weighed 10 stone.

The optic fundi were normal, but the pupils reacted rather slowly to light and accommodation. No lens opacities were seen but there was an increased reflection from the anterior cortex of the lens.

The neck was thin with obvious wasting of both sternomastoid muscles. The patient had difficulty in opening the mouth to command, an action which was performed slowly and to a limited extent only; similarly movements of the tongue were slow and stiff. Speech was monotonous and slurred. Muscular development generally was poor and power was reduced in the arms and legs. No fasciculation was seen. There was marked myotonia of all muscles of both hands. All tendon jerks were sluggish. Plantar responses were flexor. No loss to superficial or deep sensation was detected. Other systems were normal. The pulse was 70, the blood pressure 110/75 mm. Hg. There was no evidence of testicular atrophy.

Electromyography showed slow relaxation and low amplitude potentials interpreted as being consistent with the presence of myotonia.

The Wassermann and Kahn reactions were negative. The electrocardiogram, radiograph of the chest and of the temporo-mandibular joints were all normal.

The vocal cords were visualized by Mr. W. I. Daggett who noted very sluggish abduction of both cords, especially of the right. Adduction also was slow and the cord tension on phonation lacking.

The electroencephalogram was abnormal with an excess of slow activity, the significance of which was not clear.

Before admission this patient had shown no response to quinine or to amphetamine.

From the day of admission on August 12, 1951, until

treatment with A.C.T.H. was begun on October 17 the patient suffered nine attacks of myotonia of the muscles of the tongue and deglutition. Various drugs were tried in these attacks, including quinine, 0.5 g. intramuscularly, and sodium amytal, 0.25 g. intravenously, hexamethonium iodide, 20 mg. intravenously, prostigmine, 2.5 mg., and atropine 1/100 gr., procaine, 0.5 g. intravenously by slow drip, quinine, 3 gr. intravenously. Many of these substances were tried on more than one occasion but no real effect on the myotonia was ever apparent.

On October 16 treatment with A.C.T.H., 160 mg. daily, was begun. Thereafter daily recording of blood pressure and urinary chlorides (Fanti's test) was carried out and frequent eosinophil counts were made. The effect of the A.C.T.H. was to reduce the urinary chlorides and cause a slow fall in blood pressure from 130/80 to 105/80 mm. Hg by the end of the first test period of 14 days. After receiving 160 mg. of A.C.T.H. daily for five days the dose was raised to 200 mg. a day for the next nine days.

On October 22 the myotonia of the muscles of the hands was less; there was also marked subjective improvement. The patient claimed that he had never felt so well at any time before treatment with A.C.T.H.

By October 29 the myotonia was very obviously diminished but not quite absent.

A.C.T.H. was stopped on November 1.

Estimation of total 17-ketosteroid excretion per 24 hours at this time gave 2.8 mg. before A.C.T.H. and 3.2 mg. after A.C.T.H. and 4.0 mg. on each of two occasions. Though the pre-A.C.T.H. level of 17-ketosteroids is below normal, the response to A.C.T.H. was considered to be only moderate.

On November 6 myotonia was noticed to be returning. The blood pressure was 130/80 mm. Hg, and by November 20 myotonia had returned to about the degree present before treatment. The patient's voice was again slow and monotonous and he had suffered one attack of trismus.

In order to simulate the pain A.C.T.H. injections caused, a 2% solution of saline was used as a placebo. On November 22 2% saline was given and continued thereafter in exactly the same manner as A.C.T.H. until December 5. Neither the ward staff nor the house physician knew that saline was being used. No change in myotonia occurred, and on December 5, without a break being made in the continuity of injections, A.C.T.H. was substituted at 200 mg. daily; seven days later the myotonia had again largely disappeared. On December 20 the patient's weight was 11 st. 1 lb. 2 oz.

On December 21 the patient was sent home. He continued to have 150 mg. of A.C.T.H. daily administered by the district nurse. On January 14, 1952, he was readmitted to King's College Hospital. The serum K level (done as an out-patient) was 16.5 mg. per 100 ml.

Improvement in his condition was now striking, and only a trace of myotonia in the muscles of the hands remained. Muscle strength was better than at any time since the onset of his condition. There had been no further attacks of trismus of the jaw muscles. His wife noticed that his scalp hair had started to grow again.

He was not aware of any change in libido or potency. A.C.T.H. was now discontinued owing to the shortage of supply. By January 21 there was a minimal return of myotonia but percussion of the thenar eminence did not produce the prominent myotonic response observed before treatment with A.C.T.H. His weight was 11 st. 5 lb. 6 oz. and he was discharged home on February 18 to be followed up as an out-patient. He was seen again on February 13, 1953, when the myotonia was now apparent but much less than before treatment with A.C.T.H. The patient himself remained delighted at the results. However, the myotonia steadily increased and again he was troubled by difficulty in swallowing his saliva, and his voice became monotonous and indistinct. He continues to attend a follow-up clinic at regular intervals and is anxious to have further A.C.T.H.

Case 2.—Mr. M. was aged 48. In 1943 while in the Army noticed a tendency to stumble and that his limbs were becoming thin. The weakness became so marked that he was unable to carry a bucket. He developed foot drop and was given a walking caliper. More recently he had found difficulty in holding up his head. He had been bald since 1927. He has three children, aged 26, 23, and 17, all alive and well.

There is no family history of any neuromuscular disorder nor of poor vision.

On examination there was moderate baldness and bilateral ptosis with frontalis contraction. There was wasting of the sternomastoids, supraspinati, infraspinati and rhomboids, and of muscles of the forearms with decrease in tone. The muscles of both hands showed moderate wasting but also a well marked degree of myotonia.

In the legs there was bilateral drop foot with slight pes cavus, wasting, and weakness of dorsiflexion of both feet. Muscle tone was normal.

The reflexes were absent in the arms. The knee jerks were sluggish and the ankle jerks absent. The plantars were flexor. The right testicle was small and atrophied. The blood pressure was 130/90 mm. Hg. Other systems were normal.

Among the preliminary investigations electromyography showed a typical myotonic reaction. The electrocardiogram was normal. The electroencephalogram was abnormal with a large amount of diffuse, irregular 3-6 c/s. activity especially marked over the left hemisphere.

The patient received a course of A.C.T.H., 100 mg. daily, for 10 days, and then 150 mg. daily for 15 days, after which there was an improvement in the myotonia. He became able to carry out rapid repetitive gripping of the observer's hand at a higher rate than before treatment. Electromyography confirmed the improvement in myotonia. No such benefit followed the placebo injections of hypertonic saline. Improvement persisted for six to eight weeks following cessation of A.C.T.H. Thereafter he slowly returned to the pre-treatment condition.

Case 3.—Mr. C. was aged 39. In 1938 became aware of difficulty in relaxing his grip and developed a tendency to trip over minor irregularities in the ground. The

muscles of the neck later became weak and he had difficulty in raising his head when recumbent, having to turn his head sideways in order to do so. Difficulty in controlling micturition necessitated the use of a urinal at night. In 1939 treatment with quinine and benzedrine was without effect. All disabilities are worse in the cold weather.

His grandfather and father were both bald at an early age and his father also had cataracts.

His appearance was typical of severe dystrophia myotonica with baldness, ptosis, myopathic facies and eversion of the lower lip. Speech was monotonous and indistinct. All muscles were wasted, the sternomastoids being represented only by fibrous cords. The left eye showed early cataract formation, while myotonia of hand grips was marked. All tendon reflexes were absent, the left plantar was flexor, the right being extensor. Bilateral pes cavus was present. Both testes were atrophic. Blood pressure was 100/70 mm. Hg.

The basal metabolic rate was minus 16%. The plasma cholesterol level was 272 mg. per 100 ml. The electrocardiogram showed a left bundle branch block. The serum potassium level was 14.9 mg.%, and the urinary ketosteroids were 5.8 mg. in 24 hours. A radiograph of the skull was normal.

The report on the electroencephalogram on August 26, 1952, was as follows:—

“Markedly abnormal, pathologically flat, with an almost total absence of regular rhythmic activity of any frequency. On overbreathing a small amount of alpha activity is seen. Photic stimulation produced following only at slow frequencies but no abnormal wave forms were seen. The suppression of activity in the resting record is unlikely to be solely the effect of anxiety and muscular tension. Such flat records are seen in a few diffuse, mainly basal, pathological conditions such as Huntington's chorea.”

On October 21 a course of injections of 2% saline was started and continued for ten days. No change followed. On October 28 the E.E.G. was essentially similar to the previous record but rather more normal.

On October 30 treatment was changed to A.C.T.H., 50 mg. twice a day. (The dose was less than in the previous cases owing to inadequate supplies being available.)

By November 10 the only change was that he had regained his ability to raise his head from the pillow without having to turn his head sideways to do so. The myotonia was not clinically altered.

On November 17 the serum potassium level was 15.6 mg. per 100 ml. The electrocardiogram showed a left bundle branch block as before. On November 21 A.C.T.H. was discontinued. The electroencephalogram showed an increase in alpha rhythm but otherwise little change.

Case 4.—Mr. H., aged 34, had difficulty in relaxing the hand grip which was first noticed by his own doctor 10 years before. He had always been of slight, even frail, physique.

On examination he showed the appearance of dystrophia myotonica with severe frontal baldness and

wasting, especially marked of the facial muscles and sternomastoids. The grips were both myotonic. The testicles were abnormally small. A few small lenticular opacities were present in both eyes. Blood pressure was 170/110 mm. Hg. Other systems were normal.

The electrocardiogram was normal. The electroencephalogram was abnormal with considerable excess of diffuse 4–6 c/s. with some potentials down to 2 c/s. Radiographs of the skull and chest were both normal. The haemoglobin was 104%. The serum potassium level was 19.4 mg. per 100 ml.

On March 11, 1952, A.C.T.H., 50 mg. b.d., was begun.

By March 18 the patient subjectively felt better but no objective improvement was noted, but by March 31 he was able, for the first time, to raise his head and neck up off the pillow and to sit upright in the normal manner without having first to turn on to his side as he had to before A.C.T.H. He had gained 3 lb. 11 oz., and was able to walk faster.

On April 3 treatment was changed to placebo injections of hypertonic saline. On April 8 he was worried about his failure to gain further weight. On April 13 injections of saline were stopped but improvement was still maintained. By April 30 he had relapsed to the condition before A.C.T.H. was begun, with difficulty in walking rapidly and severe myotonia, and again he had to turn sideways to get his head off the pillow.

Discussion

Adrenocorticotrophic hormone (A.C.T.H.) was chosen in preference to cortisone since in both the previously reported series of cases (1 and 2) cortisone has been found to produce little or no effect. Shy and McEachern suggest that this difference might be due to the power of A.C.T.H. to bring about a shift of potassium from inside the cells of myotonic muscle. It is possible that alterations in muscle function are reflected in changes in the level of serum potassium, though such changes may be little more than a very rough indication of alteration in the dynamics of muscle biochemistry. Weakness of muscle can be associated with a fall in the serum potassium level, as in familial periodic paralysis, or conversely with a rise, as in Addison's disease.

In a review of the role of potassium in physiological processes, Fenn (1940) emphasizes the essential part played by potassium in the physicochemical structure of muscle cells, and points out that potassium moves out of the muscle cell during contraction and that to some extent this is under the control of the adrenal cortex. If this be so it may explain why A.C.T.H. relieves myotonia and cortisone does not. Presumably the effect is mediated by a fraction of the total adrenal cortical secretion which is the result of A.C.T.H. stimulation and this function is different from that of cortisone.

That A.C.T.H. has an effect on potassium is also

reported by Bartter, Fourman, Forbes, Jeffries, and Albright (1949) who found that following administration of A.C.T.H. there was a large but transient loss of potassium in the urine. On the other hand, Farago, Rochlin, Schilling, Vawter, and Armstrong (1951) have reported that A.C.T.H. causes a rise in muscle potassium in human subjects, though these observers are careful to point out that their results must be viewed with caution as they are preliminary.

In the present series the only real effect appeared to be on the myotonia. Thus the patient showing the best response was Case 1 in whom the myotonia was particularly marked and the dystrophic process less in evidence. Those others where wasting, weakness, and the dystrophic features dominated the picture showed little response to treatment.

No explanation of the mode of action of A.C.T.H.

in relieving myotonia can at present be offered, but a further study of its effect on muscle potassium may prove to be of value.

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