REDUCED MUSCLE $\alpha$-GLUCOSIDASE (ACID-MALTASE) ACTIVITY IN HYPOTHYROID MYOPATHY

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Summary A detailed biochemical study of muscle from a patient complaining of disabling cramps revealed a lowered activity of $\alpha$-glucosidase (acid-maltase), which was the only abnormality detected. A year after the onset of symptoms hypothyroidism was diagnosed. Treatment with L-thyroxine relieved all symptoms, and the muscle acid-maltase activity was found to be normal six months after the initiation of treatment.

Introduction In the following case the presenting symptoms suggested McArdle's disease (type-v glycogenosis: lack of muscle phosphorylase), and for this reason a detailed biochemical investigation was undertaken.

Case-Report A fire officer, aged 28 years, noticed painful cramps and stiffness in the muscle with exercise in January, 1968. The cramps affected only those muscles involved in any particular exercise and were not affected by cold weather. His exercise tolerance progressively decreased, and some six months after the onset he would have severe cramp on walking 100 yards or after gripping objects for a few minutes. During this period he became aware of considerable muscle development with an increase in weight of 2–3 stone (12–18 kg.). From being a man of slender frame he developed the physique of a professional weight-lifter though he never engaged in any body-building activities. During 1967 and 1968 he had nine brief episodes of central chest pain accompanied by breathlessness. On examination the most notable finding was the massive enlargement of all
muscle-groups: there was no obesity and the muscles were normal on palpation. The initial muscle action was always strong, but weakness with the onset of severe cramp followed sustained activity. During the cramp the appropriate muscles became tender and were shortened, and electromyography revealed motor-unit potentials so that the shortening was due to muscle contraction and not contracture. The thyroid was palpable but not enlarged. There were no other abnormal signs either in the nervous system or on general examination. Electrocardiograms (E.C.G.) taken over intervals showed low-voltage or inverted T waves in all leads and QRS complexes of low-normal amplitude. In April, 1969, the patient began to complain of some intolerance to cold, and it was noted clinically that the skin was excessively dry with keratosis of the hands and there was some coarseness of the voice. The ankle-jerk reflex-time was normal. Primary myxœdemata was diagnosed clinically, and this was confirmed by tests of thyroid function. On May 3 daily L-thyroxine therapy was started; the initial dose was 0.05 mg. and this was increased over 18 days to a maintenance dose of 0.2 mg. Within 4 weeks of first taking the L-thyroxine the patient could exercise lightly without cramps. The E.C.G. 3½ months after the start of treatment was entirely normal. On examination in October, 1969, 21 months after the onset of symptoms, he had no complaints and was back at work. Muscle bulk had decreased, and forearm girth was 3 cm. less than in September, 1968.

Investigations

The following were normal: full blood-count; Wasserman reaction; glucose-tolerance test; glucose-assimilation test; lactate increase on ischemic exercise; serum electrolytes, urea, B₁₂, folic acid, alkaline phosphatase and carotene; blood-pH before and after exercise; urinary creatine/creatinine ratio; D-xylene excretion; urinary aminoacids; urinary 17-ketosteroids and hydroxy corticoids; faecal fat; X-ray chest and skull; intravenous pyelogram and adrenal tomogram; immunofluorescence test for antibody to skeletal muscle and gastric parietal cells; forearm blood-flow. The mean values of estimations of serum cholesterol (348 mg. per 100 ml.), uric acid (7.8 mg. per 100 ml.), and globulin fraction of the serum-proteins (4.1 g. per 100 ml.) were elevated before treatment; and the uric acid (6.1 mg. per 100 ml.) was slightly abnormal after treatment. Thyroid studies (April–May, 1969). — Basal metabolic rate —27%. Serum-protein-bound-iodine less than 1.0 μg. per 100 ml. (3 estimations). At 4, 24, and 48 hours ¹³¹I neck uptake (%) of ingested dose 4.1, 3.6, and 1.8 respectively (normal range for these times 7–30, 19–51, and 19–49). T₃ red-cell uptake 10% (normal range 11.5–19.5). Thyroglobulin precipitation test strongly positive. Thyroglobulin red-cell titre 1/4000. Immunofluorescence test for antibody
to thyroid microsomes strongly positive. Thyroid antibody latex test positive. These results indicated severe hypothyroidism in the presence of antithyroid antibody.

**Exercise tolerance.**—Changes in the exercise tolerance of the patient, measured with a handgrip ergometer, are shown in fig. 1. The institution of a low-carbohydrate diet from February, 1969, until a week before commencing L-thyroxine treatment, had no significant effect on the patient’s ability to do work. However, within 3 weeks of the start of the L-thyroxine therapy exercise tolerance began to increase steadily, and within a month the patient could perform normal amounts of work without discomfort.

**Serum-enzymes.**—The activities of serum-enzymes during the course of the disease and its treatment are summarised in fig. 2. The initial trend was a consistent generalised increase in enzyme activities. After the initiation of a low-carbohydrate diet the levels of serum-enzyme activity decreased considerably. L-thyroxine therapy had an even more marked effect, and within 5 weeks the serum-enzyme values had returned to normal.

**Histopathology.**—Four biopsy specimens (three taken before and one 6 months after the start of treatment) were examined. The only abnormality was a consistent increase in the mean fibre diameter in all four, the value before treat-

![Graph of work tolerance on handgrip ergometer.](image)

**Fig. 1**—Work tolerance on handgrip ergometer.
L1, L2 = start and withdrawal of low-carbohydrate diet.
T = start of L-thyroxine therapy.
α-GLUCOSIDASE ACTIVITY OF MUSCLE BEFORE AND 6 MONTHS AFTER L-THYROXINE THERAPY

<table>
<thead>
<tr>
<th>Controls (7)</th>
<th>α-glucosidase activity (nmol glucose/g./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient: (a) †</td>
<td>19.0</td>
</tr>
<tr>
<td>(b) †</td>
<td>22.1</td>
</tr>
<tr>
<td>(c) †</td>
<td>21.7</td>
</tr>
<tr>
<td>(d) †</td>
<td>41.4</td>
</tr>
</tbody>
</table>

* Mean in parentheses. † Before treatment. ‡ After treatment.

ment being 84 µ and after treatment 83 µ (controls 45 µ). There was no abnormality of staining reaction, and in particular there was no evidence of glycogen-storage disease (this histological finding was supported by Dr. Brenda Ryman’s finding of a normal glycogen level on quantitative analysis). The following enzymes were studied histochemically and were normal: phosphorylase, lactate, and succinic dehydrogenase. Despite the normal light microscopy, electron microscopy showed generalised sarcolemmal thickening and focal myofibrillar degeneration.

Muscle enzymes.—α-glucosidase (lysosomal acid-maltase) activity, estimated at pH 3.7, in four biopsies from the patient was compared with control values (see accompany-

![Fig. 2—Changes in activities of serum lactate-dehydrogenase (L.D.H.), creatine phosphokinase (C.P.K.), aldolase (Ald.), glutamic-oxalacetic transaminase (G.O.T.), and glutamic-pyruvate transaminase (G.P.T.).](image)

The elevation is a multiple of maximum normal value. L1, L2 = start and withdrawal of low carbohydrate diet. T = start of L-thyroxine therapy.
Fig. 3—Variation of $\alpha$-glucosidase activity (nmoles glucose/g. tissue/min.) with pH of incubation medium before treatment with L-thyroxine.

ing table). The activity was considerably below normal in the three biopsies taken before treatment. 6 months after the start of L-thyroxine therapy the acid-maltase level was in the lower-normal range. The variation of maltase activity with pH is demonstrated in fig. 3. It is below normal at all pH values, but shows the normal pattern of decreasing enzyme activity as the pH approaches neutrality.

Muscle enzymes estimated and found to be normal were L.D.H., malate dehydrogenase, C.P.K., and aldolase. Phosphorylase, amylo-1, 6-glucosidase, and phosphofructokinase were found to be present at normal activity levels by Dr. Ryman, who confirmed the low level of acid-maltase activity in the muscle before treatment.

**DISCUSSION**

The association of muscle hypertrophy and cramps with myxœdema has been well recognised since the description by Hoffman, and hypertrophy, cramps, and slowness of movement are recognised in cretinous children as the Debré-Semelaigne syndrome. In this patient the muscle disability was by far the dominant symptom, and the muscle hypertrophy the major sign of hypothyroidism. There was no abnormality in the ankle-jerk reflex-time though this is usually prolonged in the Hoffman syndrome. The increased muscle bulk noted clinically was reflected in the significant increase in muscle-fibre diameter. In the biopsy 5 months after treatment the mean fibre diameter was still above normal.
Before treatment with L-thyroxine α-glucosidase activity was low at acid and neutral pH, unlike the cases, described by Hudgson et al.,² of type-II muscle glycogenosis where the acid-maltase deficiency was of a similar order to that of the present case but at neutral pH the maltase value was normal. 6 months after the start of treatment acid-maltase activity was found to be normal, suggesting that the low activity was the result of hypothyroidism. This finding has not previously been reported, although reduced activity of other enzymes concerned with glycogen metabolism has been described in hypothyroidism.³

The normal muscle-glycogen content in the presence of a reduced acid-maltase activity is an apparent anomaly since an accumulation of glycogen is a constant feature in reported cases of muscle acid-maltase deficiency. It seems likely, therefore, that the acid-maltase deficiency of hypothyroidism differs in some fundamental respect from the deficiency in type-II muscle glycogenosis.

The serum-enzymes were elevated to a higher degree than is usual in hypothyroidism.⁴ Before myxedema was diagnosed, treatment with a low-carbohydrate diet was given for several months because of the suggestion that in patients with acid-maltase deficiency a reduced carbohydrate load may reduce the rate at which glycogen accumulates.² On this diet there was a marked decrease in serum-enzymes but no clinical improvement. The enzymes returned to normal within 5 weeks of initiating thyroxine therapy, and only then did the ability to carry out sustained muscular work improve.

One can only speculate as to the relation of the muscle-cramps to the enzyme deficiency in this patient. An experimental investigation of the effect of altered thyroid function on muscle acid-maltase activity has been started.

We are grateful to Dr. Brian McArdle for discussion and advice, to Dr. Ryman, Royal Free Hospital Medical School, for confirming the muscle acid-maltase activity and for carrying out other biochemical studies; to Dr. Victor Dubowitz and Dr. Peter Hudgson for help; and to Dr. Denis Boyle for advice and for referring the patient. This study was supported by the Muscular Dystrophy Group of Great Britain.

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REFERENCES


The accompanying table shows that the enzyme activities were unchanged 3 months and 6 months after thyroid ablation by 1911. We therefore conclude that, in our patient with myopathy, the reduced acid-maltase activity was not necessarily related to the hypothyroidism, even though the muscle enzyme level did increase by almost 100% after L-thyroxine therapy. However, it does not necessarily follow that the reduced enzyme level made no contribution to his symptoms. Dr. Koster points out that heterozygotes for Pompe's disease are symptom-free; but it is also true that patients with acid-maltase deficiency, restricted to skeletal muscle, develop a severe myopathy in the presence of enzyme levels similar to those described in our patient.

Admittedly, in these cases the myopathy may be due to the storage of glycogen, a feature which was absent in our case. Nevertheless, the fact that the muscle symptoms in this patient were more severe than is usual in myopathies suggests the possibility that the muscle enzyme deficiency may have played some part in the development of the clinical features. Perhaps a certain degree of acid-maltase deficiency may be compatible with normal function but may render the muscle more vulnerable to other potentially myopathic conditions such as myasthenia.

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