THE TREATMENT OF MYOTONIA CONGENITA

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Congenital myotonia was first described, in 1876, by Julius Thomsen,[10] a Danish physician, who was personally afflicted with it. He reported the same condition in 20 other members of his family, extending over 4 generations. At the time, comment was made on the frequent association with psychosis. Numerous cases and families have since been described. A large series has been reported by Thomasen,[9] including descendants of the original recorded case. The supposed psychotic accompaniment has largely been disproved. About one-quarter of the cases are familial and inherited as a Mendelian dominant. The characteristic feature of the disease is myotonia, which may manifest itself during childhood, producing difficult and delayed walking, but more usually showing first signs between the ages of 6 and 12 years, becoming more pronounced at the time of puberty. The intensity of the myotonia varies a little from time to time, but usually does not increase once adulthood is reached. All skeletal muscles may become involved to a greater or lesser extent. Initiation of movement is difficult. The speed of contraction may be prolonged, and so, to a marked degree, is the period of relaxation. With repetitive movement the myotonia diminishes, only to return when the movement is altered; reflex after-spasm is a prominent feature and adds considerably to the difficulty.[3]

The myotonia may be produced by direct percussion of the muscle and by repeated, but not single, electrical stimuli. This explains the myotonia produced by testing for the skin reflexes and the absence of myotonia following single tendon jerks, which are equivalent to single electrical stimuli.

Any skeletal muscle may be involved, producing its disability accordingly, e.g. strabismus, respiratory difficulty, etc.

In most cases the muscles appear larger than normal and this is usually confirmed by histological evidence of increased size of muscle fibre.

In some cases the patient complains of increased stiffness in cold weather. The term paramyotonia is used in those cases which show a marked response to cold, and in whom

a state of flaccid paralysis sometimes develops. Some authors consider this term an unnecessary qualification.[8]

CASE REPORTS

Case 1

Mrs. L.P., aged 35, complaining of severe stiffness of all muscles for the past 4 years. This had become so severe that she was unable to move out of the house. With repeated activity the stiffness improved but any change of direction resulted in severe stiffness and frequent falls, likened to a falling lead pipe. This distressing condition was accompanied by moods of depression and an extremely labile personality. The stiffness was first noted at the age of 11 years. At the age of 17 the condition deteriorated and was accompanied by a dull ache in the muscles which, amongst other things, was diagnosed as rheumatic fever.

The paternal history was not obtainable, but there was no myotonia on the maternal side. The patient has 2 children, both showing early signs of myotonia (described below). In recent years she has complained of a dull ache in the epigastrium causing her to vomit now and then, and of a 'vibrating sensation' throughout the body.

On examination no abnormality other than the myotonia and labile emotional state was detected. The muscles of expression and deglutition were least affected, the rest of the skeletal musculature showed severe myotonia. After grasping, the hands could not be relaxed for 30 seconds.

Blood examination. Haemoglobin 17·9 g. per 100 ml. Red cells normal in appearance.

Leucocyte count 8,200 per c.mm.; normal differential count.

Erythrocyte sedimentation rate 1 mm. in the first hour.

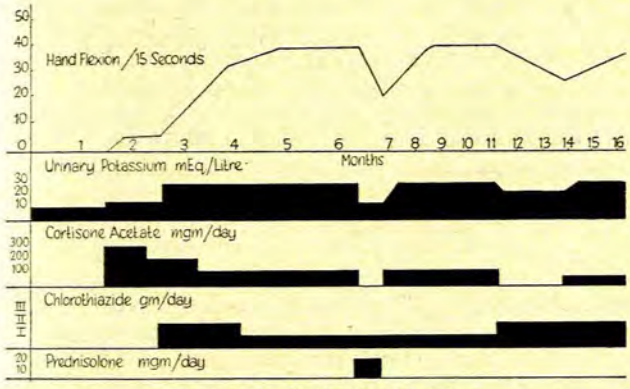

Fig. 1. Case 1. Results of treatment.

Wassermann reaction negative. Serum CO_2 content 24 mEq./litre.

Serum potassium 4 mEq./litre. Serum sodium 130 mEq./litre. Serum chloride 97 mEq./litre. Serum calcium 4·7 mEq./litre. Plasma inorganic phosphorus 2 mg./100 ml.

Histological section of muscle revealed slight hypertrophy of muscle fibre.

The 24-hour urinary potassium excretion studies are shown in Fig. 1.

Treatment and progress. There was no response to treatment with quinine, local 2% procaine, procaine amide, intramuscular injections of 2 c.c. of 50% $MgSO_4$ solution daily for 10 days, or to intravenous or subcutaneous soluble insulin, 20 units. No improvement in the myotonia followed curarization. There was no change on restriction of, or loading with, sodium. Ion-exchange resins in the sodium phase had to be abandoned after 2 days because of vomiting and diarrhoea, the patient refusing further therapy. A course of therapy designed to deplete body potassium was begun as illustrated in Fig. 1; dramatic results followed the addition of chlorothiazide, which has a marked potassium-depleting effect. The dosage has been adjusted as shown in Fig. 1 and for the past year the patient has been free of myotonic symptoms and able to run her household and work as a saleswoman. The emotional lability has improved.

Case 2

R.P., 13-year-old son of case 1. Height 4 feet. First developed myotonia at the age of 12 years. His symptoms have been mainly confined to the hands and are not troublesome enough to warrant therapy.

Case 3

I.P., 11-year-old daughter of case 1. Height 4 feet. The short stature is familial, the father's height being only 5 feet. Prominent musculature. First noticed myotonia at the age of 9 years. The myotonia has been of moderate severity and has prevented her participation in sporting activities. Her stiffness has made her the object of ridicule at school. Intellectually bright, and top in her class.

All investigations were normal. A course of chlorothiazide was started. For the past year a careful watch has been kept on the renal tract for the development of hypokalaemic tubular damage, but this has not occurred. The serum potassium is at present 3 mEq./litre and there has been a marked improvement in the myotonia.

Case 4

O.P., aged 17 years, has suffered from myotonia since the age of 5 years. Walking commenced at the age of 2. Fortunately, his myotonia was relieved to a degree by quinine and he has been able to cope with his schooling. A course of cortisone acetate, 50 mm. *t.d.s.*, was begun. Slight improvement was noted at the end of 3 weeks, enhanced by the addition of chlorothiazide. The dose of cortisone has been reduced and he is steadily improving; he is now able to play sports and has obtained a motor driver's licence.

Case 5

L.L., aged 53 years, complaining of severe muscle stiffness for the past 12 years. On examination he showed considerable sternomastoid atrophy, cataracts, and the baldness associated with myotonia dystrophica. There was no evidence of testicular atrophy. The patient is one of a large family of dystrophics, but has been included in this series not because of the relationship to myotonia congenita, which Mass and Patterson[6] have postulated, but because of the severity of the myotonia. The myotonia affects chiefly the limbs, totally incapacitating the patient. Besides the muscle dystrophy there was a free aortic incompetence of syphilitic origin, an old penile scar, and numerous gouty tophi.

Blood examination. Haemoglobin 16·0 g.%. Leucocytes, 7,100 per c.mm.; normal differential count. Erythrocyte sedimentation rate 4 mm. in the first hour. Prothrombin index 99%. Wassermann reaction negative. *Treponema pallidum* immobilization test 100% positive. Serum uric acid 6 mg./100 ml. Blood urea 23 mg./100 ml. Serum potassium 4·4 mEq./litre. Serum sodium 140 mEq./litre, plasma CO_2 content 29·2 mEq./litre. Total serum protein 6·1 g.%. Electrophoretic pattern of proteins normal.

Cerebrospinal fluid contained 4 lymphocytes per c.mm. and 50 mg. of protein per 100 ml.

The urine was microscopically and chemically normal. Urinary potassium 39 mEq./litre, 17-ketosteroids 10·6 mg. in 24 hours (estimated as dehydro-iso-androsterone), follicle-stimulating hormone less than 6 mouse units.

X-ray of the chest confirmed the left ventricular enlargement detected on examination.

Treatment and progress. A course of cortisone acetate and chlorothiazide was started, and dramatic improvement occurred within 2 weeks. The cortisone has been reduced and is now maintained on 25 mg. of cortisone acetate daily. Though the most troublesome symptom has been relieved, the prognosis in this condition is poor, the atrophy is progressive, and in time all muscles will be affected. Myotonia dystrophica contrasts sharply with myotonia congenita, in which atrophy does not occur and life is not shortened. It is doubtful whether myotonia congenita should be grouped with the muscle dystrophies.

DISCUSSION

There are many aspects of muscle physiology which are incompletely understood. The following is an over-simplified scheme, which only suffices as a framework for picturing some of the major changes which occur during muscular activity (Fig. 2): Muscle consists of 80% water, 17% protein

and the remaining 3% carbohydrates, fats, phosphates, etc.[4] There are 3 major proteins concerned. Myogen forms the bulk of the sarcoplasm; it is water soluble and contains the major enzyme systems. The second is myosin, which is insoluble in water, markedly hydrophilic, and contractile, and carries a negative charge, which is neutralized by Mg^{++} or K^{+}. The third protein is actin, which in the resting state is fibre-like and known as F-actin. On stimulation F-actin

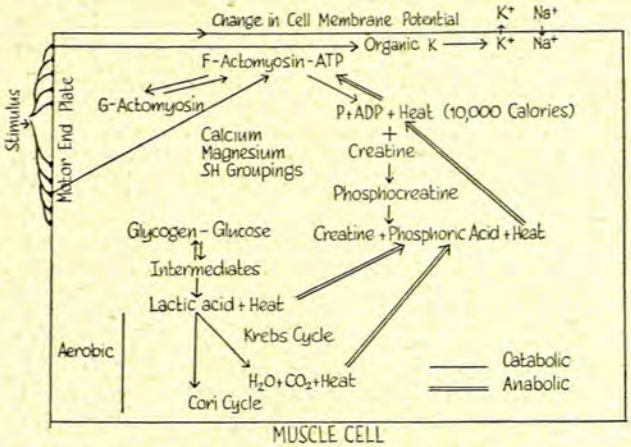

Fig. 2. Schema of muscle-cell metabolism. ATP=adenosine triphosphate. ADP = adenosine diphosphate.

polymerizes to a globular form known as G-actin. The F-actin combines with myosin, forming F-actomyosin, which requires magnesium and sulphhydril (SH) groups for strong linkage.[1] In the resting state adenosine triphosphate is absorbed onto F-actomyosin, the negative charges being neutralized by potassium. Contraction is initiated when the nerve impulse is received and transmitted at the muscle end-plates, causing an ionic disturbance with transfer of ions, particularly liberation of organically bound intracellular potassium in the ionized form, which diffuses out of the cell. At the same time some Na^{+} diffuses into the cell, associated with changing cell-membrane potentials. Fig. 2 outlines some of the chemical and heat changes that occur with muscle contraction and relaxation, the latter being the anabolic state of the cycle.

From both clinical and experimental evidence it would appear that a role of potassium, obscure as it may be, is by virtue of its concentration within the cell (intracellular/extracellular ratio) to produce changes in the contractile ability of the muscle fibre. Extreme depletion, on the one hand, and potassium intoxication, on the other, both result in flaccid paralysis.

Important changes occur with other ions; one may cite the role of sodium and potassium in familial periodic paralysis;[2] magnesium depletion;[5] SH-group depletion;[7] and KCl given intra-arterially causing tonic contraction of muscle.[11] On several occasions it has been possible to demonstrate the mild myotonia in cases of myotonia dystrophica only after a loading dose of oral potassium or intravenous potassium infusion.

It was decided to observe the effects of altering the sodium, potassium and magnesium concentrations in case 1. There was no response to loading with magnesium or the addition of tri-iodiothyronine. The myotonia persisted with curarization, eliminating the possibility of a cholinesterase deficiency. There was no improvement with NaCl loading or depletion. Ion-exchange resin in the Na phase produced nausea and diarrhoea, and the patient refused this therapy. There was no response to insulin, the dosage being limited by the hypoglycaemic effect. Intravenous 40% glucose produced no change. Cortisone acetate was administered as shown in Fig. 1, the response being graded by counting the number of hand flexions and extensions per 15 seconds. After 3 weeks there was some improvement, which was enhanced dramatically with the addition of chlorothiazide. The urinary potassium excretion was doubled. Three weeks later tri-iodiothyronine was added to increase the metabolism and possibly increase the potassium turnover; as this calorific agent was considered unnecessary and of no value, it was stopped after 16 weeks.

The response to treatment was correlated with potassium depletion but, in order to eliminate the possibility of a specific corticosteroid effect on muscle metabolism, the cortisone acetate was replaced with an equivalent dose of prednisolone. The myotonia increased, improving once again on reverting to cortisone acetate. The patient was not aware of the change in therapy at the time. For 2 months adequate control was maintained with increased chlorothiazide, but eventually the additional steroidal depletion effect was needed.

The improvement in case 3 on chlorothiazide, and the excellent response to chlorothiazide-cortisone potassium-depletion therapy in cases 4 and 5, with subsequent reduction of steroid to a minimum maintenance dose, confirm the therapeutic value of this approach.

The cortisone was considered necessary in commencing therapy, in order to enhance the potassium loss and deplete the body stores. Though low serum-potassium levels have been maintained for 18 months in one case, there has been no renal damage, no salt retention, no hypertension, and remarkably little mooning of the face. This has been attributed to the concomitant administration of chlorothiazide.

It must be stressed that potassium depletion is not without danger and must only be undertaken under strict medical supervision. Cortisone must be withheld as long as possible in adolescents because, especially during this period of rapid growth, these glucocorticosteroids may impair protein metabolism. In adults the administration of anabolic steroids largely overcomes this effect.

SUMMARY

Four cases of myotonia congenita, and one of myotonia dystrophica with severe myotonia, are presented. In the 4 cases treated, the response to therapy over the past 18 months has been most gratifying.

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