MYOPATHY OF HYPOTHYROIDISM

BY

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Few present-day physicians, aside from endocrinologists, know that hypothyroidism may cause a profound myopathy. Past generations of clinicians, however, were well aware of this. As long ago as 1880, Ord described a patient as follows:

"Her strength failed, her activity, bodily and mental, declined; her movements became slower and slower; and the muscles of the neck in particular were from time to time affected with remarkable weakness. Of late she could not keep her head erect; in spite of all her efforts to the contrary it would fall forward, and the chin, resting on the lower part of the neck, would hinder swallowing and even embarrass her breathing. She had become unable to raise herself from a stooping position; her gait was staggering like that of a drunken person; she often fell down by reason of the knees giving way . . ."

Necropsy showed that all organs, including muscle, had a massive increase in connective tissue. Years later, Tatum (1913) made complete thyroidecomies on rabbits and observed that striated muscle had a serious infiltration, atrophy, and fatty degeneration. Some fibres contained vacuoles and others were hyaline.

There are many reports, particularly in the literature of the first half of the 20th century, that describe myopathy in patients with clinically-established hypothyroidism. Muscular symptoms as the earliest feature of hypothyroidism were stressed by Wilson and Walton (1959). The present paper reports three patients with hypothyroidism in whom the muscular symptoms were the first to be observed. These three patients represented 5·6 per cent. of all patients with acquired myopathic disorders seen during the past 2 years.

Case Reports

Case 1, a 45-year-old woman, had had pain in the entire spine for the previous 7 years and, for the past year, in the thighs, calves, arms, hands, and fingers. The pain was in the muscles rather than in the joints and was especially bad at night, awakening her three or four times. She had not noticed any specific weakness, although she had felt generally exhausted for about 8 months. For about a year she had had symptoms suggesting carpal tunnel syndrome, the lateral three fingers of the right hand becoming numb as often as a dozen times per day. She had been quite depressed during the previous year. She had noted no hair fall or change in her voice.

Examination.—The thyroid was not enlarged and the pulse rate was within normal range. The joints were all normal. The patient was able to hold her neck off the couch for only 45 seconds (normal time> 60), and could arise from the supine position only with the greatest difficulty unless she used her hands. She was able to perform deep knee bends only very awkwardly. There was definite weakness of the deltoid and the iliopectos muscles. When lying supine, she was able to hold the straight lower limb at 45° to the horizontal only for 35 seconds on the right and 20 seconds on the left (normal time> 60).

Laboratory Findings.—Creatine phosphokinase (CPK) 99 units (normal value< 12); protein-bound iodine (PBI) 4·2 µg./100 ml.; red blood cell uptake of triiodothyronine (T3) 31 per cent. (normal values 25-35); and 24-hr. radioactive iodine uptake 16 per cent. (normal> 20 per cent.). The photomotogram ("one half of the relaxation time" of the Achilles reflex) was 280 msec. (normal value< 380). The electromyogram was normal.

Muscle Biopsy.—There was an increase in numbers of sarcolemmal nuclei, many of which were hyperplastic and many of which were centrally located. An occasional arteriole was infiltrated by lymphocytes.

Treatment.—It was believed that this patient had idiopathic polymyositis and it was decided to observe her for a short while before starting any definitive therapy. After 6 weeks the thyroid function tests were repeated; now the radioactive iodine uptake was 5 per cent. in

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24 hours; and the PBI 2·5 μg./100 ml. Red blood cell uptake of T₃ was 29 per cent. The patient then mentioned that previous tests had shown low thyroid function; we learned from her former doctor that 2 years ago her PBI had been 2·5 μg./100 ml., and that she had taken a small dose of thyroid for approximately 6 months.

The patient was started on thyroxine, 0·2 mg. daily, which was later increased to 0·3 mg. daily. She was now found unable to arise from the supine position without the aid of her arms; 3 months later she felt no better, and muscle testing showed no improvement. Thyroxine was stopped and triiodothyronine started, gradually reaching a dose of 25 μg. four times daily. A month later, when there was still no improvement, prednisone (7·5 mg. daily) was added.

After 3 months on the combined therapy, muscle strength remained unchanged, and the prednisone dosage was increased to 40 mg. daily; 4 months after starting the high dose of prednisone she felt more energetic, and muscle pain was abating, and there was marked objective improvement in muscle strength. The prednisone was gradually withdrawn over the following 2 months and when she was last seen she was without symptoms or signs.

**Case 2, a 65-year-old man**, complained that for the past 2 years he had experienced severe muscle cramps that recently had become disabling. They affected the muscles of the four limbs, the trunk, and the face. They were so severe that they had enforced his temporary retirement, and so prolonged that they caused contraction of the neighbouring joints. The cramps were precipitated by cold in particular, and by sudden changes of posture. Some observers had thought that he had myotonia.

The patient had been bald since the age of 21, and there was a family history of baldness. The family history was further significant in that one brother and a sister experienced severe muscle cramps.

**Examination.**—There was slight weakness of the shoulder girdle and of both ilioiopsoas muscles. The pulse rate was within the normal range. The thyroid gland was slightly enlarged and contained several small nodules.

**Laboratory Findings.**—Raised CPK levels 198 and 240 units; PBI 1·6, 1·9, and 2·0 μg./100 ml.; serum thyroxine iodine < 1·0 μg. (normal value > 3·4); red blood cell uptake of T₃ 23, 25, and 27 per cent.; 24-hr. radioactive iodine uptake 21 per cent.

**Muscle Biopsy** (Fig. 1).—Definite variation in muscle fibre size, a mild increase in the numbers of sarcosomal nuclei, and a solitary focus of chronic interstitial infiltrate. Electromyography was normal.

**Treatment.**—It was considered that this patient had hypothyroid myopathy and he was started on thyroxine, gradually increasing to a dose of 0·2 mg./day. Seen 2 months later he was without symptoms and the muscle strength was considered to be normal.

**MYOPATHY OF HYPOTHYROIDISM**

Case 3, a 28-year-old woman, complained of aching in the calves, thighs, buttocks, and arms. The pain in the lower limbs was constant but occurred in the arms only with exertion. This myalgia had been present for 1 year and was becoming progressively worse. There was an associated feeling of exhaustion and lethargy that was worse just after her menstrual periods.

The family history was significant in that her aunt had suffered from similar muscle pains for several years.

**Examination.**—There was neither enlargement nor tenderness of the thyroid gland and the pulse rate was within the range of normal. The muscles showed mild weakness of external rotation of both shoulders, and of extension and adduction of both hips, difficulty in arising from the supine position with the arms crossed over the chest, and considerable tenderness of the thighs and buttocks.

**Findings.**—These were initially unhelpful apart from the presence of a slight rise in serum aldolase, to 2·7 m. units/ml. serum (normal value < 2·5). Electromyogram
normal. PBI 5·2 and 8·0 μg./100 ml.; red blood cell uptake of $T_3$ 20 per cent.; 24-hr. radioactive iodine uptake 20 per cent. Photomotogram 280 msec.

Muscle Biopsy (Fig. 2).—A rare muscle cell had a mild increase of basophilic staining and several nuclei located centrally.

![Muscle biopsy](image)

Fig. 2.—Muscle biopsy (Patient 3). A single fibre shows increased basophilia, and four hyperplastic centrally-located nuclei (the number of nuclei is more convincingly seen in the original preparation). Haematoxylin and eosin. × 1,000.

Progress.—It was considered that this patient probably had low-grade chronic polymyositis. During the next few months, however, she saw several doctors including two general physicians, an endocrinologist, and a neurologist, whose consensus was that she probably was psychoneurotic and had no significant endocrine or muscle disease. Studies during this time showed normal values for serum aldolase, serum hydroxybutyric dehydrogenase, CPK, and serum glutamic oxalacetic transaminase (SGOT). The PBI was 5·4 μg./100 ml., and the photomotogram 340 msec.

Second Consultation.—When seen 9 months after the first consultation, the patient complained of general weakness, spells of drowsiness, aching and twitching of muscles, pain in the chest, soreness in the jaws, alternating diarrhoea and constipation, palpitations of the heart, trembling of the extremities, dizziness, a feeling of lack of oxygen, and poor circulation. Examination now showed that the thyroid gland was mildly but diffusely enlarged. All muscle groups were now considered to be normally strong. The radioactive iodine uptake was 15 per cent. Further thyroid function studies showed PBI 6·1 μg./100 ml.; red blood cell uptake of $T_3$ 23 per cent., and photomotogram in the hypothyroid range (420 msec.). The radioactive iodine uptake, repeated 1 month later, was only 11 per cent.

Treatment.—Hypothyroid myopathy was now diagnosed and the patient started on thyroxine, but after taking 0·2 mg. of the hormone daily for 3 weeks she noted no improvement at all; her muscle aches and pains and the complaints of weakness were as severe as before and examination showed weakness of both iliopsoas muscles. The thyroxine was then increased to 0·3 mg./day, and 3 months after starting the drug she began to feel much less tired than before, but discomfort in the joints of the fingers and knees appeared; 6 months after starting the thyroid hormone, however, most of the symptoms had disappeared. She estimated that her muscles were about 75 per cent. better, but objective testing showed residual weakness of both iliopsoas muscles. CPK at this time was raised to 35 units. She has not been seen since.

Special Studies

Antibodies to muscle were looked for, as reported in detail elsewhere (Fessel and Raas, in press), using direct and indirect fluorescent antibody methods, complement-fixation with muscle antigen, and double diffusion in agar with a saline extract of muscle.

Thyroid Antibodies were looked for by the tanned red-cell method.

Glycogen and phosphorylase levels were measured in the muscles of all patients.

It was not possible to demonstrate the presence of antibodies to muscle in the patients' serum or muscles by the above methods. Thyroid antibodies were present in only one serum (Patient 2), in the low titre of 1:140. The phosphorylase levels were low in two of the muscles studied. In one muscle with low phosphorylase levels, glycogen synthetase was present in normal amounts. Glycogen levels were normal in two of the muscles; there was insufficient tissue for this estimation in one muscle that contained a low phosphorylase level. These observations are being pursued.


MYOPATHY OF HYPOTHYROIDISM

Discussion

The three patients were each referred for the diagnosis of their muscle complaints; in none was there clinically obvious hypothyroidism. This experience re-emphasizes the statement by Wilson and Walton (1959) that muscular symptoms may be the first manifestations of hypothyroidism. Those physicians who have experience in treating hyperthyroidism with radioactive iodine know that complaints of myalgia and cramps may portend hypothyroidism. But the observation came as a surprise that among 53 patients seen in a community hospital for various acquired disorders (Table), three (5.6 per cent.) had unexpected hypothyroidism.

It is worth stressing that the thyroid function tests were normal when two of the three patients were first seen. In one subject, the thyroid function tests fell to within the hypothyroid range only after 10 months. Bergouignan, Vital, and Bataille (1967) reported the case of a patient with muscle pains for 4 years, during which he made diverses pérégrinations médicales, before the diagnosis of hypothyroidism was reached. Presumably, in some patients, the tissue response is a more sensitive indicator of thyroid deficiency than the laboratory tests. It would seem worthwhile, therefore, to make repeated tests of thyroid function in patients with so-called idiopathic polymyositis while that they are under observation.

This experience is reminiscent of that of Jellinek and Kelly (1960) with cases of cerebellar degeneration in association with myxoedema; they pointed out that the features of myxoedema were by no means clinically obvious in some, and that three of their six patients had been seen by general physicians who failed to recognize the myxoedema.

In my Patients 1 and 3 the muscular symptoms were not totally reversed after several months of replacement therapy with thyroid hormone. This might be thought to demonstrate that these were not true cases of hypothyroid myopathy. Yet the same irreversibility by treatment with thyroid hormone was seen by Astrom, Kugelberg, and Muller (1961) in two of their eight patients, and by Rimbaud and Passouant (1947) in one of theirs. The two patients reported by Bergouignan and others (1967) each had a symptomatic recovery after thyroid therapy, but a second biopsy showed persistent abnormalities—sarcoplasmic masses and ringed-fibres were prominent both before and after treatment. Wilson and Walton (1959) presented a patient whose strength recovered with thyroxine but who relapsed when thyroid extract was substituted. They suggested the possibility of a defect in the breakdown of thyroid to thyroxine. Rimbaud and Passouant (1947) wondered whether the muscle fibres under certain circumstances might become unresponsive to thyroid hormone. On the other hand, this may have to do with the length of time necessary for complete recovery; it took 3 months for strength to return in one patient of Nickel, Frame, Bebin, Tourtellotte, Parker, and Hughes (1961), 5 and 6 months in two of the cases reported by Norris (1966), and 6 months in my Patient 3.

Lambert and Sayre (1955) studied the effect of thyroidectomy on rabbits and observed that whilst the electromyographic abnormalities quite rapidly disappeared after replacement therapy with thyroxine, the resolution of the structural changes in the muscles took a great deal longer. Analogous situations are those in which the colonic abnormality (Kelley and Stewart, 1964), cerebellar disorder (Jellinek and Kelly, 1960), and renal lesion (DiScala, Salomon, Grishman, and Churg, 1967) associated with myxoedema did not recover after adequate replacement with thyroid hormones; the thyrotoxic myopathy progressed despite proper treatment of hyperthyroidism (Schwarz and Rose, 1963), and the myopathy seen in hyperparathyroidism had not been completely reversed one year after parathyroidectomy (Bischoff and Esslen, 1965).

The various sorts of muscular disorder that may be seen in hypothyroidism include:

(1) Hypertrophy of muscle with or without myotonia, both in acquired myxoedema (the so-called Hoffman syndrome) and, also, in congenital hypothyroidism (the so-called Debré-Semelaigne syndrome);

(2) Atrophy of muscles described by Alajouanine and Nick (1945), and seen by Rimbaud and Passouant (1947) in a case that progressed despite the use of thyroid replacement.

Severe pain, a prominent feature in one of my patients, has not usually been reported as a major problem of hypothyroid myopathy. Pain was not emphasized by Rimbaud and Passouant (1947) in their review, or by Nickel and coworkers (1961) who studied 25 patients with known myxoedema. Although Nickel and others (1961) found that muscle cramps were present in fourteen of their patients, they did not see persistent pain. Alajouanine and Nick (1945) and Bergouignan and others (1967), however, emphasized the presence of pain in their four patients.

Each of my three patients had features that would entitle one to diagnose polymyositis according to the usual criteria: namely, the presence of muscle pain or weakness, increase in those serum enzymes
considered to reflect muscle damage, and abnormalities in the muscle biopsy. Although only one showed a slight cellular infiltrate in the biopsy, other authors have seen considerable infiltrates in the muscles of hypothyroid patients. Garcin and Bertrand (1935) reported a patient who not only had degenerative and regenerative changes in the muscles, but also massive infiltration of histiocytes. Rimbaud and Passouant (1947) indicated that in one of their cases there was a marked cellular infiltrate with lymphocytes. Astrom and others (1961) reported on eight patients, of whom one showed severe acute degeneration of muscle fibres together with invasion by macrophages and lymphocytes. This sort of histopathological appearance in conjunction with the clinical picture of muscle pain and weakness raises the question of the diagnostic significance of the term polymyositis; although it is not the purpose of this paper to discuss this in any detail, it is worth pointing out how unspecific this term is and how important is the pursuit of possible underlying aetologies in patients diagnosed as having polymyositis. Not only may polymyositis be part of an underlying connective tissue disease or a remote effect of a neoplasm, but it may also reflect an underlying endocrine disorder; hypothyroidism, hyperthyroidism, Cushing's syndrome, and hyperparathyroidism must always be considered.

The prevalence of hypothyroidism in patients with myopathy is difficult to estimate, but as shown in the Table, among my 53 patients with acquired muscle diseases seen in a community practice, there were three (5.6 per cent.) with hypothyroidism. Each case of hypothyroid myopathy was at one time thought to be polymyositis: if these two groups, i.e. those with polymyositis and those with hypothyroidism, are added together, it is seen that three (9.1 per cent.) of 33 patients with polymyositis had hypothyroidism. Whether myopathy truly results from hypothyroidism in an individual patient or is coincidental is difficult to state with certainty; this is so even if there is an improvement after treatment with thyroid because idiopathic polymyositis may undergo spontaneous remission. Yet it seems extremely improbable that among 53 patients with miscellaneous disorders there would be three with hypothyroidism; this high prevalence of hypothyroidism in a group of patients with myopathies makes it seem likely that there is a causal relationship between the two conditions.

Contrariwise, the prevalence of myopathy in hypothyroidism is easier to estimate. Nickel and others (1961) performed biopsies in twelve patients and found myopathic changes in all of them. Saito, Hibi, Kawazura, and Fukuyama (1963) and Ekbom, Hed, Herdenstam, and Nygren (1966) saw raised serum levels of creatine phosphokinase in all patients with hypothyroidism. In their 75 patients, Collins, Zimmer, Johnson, and Kough (1964) recorded neuromuscular complaints in 54 (72 per cent.), complaints of weakness in 33 (44 per cent.), and muscle cramps or stiffness in fifteen (20 per cent.). Thus, although the precise prevalence depends upon the mode of detection, a muscle disorder is extremely common in hypothyroidism.

Possible mechanisms for the myopathy seen in hypothyroidism include an autoimmune reaction affecting the muscle, infiltration by "myxoedema", or a disorder of the muscle membrane. An autoimmune reaction might independently cause chronic thyroiditis and hypothyroidism, and polymyositis. Two facts are against this idea: only one patient's serum contained thyroid antibodies, which are almost always seen in chronic thyroiditis; and no antibodies against muscle were demonstrated in any patient (Fessel and Raas, in press). It seems most likely that thyroid deficiency affects the muscle cells directly. A serous infiltration of muscle was seen in experimental cretinism by Tatum (1913), although this finding in human myxoedema is mentioned in only occasional case reports and was not seen in the biopsies of the three patients reported here. Thyroxine is well known to have important effects on the cell membranes. For example, Gustafsson, Tata, Lindberg, and Ernst (1965) observed that thyroidectomy led to an increase in the total amount of mitochondria in muscle and that the ratio of cristae to matrix within the mitochondria was increased. Norris and Panner (1966) saw important changes in the mitochondria by electron microscopy in their case of hypothyroid myopathy. The serum enzymes may rise to high levels in hypothyroidism, presumably because thyroid deficiency permits leakage across muscle membranes and, possibly, actual muscle necrosis (Saito and others,

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>Polymyositis</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>21</td>
</tr>
<tr>
<td>Secondary to cancer or collagen disease</td>
<td>9</td>
</tr>
<tr>
<td>Hypothyroid myopathy</td>
<td>3</td>
</tr>
<tr>
<td>Others (including five endocrinopathies)</td>
<td>20</td>
</tr>
</tbody>
</table>
MYOPATHY OF HYPOTHYROIDISM

1963; Griffiths, 1965; Ekbom and others, 1966). The evidence suggests that thyroid deficiency has a direct action on muscle, most likely on the various cell membranes.

Summary

Three patients with hypothyroidism whose presenting symptoms were in the muscles were seen among 53 patients with acquired myopathy observed during a 2-year period. Pain was a prominent feature. Two of the patients required prolonged replacement of thyroid hormone for reversal of the muscle reaction, and in one prednisone was also necessary. Evidence suggests that the relationship between hypothyroidism and a muscle disorder may be causal rather than coincidental. The mechanism is unexplained.

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Dr. Hibbard Williams estimated the muscle phosphorylase and glycogen levels; Dr. Hugh H. Fudenberg made the thyroid antibody titrations; Dr. Alvin Glass performed and interpreted the electromyograms. Patients 2 and 3 were referred by Drs. Alvin Glass and W. H. Tu.

REFERENCES

Myopathie hypothyroïdienne

Parmi 53 malades atteints de myopathie acquise et observés pendant 2 ans on a trouvé trois cas d’hypothyroidisme se manifestant par des symptômes musculaires, et principalement par la douleur. Une thérapie prolongée de remplacement par l’hormone thyroïdienne pour renverser la réaction musculaire était nécessaire chez deux d’entre eux et le traitement par la prednisone chez un. Les données existantes suggèrent que le rapport entre l’hypothyroidisme et l’atteinte musculaire n’est pas fortuit, mais le mécanisme de ce rapport n’est pas connu.

Miopatía hipotiroidea

Entre 53 enfermos con miopatía adquirida, observados durante dos años, se encontraron tres casos de hipotiroidismo con síntomas reveladores en los músculos, particularmente el dolor. Una terapia prolongada de substitución por la hormona tiroidea para invertir la reacción muscular fue necesaria en dos de ellos y el tratamiento por la prednisona en uno. Los datos sugieren que la relación entre el hipotiroidismo y la sintomatología muscular no es casual, pero el mecanismo de esta relación no es conocido.
Myopathy of hypothyroidism.

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