CHRONIC THYROTOXIC MYOPATHY

A REPORT OF TWO CASES

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Loss of weight is one of the cardinal symptoms of thyrotoxicosis. General muscular wasting forms an integral part of this process and is, at times, very striking. Very different in character is the local disorder of muscle with severe wasting and profound weakness, which occasionally attends thyroid disease.

Starling[1] in 1938, suggested the following classification of these localized muscular disorders:

1. Exophthalmic ophthalmoplegia
2. Thyrotoxic myopathy; (*a*) acute, (*b*) chronic
3. Thyrotoxic periodic paralysis
4. Myasthenia gravis associated with thyrotoxicosis.

Acute thyrotoxic myopathy is said to be characterized by rapidly progressive weakness involving the bulbar, limb and trunk muscles, with a fatal termination in one or two weeks following respiratory paralysis. This syndrome is not universally accepted as a separate entity,[2] since the few cases reported cannot readily be distinguished from myasthenia gravis occurring in association with thyrotoxicosis.

Chronic thyrotoxic myopathy is characterized by severe muscular atrophy, which frequently involves only a few muscle groups and which often overshadows the other manifestations of thyrotoxicosis. Such disproportionate involvement of an organ or a system in thyrotoxicosis is well recognized. It is perhaps best demonstrated in the so-called 'masked thyrotoxic' cardiac case, where the cardiac features dominate the clinical picture.

In this paper we report two cases of chronic thyrotoxic myopathy in which complete recovery took place.

CASE REPORTS

Case 1

J. de K., White male 49 years old (Fig. 1). After a prolapse of the rectum in April 1953, this patient had experienced loss of strength and energy, tremor, increased sweating, irritability and nervousness, dyspnoea and palpitation on exertion. His weight had dropped from 142 lb. to 128 lb. A prominent symptom at this time was pain, stiffness and weakness, affecting the thigh muscles.

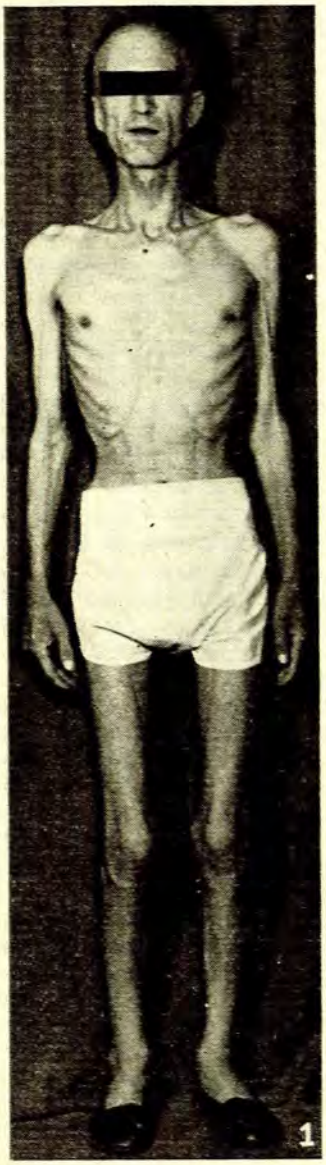

Fig. 1. Case 1. Note extreme emaciation.

In July 1953 a diagnosis of thyrotoxicosis was made (a single BMR reading was said to have been +85%). The administration of methyl thiouracil resulted in gain in weight to 141 lb., symptomatic improvement and slowing of the pulse. Treatment was discontinued in October 1953 because of marked enlargement of the thyroid gland.

In April-May 1954 for one month, the patient had painful, tender, red swellings involving the wrists, metacarpo-phalangeal and proximal interphalangeal joints of both hands and the right knee-joint. Cortisone (dose unknown) was given for 2 weeks, with improvement in the joints. By June 1954 his weight had dropped to 117 lb. and there was, once again, pain and weakness of both thighs, with the development of contractures involving the knees and some of the hand joints. Oral hydrocortisone was given for 2 weeks with no improvement. Thereafter, his weight continued to fall despite a good appetite; the patient lost strength and became shaky; dyspnoea and palpitation recurred.

In January 1955, he was admitted to Groote Schuur Hospital for the first time.

On examination he was found to be extremely wasted (97 lb.). The eyes were staring, but showed no lid-lag, lid-retraction or exophthalmos. A firm, symmetrical thyroid enlargement was present. There was gross wasting of the small muscles of the hand with fixation of several joints and Dupuytren's contractures. Ulnar deviation was present. The knees were partially flexed owing to contracture of the posterior thigh-muscles and there was very gross wasting of these and the anterior group. The wasted muscles were not tender and the skin was normal. Motor power was markedly diminished. The tendon reflexes were normal.

The pulse varied from 90 to 120 beats per minute (the sleeping pulse-rate exceeded 90). There was no tremor; palmar erythema was present, but the palms were not unduly warm or damp.

Haemoglobin 16·5g.%. Leucocyte count 9,700 per c.mm.

E.S.R. 28 mm. in 1st hour (Westergren).

Routine urine examination showed no abnormality.

Special Investigations

X-rays of the hands and knees showed demineralization around the affected joints. The chest film revealed scattered calcified shadows compatible with healed pulmonary tuberculosis.

The electrocardiogram was normal apart from tachycardia.

Serum sodium 138·7, potassium 4·4, chloride 103 mEq./l.

Serum CO_2 combining power 66 vols.%.

Serum calcium 10·1, inorganic phosphorus 4·3 mg.%.

Serum alkaline phosphatase 9·5 units (Bodansky).

Serum albumin 3·8, globulin 1·7 g.%.

Blood urea 29 mg.% on 28 January, 29 mg.% on 16 February 1955.

Serum uric acid 4·5 mg.%.

Thymol turbidity 1, thymol flocculation 0.

Serum cholesterol 177 mg.% (1 February), 194 mg.% (4 March), 198 mg.% (1 April), 204 mg.% (14 May 1955).

Glucose tolerance test: Fasting blood-sugar 73 mg.%; (50 g. of glucose given by mouth) after one hour 150 mg.%, after two hours 125 mg.%.

Urea clearance test (maximum): 1st period 152·5% standard, 2nd period 151·5% standard.

Urine calcium 261 mg./day on 6 February, 212 mg./day on 7 February 1955.

24-hour urine creatinine/creatine excretion (average of several days' collection) (see chart in Fig. 2): 9-11 February 830/350 mg., 24-28 February 1,080/255 mg., 3 March 1,180/200 mg., 18 March 1,010/125 mg., 2 April 800 mg./nil 30 April-3 May 1,020 mg./nil.

Blood Wassermann and Berger reactions negative.

B.M.R.: +32%, +22%, +12% (on successive days before institution of therapy).

Thorn test: Normal eosinophil response to 8-hour intravenous infusion of ACTH.

Neostigmine test: No improvement following 0·5 mg. of neostigmine intravenously.

Lumbar puncture: Normal hydrodynamics and CSF.

Muscle Biopsy: There was some variation in thickness of muscle fibres, with focal areas of sarcolemmal nuclear proliferation; one such area was seen around a necrotic muscle fibre.

No facilities were at hand for radioactive iodine tests or estimation of protein-bound iodine.

Course

On 24 February propyl thio-uracil was commenced in a dose of 200 mg. t.d.s. This was reduced to 100 mg. t.d.s. after 2 weeks.

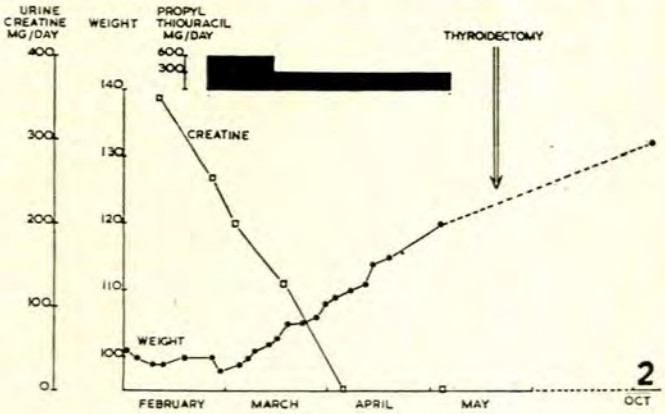

Fig. 2. Case 1. Chart showing response to therapy.

The response which ensued, while not dramatic, was steady and maintained. Within 8 weeks weight had risen from 97 to 114 lb., the tachycardia had resolved, and urine creatine had dropped progressively from the initial reading of 350 mg./day to *nil* on 2 April (see chart in Fig. 2). *Pari passu* with these observed improvements, strength and muscle bulk returned and general symptomatic well-being was restored.

During this therapy the thyroid gland enlarged (maximal neck circumference rose from 13¾ inches to 15¼ inches). Laevothyroxine, 0·1 mg. t.d.s., was administered and reduction in the size of the gland was noted.

On 20 May 1955 subtotal thyroidectomy was performed (Prof. J. H. Louw). The operation passed off uneventfully. Histology of the excised gland showed 'acini lined by low cuboidal epithelium containing thin, pale-staining, eosinophilic colloid. The acini also showed intraluminal papillary projections and, in many, evidence of active resorption of colloid'. These changes were considered to be consistent with diffuse toxic hyperplasia which had been treated.

The patient was discharged on 5 June and subsequent examinations have shown continued improvement in muscular strength and general health. The weight rose steadily after operation to 132 lb.

On his most recent visit (October 1955, 6 months after thyroidectomy) he was in excellent health and had resumed his previous occupation. The only complaint was mild stiffness in the fingers.

Case 2

Mrs. I.R., White female 53 years old. For about 8 months the patient had been aware of general weakness, tiredness and loss of energy; there was increased nervousness, increased sweating, decreased tolerance for warm weather, and palpitation. She had lost 50 lb. in weight, despite an increase in appetite, and had noticed prominence of the eyes with a gritty sensation on closing the lids. Apart from the general weakness she felt particularly weak in the legs, and for some months had been unable to raise herself from a sitting position or to climb stairs.

A few months before admission to hospital a 4-week course of methyl thio-uracil had induced amelioration in her symptoms, with return of strength and vigour. This improvement persisted for about a month after cessation of therapy.

She was admitted to Groote Schuur Hospital on 4 April 1956. Mild thyrotoxicosis was present clinically, as evidenced by warm moist palms, a fine tremor of the outstretched fingers, and tachycardia of the order of 85-90 beats per minute.

The eyes showed bilateral exophthalmos with increased resistance to pressure over the eyeballs. There was lid-lag and lid-retraction, limitation of external-rectus movement and diplopia on looking upward and to the right. The conjunctivae were injected and oedematous.

The thyroid gland was firm, nodular, and asymmetrically enlarged; there were no signs to suggest malignancy.

Generalized muscular weakness was present, but the muscles of the pelvic girdle were disproportionately weak. The patient could not raise her legs while lying in bed and was incapable of rising from a supine position on the ground. Her efforts to achieve the latter movement were reminiscent of those seen in pseudo-hypertropic muscular dystrophy. All the leg muscles were wasted, especially the quadriceps. No fasciculation or fibrillation was seen. Deep reflexes were normal and there was no sensory loss.

Over the anterior and lateral aspects of the tibiae there were firm, reddish, raised areas of thickened subcutaneous tissue suggestive of pretibial myxodema. Some lesions formed well-defined, elevated plaques.

Comment. While thyrotoxicosis was unquestionably present, it must be stressed that its clinical manifestations were far from severe. The signs of ocular involvement and, in particular, the muscular wasting and weakness were quite disproportionate to the degree of manifest toxicity.

Investigations

Blood Wassermann and Berger reactions negative.
B.M.R.: +14%; +12%.
Serum cholesterol 136 mg.%.
Serum albumin/globulin: 3·7/2·7 g.%.
Blood urea 25 mg.%.
Thymol turbidity and flocculation: 1 and 0.
Lumbar puncture: Normal dynamics and pressure. CSF normal chemically and microscopically.

Neostigmine test: 2 separate tests, after 0·5 mg. of neostigmine intravenously, produced no alteration in muscular power. 24-hour urine creatinine/creatine excretion: 10 April 460/285 mg., 18-21 April 840/160 mg., 22-24 April 470/245 mg.

Skin biopsy (taken from a thickened plaque over R. tibia). There was deposition of an acid mucopolysaccharide in keeping with that seen in pretibial myxoedema; the corium showed increased vascularity and negligible inflammatory cell infiltration; there was destruction of collagen and elastic fibres, around which the mucin had particularly aggregated.

Course

On 26 April therapy was instituted with methimazole, 20 mg. twice daily; in addition, in view of the hyperophthalmopathia, laevo-thyroxine, 0·1 mg. t.d.s., was administered with the hope of inhibiting endogenous pituitary thyrotrophin production.

Immediate and striking response followed this treatment. The weight rose from 137 lb. to 145 lb. after 10 days of treatment and 152 lb. after a month. The dose of methimazole was gradually reduced as control of the thyrotoxicosis was achieved.

There was regression of all symptoms, the most dramatic evidence of which was the increase of muscle power in the legs. Within 4 weeks of starting therapy the patient was able to walk up 4 flights of stairs without assistance and with no undue fatigue, and she was able to stand up from a supine position rapidly and easily.

All the thyrotoxic signs gradually abated. The eyes improved slowly; the 'gritty' sensation disappeared, proptosis diminished, and the eyeballs felt less tense; conjunctival injection was reduced. Simultaneously the thyroid gland became smaller, until by the first week of June it was no longer visibly enlarged.

Measurements undertaken by the Department of Physiotherapy showed marked increase in the power of the individual muscle-groups. Measurements of thigh and calf circumferences showed remarkable increment.

On 4 June methimazole was stopped and Lugol's iodine was given pre-operatively. Partial thyroidectomy on 22 June was followed by continued improvement. Histology of the excised gland was that of a multi-nodular goitre with no evidence of malignancy.

DISCUSSION

Chronic thyrotoxic myopathy is a rare condition, as judged by the paucity of cases in the medical literature.[2–6] Kite *et al.*,[3] in 1954, reviewed the clinical features of the condition from an analysis of 43 recorded instances of the disease. They excluded many other cases because of inadequate data, but did not include the apparently acceptable patients, 9 in number, reported by Millikan and Haines.[2]

The majority of patients were male, usually in middle life. The onset was gradual, with slow progression of symptoms over months or years. Predominant were loss of weight, muscular weakness and atrophy. Severe muscle cramps were frequently experienced. The muscles of the shoulder and pelvic girdles were maximally affected, with lesser involvement of peripheral muscles; fasciculation was not uncommon, and the majority of patients showed preservation, or even increase, of deep tendon reflexes. Thyroid enlargement was present in most patients, as was a rapid, fine tremor. Eye signs suggestive of hyperthyroidism were found in about 1/3rd of the total number. Other manifestations of thyroid over-activity were not prominent. The majority showed a raised BMR; a minority exhibited a high urinary excretion of creatine. In the few cases reported in recent years in which radio-active iodine tests and serum protein-bound-iodine examinations were performed, these tests confirmed hyperthyroidism.[2] Occasionally a limited response to neostigmine injection was noted. All the patients who had been followed up showed complete recovery after treatment of the hyperthyroidism.

DIFFERENTIAL DIAGNOSIS

A disorder characterized by such severe weakness and wasting may be confused with numerous conditions,

especially since the underlying hyperthyroidism is often difficult to appreciate clinically.

Progressive muscular atrophy develops in a similar age-group, and the clinical picture may be dominated by loss of weight, muscle wasting with fasciculation, and gross weakness. However, the hands and feet are commonly affected in progressive muscular atrophy, rarely in thyrotoxic myopathy. Bulbar palsies are more frequently seen in progressive muscular atrophy and upper-motor-neurone signs are generally present.

Recently attention has been paid to the condition of polymyositis,[7, 8] which appears to be related to dermatomyositis but which may not display the dermal lesions. Adult cases resemble the facio-scapulo-humeral or girdle type of muscular dystrophy.[9] A group has been described in which a rheumatoid type of arthritis occurs. Muscle biopsy may be necessary to distinguish this from thyrotoxic myopathy, although even this may fail to provide the diagnosis in chronic cases. Electromyography is of value. ACTH or cortisone therapy helps many cases of polymyositis, while a therapeutic trial with an antithyroid drug provides a useful diagnostic criterion in thyrotoxic myopathy.

The muscular dystrophies may be separated on the basis of distribution of weakness, family history and lack of response to antithyroid treatment.

Recently a form of myopathy associated with carcinoma has been recognized. This may be a pure myopathy or may be part of a collagen disease such as dermatomyositis.[10–12] The carcinoma may reside in ovary, breast, stomach, kidney, and many other tissues. In some cases removal of the carcinoma is followed by improvement in the neurological picture.

Finally, considerable attention has been paid to myasthenia gravis and thyrotoxicosis occurring in the same patient,[4, 13, 14] but the reported cases of this association are very few in number. In both conditions ocular palsies, creatinuria and lymphocytosis may occur. But they may be distinguished on other grounds: muscle atrophy is prominent in thyrotoxic myopathy, not in myasthenia gravis; weakness is more marked at the end of the day in myasthenia gravis; drooping of the eyelids, as opposed to lid-retraction, occurs in myasthenia gravis; bulbar palsies are common in myasthenia gravis, unusual in chronic thyrotoxic myopathy; and the response to neostigmine, while marked in myasthenia gravis, is absent, or at best limited, in thyrotoxic myopathy. Response to antithyroid treatment is a valuable point diagnostically. In thyrotoxics with associated myasthenia gravis, the myasthenic features may remit on such therapy although, conversely, a 'see-saw' relationship has been described, the myasthenia worsening as the thyrotoxicosis is brought under control, and *vice versa*.[13]

The Diagnosis in our Patients

Despite the lack of confirmation by serum protein-bound-iodine estimation or radio-active-iodine tests, there can be little doubt that our patients suffered from thyrotoxicosis. The inordinate amount of muscle wasting and weakness common to both patients is the basis for the diagnosis of thyrotoxic myopathy. Both patients exhibited other features of interest:

Case 1 presented with gross weight-loss and muscular weakness. The evidence for thyrotoxicosis was not marked. His course had been punctuated by an episode of arthritis which has left residual contractures. The muscular wasting which was present was far too gross to be explained on an arthritic basis and had, in any case, preceded the development of the arthritis by about a year. The extreme weight-loss suggested neoplastic disease, of which the arthritis and myopathy might have been the presenting features. However, the striking response to therapy renders this diagnosis unlikely.

Case 2 showed the remarkable association of thyrotoxicosis, chronic thyrotoxic myopathy, hyperophthalmopathia, and pretibial myxoedema. Her response to antithyroid therapy was equally gratifying.

SUMMARY

Two cases of chronic thyrotoxic myopathy are presented. The diagnostic features of the condition are reviewed and the differential diagnosis is briefly discussed.

We are pleased to acknowledge our thanks to Prof. F. Forman and Dr. S. Berman for their advice and interest; to Prof. J. F. Brock for permission to present case 1, who was under his care; to Prof. J. H. Louw and Mr. R. Lane Forsyth, under whose care case 2 was admitted; to Prof. G. Linder for the biochemical estimations; to Dr. C. J. Uys and Dr. G. Selzer for the pathological reports; to Mr. B. Todt for the photographs; and to Miss M. Lloyd for preparation of the chart.

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