Regular Review

Endocrine myopathies

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The effect of hormones on muscle activity and the association of muscle disease with endocrine abnormalities are fascinating subjects about which much is still to be learnt. Most endocrine diseases have an associated myopathy and, though a common feature, it may be overlooked since it is rarely the presenting complaint. Endocrine myopathies are usually reversible with correction of the underlying disturbance, but despite increasing knowledge of the metabolic effects of hormones little is known about their pathogenesis. In this article we review current knowledge from a clinical standpoint.

Thyroid disorders

THYROTOXIC MYOPATHY

Myopathy commonly occurs in hyperthyroidism. Examination of 54 unselected patients showed clinical myopathy in 44,¹ but electromyographic studies detected abnormalities in nearly all of them. Few patients, however, seek attention on account of muscle weakness. Symptoms are primarily those associated with a chronic proximal myopathy—for instance, difficulty in climbing stairs, rising from a chair, or brushing hair. Bulbar or respiratory muscle features are rare.^{2,3} The pectoral muscles are more severely affected than those of the pelvic girdle and wasting may be appreciable. Occasionally distal muscles may also be affected. The tendon reflexes are present and often brisk. An acute myopathy has been described, but is probably due to coexistent myasthenia gravis rather than the hyperthyroidism alone.¹

Electromyographic abnormalities are non-specific but there is no spontaneous electrical activity.¹ Serum creatine kinase activity is normal despite muscle weakness and wasting; serum myoglobin concentrations are normal.⁴ Routine histopathological examination shows only non-specific changes in biopsy material.¹ Histochemically there is atrophy of both fibre types,⁵ and some patients have an increased frequency of type 2 fibres.⁶ Experimental thyrotoxic myopathy in rats produces similar changes with fibre atrophy and conversion of fibres from type 1 to type 2.⁷ Ultrastructural abnormalities of the muscle are non-specific.⁸

The development of myopathy is probably a direct effect of the increased concentration of circulating thyroid hormones. The muscle atrophy is due to increased protein catabolism by thyroid hormones, with increased lysosomal activity and release of amino acids.^{9,10} The weakness in hyperthyroidism probably results from a combination of factors including reduced membrane excitability and a lower power of contraction due to an increase in the rate of relaxation.^{5,6}

Treatment of the hyperthyroidism results in full recovery from the myopathy.

THYROTOXIC PERIODIC PARALYSIS

Thyrotoxic periodic paralysis¹¹ is unrelated to the periodic paralysis of primary hypokalaemia, though similar changes in serum and urinary electrolytes and in response to administration of glucose, insulin, and potassium are found in both conditions. Almost all the cases described have occurred in patients of oriental descent, but it is not a familial condition. Men are affected six times more commonly than women. The first attack is usually between the ages of 20 and 39 years, corresponding to the age incidence of hyperthyroidism. Attacks tend to occur during the hot season and then only during the period of active hyperthyroidism. With restoration of the euthyroid state spontaneous attacks disappear and cannot be induced by administration of 9 α -fludrocortisone.

The paralysis first affects the proximal muscles of the legs and then spreads to the arms and trunk, but rarely affects the bulbar muscles. In some cases the muscles most affected are those that are most exercised. The duration of the attack appears to be directly proportional to its severity; it may last only a few hours, whereas in some cases weakness persists for one to two weeks.¹¹ During an attack electromyography shows a myopathic pattern with a decrease in the duration of the muscle action potential and an increase in polyphasic potentials.¹² Muscle biopsy specimens may show central and sarcolemmal vacuoles in addition to the changes seen in hyperthyroidism. Vacuolisation is also seen on electron-microscopical examination and the vacuoles appear to represent areas of focal dilatation of the sarcoplasmic reticulum.

Treatment is directed against the underlying hyperthyroidism and its correction abolishes episodes of periodic paralysis.

OPHTHALMOPLEGIA

Ophthalmoplegia is associated with Graves' disease but does not parallel thyroid overactivity; it may occur in euthyroid patients, when it is termed ophthalmic Graves' disease.¹³ The extraocular muscles become greatly enlarged, firm, rubbery, and resistant to passive stretching,¹⁴ which may lead to diplopia. Chronic diplopia results from tethering of fibrosed extraocular muscles. Upward and lateral gaze are most commonly affected. The ophthalmoplegia may be associated with other features of Graves' ophthalmopathy, including proptosis, and in severe cases loss of visual acuity, which is secondary to the raised retro-orbital pressure that results chiefly from the increase in muscle bulk. Diagnosis is made on evidence of bilateral extraocular muscle involvement, other evidence of ophthalmopathy, or the presence of autoimmune thyroid disease. These features are not invariable, however,

and the condition may be unilateral. Routine thyroid function tests, estimation of thyroid antibody titres, and a thyrotrophin releasing hormone test are helpful in diagnosis but do not invariably give abnormal results. The condition has been investigated in various ways: ultrasonography¹⁵ and computed tomography¹⁴ show swelling of the muscles; microscopy of diseased muscles shows myositis with interstitial inflammatory oedema, cellular and fatty infiltration, necrosis of muscles, and, later, fibrosis.^{16 17}

Graves' ophthalmopathy is regarded as an organ specific autoimmune disease, probably distinct from, though closely related to, autoimmune thyroid disease. The pathogenic mechanisms are unknown. Thyroid stimulating antibodies are not responsible^{13 18} but specific ophthalmopathic immunoglobulins reactive with eye muscle antigens are found in the serum¹⁹; there is also some evidence to suggest that there is a cell mediated immune response against retro-orbital muscle antigens²⁰ and that there is deposition of immune complexes.¹⁴

Ophthalmoplegia is treated by inducing and maintaining a euthyroid state and, when the thyroid and ocular diseases become stable, correcting the diplopia surgically. Severe proptosis may require tarsorrhaphy to protect the cornea, or orbital decompression, or both. When congestive ophthalmopathy is present and vision is threatened high doses of steroids are indicated.

THYROID DISEASE AND MYASTHENIA

Myasthenia gravis is now generally accepted to be an autoimmune disease, so not surprisingly it is seen more commonly than would occur by chance in association with autoimmune thyroid disease. Ramsay calculated from cumulative data that the prevalence of myasthenia gravis in hyperthyroidism is 0.77 per 1000 and that of hyperthyroidism in myasthenia gravis at least 50 per 1000; moreover, he deduced that about 16% of patients with myasthenia have thyroiditis, a few of whom are hypothyroid.¹ The relation appears to be that of two autoimmune conditions occurring in genetically predisposed subjects, but there is no evidence for a causative association, nor for cross reactivity of the pathogenic antibodies.

The clinical features of myasthenia in association with thyroid disease do not differ from those of myasthenia alone, where fatigable muscle weakness is typical. The muscles affected include bulbar, eye, proximal, trunk, and respiratory muscles. In the presence of hyperthyroidism the weakness might be mistaken for thyrotoxic myopathy, but the distribution and fatigability are characteristic and should suggest the diagnosis of myasthenia gravis. Ptosis and diplopia are frequent in myasthenia and may lead to confusion with ophthalmopathy in patients with thyroid disease.

The diagnosis of myasthenia may be confirmed with the edrophonium test, which gives negative results in thyrotoxic myopathy and the ophthalmopathy of Graves' disease. Electromyographic studies with repetitive stimulation may show a decremental response of postactivation facilitation and exhaustion. Single fibre electromyographic studies provide a rather more sensitive diagnostic test. Muscle biopsy is not helpful.

Myasthenic weakness is worse in the presence of hyperthyroidism or hypothyroidism,^{21 22} so that management includes correction of the thyroid dysfunction as well as conventional treatment of the myasthenia with drugs or thymectomy.

HYPOTHYROIDISM AND MUSCLE DISEASE

Pain, cramps, and stiffness of muscles are common symptoms in hypothyroidism, and mild proximal muscle weakness occurs in over a third of patients. Pseudomyotonia with delayed relaxation of muscle may occur and a prolonged tendon reflex relaxation time is typical. Myoedema, the "mounding phenomenon," may be elicited in some hypothyroid patients on direct percussion of the muscle. A rare association is Hoffman's syndrome, which is characterised by muscle hypertrophy, weakness, and slowness of movement.

The differential diagnosis is from other causes of painful, stiff muscles such as polymyalgia rheumatica and polymyositis. The reflex relaxation time is a useful diagnostic test, and the serum thyroid stimulating hormone concentration should be measured when the doctor is in any doubt. Increased serum activities of enzymes of muscle origin, particularly the creatine kinase isoenzyme, are found in hypothyroidism whether or not muscle symptoms are present.²³ Serum myoglobin concentrations are also raised.¹ Electromyographic studies show a reduction in the mean action potential duration and an increase in the number of polyphasic units in over a third of hypothyroid patients with either normal or hypertrophied muscles. Routine histopathological studies show non-specific findings, but histochemical studies have shown atrophy and reduced frequency of type 2 fibres.^{6 24} Type 2 fibres are fast twitch fibres with fewer mitochondria than type 1 fibres, which are predominantly slow twitch fibres. The apparent reduction in type 2 fibres may be a result of conversion of these fibres to type 1. This would support the findings in experimentally induced hypothyroid myopathy in rats, where there is conversion of fibres from type 2 to type 1.²⁵ The ultrastructure abnormalities are non-specific.

The clinical, biochemical, and electromyographic changes associated with muscle lesions in hypothyroidism are reversible if the patient is treated with replacement thyroid hormone.

Disorders of corticosteroids

Muscle weakness is a feature of both Cushing's syndrome and of an excess of exogenous corticosteroids. Muscle weakness and tiredness sometimes associated with myalgia are common symptoms, and proximal muscle weakness is an almost universal finding in Cushing's syndrome. The muscles of the pelvic girdle are primarily affected, and atrophy usually accompanies the weakness. The myopathy induced by exogenous corticosteroids is clinically identical with that of endogenous Cushing's syndrome. Tolerance to corticosteroids is variable and not related to age, nor does it appear to be related to the size of the dose or the duration of treatment.²⁶ Certain steroids are more likely to induce a myopathy than others—9 α -fluorinated steroids such as dexamethasone and triamcinolone appear to be particularly harmful to muscle.²⁷ Usually the onset of myopathy is insidious, but occasionally it is acute, particularly in response to exogenous corticosteroids, when it may develop over a few days.

Muscle enzyme activity is usually normal, though the serum creatine kinase activity may be slightly raised. Creatine excretion in the urine is increased, its extent correlating well with the extent of muscle weakness. The electromyographic changes in steroid myopathy are non-specific, but typically there is no spontaneous electrical activity. The histochemical and histological features consist of atrophy of type 2b fibres and an increase in the numbers of lipid droplets in type 1 fibres. Changes of ultrastructure include mitochondrial

abnormalities, increased numbers of lipid droplets, and deposits of subsarcolemmal glycogen.

In patients receiving steroid treatment for a non-myopathic problem diagnosis is easy. But during the treatment of polymyositis or other collagen vascular diseases which may themselves be associated with muscle weakness the differential diagnosis may be difficult. Features which favour a corticosteroid induced myopathy include the presence of other evidence of corticosteroid excess, absence of an increase in serum creatine kinase activity in the presence of creatinuria, absence of spontaneous electromyographic activity, and atrophy of type 2 fibres without cellular infiltration in the muscle biopsy specimen.²⁶

Corticosteroids affect muscle function by several mechanisms: alterations in the function of the sarcoplasmic reticulum,²⁸ in the properties of muscle membrane,²⁹ and in neuromuscular transmission.³⁰ They also have a major effect on muscle bulk, with atrophy affecting fast twitch muscles (predominantly type 2 fibres) more than slow twitch muscles (chiefly type 1 fibres). The atrophy results from diminished protein synthesis due to impaired formation of peptide chains,³¹ and from an increase in the breakdown of muscle protein.³²

Full recovery may be expected with treatment of Cushing's syndrome, though it may take several months. When myopathy results from the use of exogenous corticosteroids these should be stopped or the dose reduced to a maintenance level. If it is essential to continue treatment alternate day administration may be preferable.³³ The muscle atrophy induced by fluidocorticoids in rats may be partially prevented by endurance training,³⁴ which suggests that patients at risk of developing steroid myopathy should be encouraged to take exercise.

In primary hyperaldosteronism muscle weakness is a common presenting symptom and occurred in 105 of 145 cases investigated by Conn *et al.*³⁵ Periodic episodes of weakness characteristically occur and are probably due to hypokalaemia. Muscle power improves and the episodes of periodic weakness disappear when the disorder is treated.

Addison's disease is associated with muscle weakness and fatigability, which is thought to be due to the electrolyte abnormalities, and rapidly improves with steroid replacement therapy.

Pituitary disease

Nelson's syndrome sometimes occurs after bilateral adrenalectomy for Cushing's disease. It is characterised by increasing skin pigmentation with a pituitary tumour which secretes adrenocorticotrophic hormone, and proximal myopathy has been observed in association with this syndrome.³⁶ The electromyographic findings are abnormal in these patients, and the muscle biopsy shows increased lipid droplets in the type 1 fibres. The features are presumably a direct result of the excess of circulating adrenocorticotrophic hormone.

Acromegaly is associated with an increase in muscle bulk; in half the patients there is also a mild weakness of the proximal muscles, affecting predominantly flexors of the hip and deltoids.³⁷⁻³⁸ Changes in serum enzyme activities and in electromyographic, microscopical, and histochemical characteristics have been reported.³⁷⁻³⁹ The mechanism of the muscle dysfunction in acromegaly is not known.

In hypopituitarism muscle weakness, difficulty in walking, and contractures of the legs are sometimes seen in adults. In children with hypopituitary dwarfism muscle development is

poor owing to diminished protein synthesis within the muscle but is reversible when the condition is treated with growth hormone. This stimulatory effect of growth hormone on protein synthesis has been shown experimentally.⁴⁰

Parathyroid disease

HYPERPARATHYROIDISM

Muscle weakness is rarely a presenting feature of hyperparathyroidism but its occurrence is well documented.⁴¹⁻⁴² Characteristically there is weakness of proximal muscles which tends to affect the pelvic girdle muscles earlier and more severely than the pectoral muscles. Distal muscle groups may also be affected in severe cases. Easy fatigability and pain on effort are characteristic; fasciculation of the tongue is sometimes seen. The tendon reflexes tend to be exaggerated. Serum activities of muscle enzymes are usually normal but creatinuria may be found. Muscle biopsy specimens show changes in type 2 fibres similar to those seen with denervation atrophy,⁴² though in one study electron microscopy showed mild abnormalities in type 1 fibres only.⁴³ Electromyographic findings vary with changes which are consistent with neurogenic and primary myopathic disturbances. The pathogenesis of the condition is not understood, with the exception of the myopathic syndrome which occurs in secondary hyperparathyroidism associated with uraemia—where deposition of calcium in blood vessels leads to ischaemia of the muscle fibres.⁴⁴ In primary hyperparathyroidism the muscle weakness appears to relate more to the duration of the condition than to the degree of hypercalcaemia and is not associated with hypophosphataemia, age, or the sex of the patient. Whether it is true myopathy is in doubt, since biopsy and electromyographic changes are equally consistent with a neuropathic basis. The muscle weakness responds to treatment of the underlying hyperparathyroidism.

HYPOPARATHYROIDISM

The characteristic neuromuscular feature of hypoparathyroidism is tetany but muscle cramps, weakness, and paraesthesiae also occur. Abnormalities have been reported on electromyography and in muscle biopsy specimens,⁴⁵ which resolve when the serum calcium concentration is restored to normal.

Conclusion

Normal muscle function depends on a well balanced hormonal profile. Hence not surprisingly myopathy is commonly associated with disturbances in endocrine function. Clearly there is a need for further studies to elucidate the mechanisms.

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