The Investigation of Inflammatory Myopathy

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The diagnosis of polymyositis is generally held to rest upon a clinical history of proximal muscle weakness, often associated with pain and tenderness, a raised serum creatine phosphokinase (CPK), myopathic features on electromyography (EMG) and a perivascular cell infiltration with or without muscle fibre degeneration on muscle biopsy[1]. Fundamental problems of disease classification in polymyositis remain, since not all these criteria need be met for the diagnosis to be made. For example, the CPK is said to be normal in up to 30 per cent of cases.

The immediate prognosis in polymyositis, as in several other myopathies, is determined by respiratory function, since there may be a risk of respiratory muscle weakness leading to ventilatory failure. Serial measurements of peak flow rate, lung volumes and/or peak expiratory pressure are therefore mandatory in the acute phase of polymyositis.

It is well known that polymyositis may induce muscle breakdown sufficient to cause myoglobinuria[2]. Even in the absence of myoglobinuria muscle breakdown may be severe, as is demonstrated by the raised plasma CPK and the extent of the negative nitrogen balance[3] (Fig. 1). The ability of muscle to regenerate may be hindered by the catabolic effects of corticosteroids, which are often prescribed in high doses. Thus a common clinical dilemma is presented by the patient with polymyositis treated for several months with steroids whose weakness seems intractable. Is this due to continuing disease or is the corticosteroid therapy responsible?

Until recently, clinical assessment of the patient's condition, and estimation of the ESR and plasma CPK activity were the only measures available for judging disease severity on a regular basis. As the ESR is normal in up to 45 per cent of cases, the limitations have been even greater. A number of new investigations are now available to explore the pathogenesis and consequences of polymyositis and promise to be of value as much in the assessment of whether treatment is appropriate in an individual patient as in a controlled trial of a particular therapy.

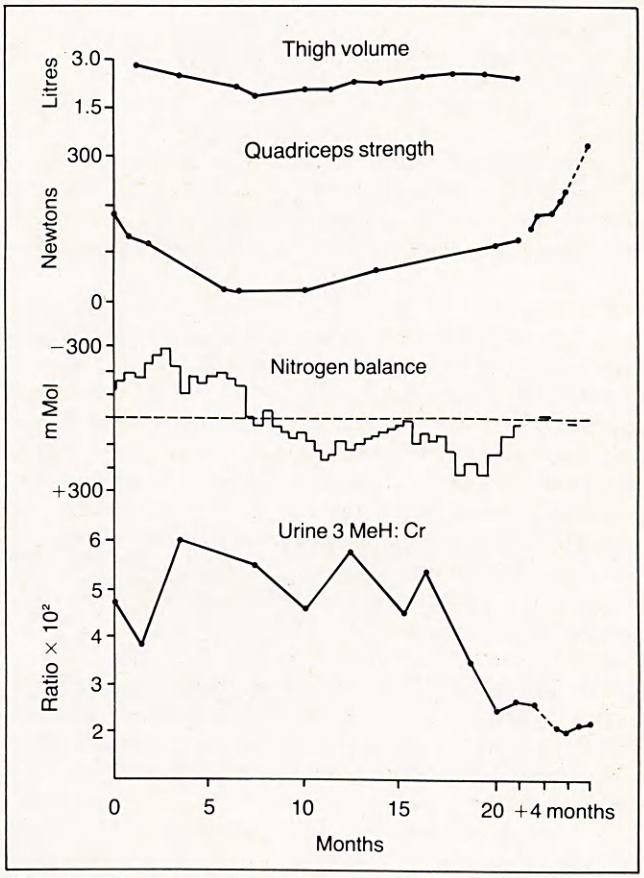

Fig. 1. *Changes in thigh volume, quadriceps strength, nitrogen balance (4 day periods) and urinary 3-methyl histidine:creatinine ratio (which is proportional to the myofibrillar breakdown rate) in the patient with polymyositis during the period of deterioration and subsequent recovery. Note that the urinary 3-methyl histidine creatinine ratio remains elevated during the period when nitrogen balance had become positive and while there was a net increase in quadriceps muscle strength and thigh volume. (Courtesy Ellis Horwood (Publishers) Ltd, Chichester[4].)*

Causes of inflammatory myopathy

Several classifications of polymyositis and dermatomyositis have been suggested. Those of Walton and Adams[5] and Bohan and Peter[6] are commonly used (Table 1). Rowland *et al.*[7] discussed disease classification at some length, concluding that while polymyositis is a heterogeneous group of conditions, dermatomyositis is probably homogeneous. Attempts at classification are likely to be frustrated until a sounder understanding of the causes and consequences of inflammatory myopathy is gained.

Table 1. Classification of polymyositis and dermatomyositis.

Walton and Adams Classification (1958)
1. Pure polymyositis.
2. Polymyositis with some evidence of collagen-vascular disease.
3. Collagen-vascular disease complicated by polymyositis.
4. Polymyositis in association with malignant disease.

Bohan and Peter Classification (1975)
1. Primary idiopathic polymyositis.
2. Primary idiopathic dermatomyositis.
3. Dermatomyositis (or polymyositis) associated with neoplasia.
4. Childhood dermatomyositis (or polymyositis) associated with vasculitis.
5. Polymyositis (or dermatomyositis) associated with collagen-vascular disease.

A considerable literature now exists which discusses the probable role of autoimmunity in the aetiology of both polymyositis and dermatomyositis[8,9]. Most investigators consider that a cell-mediated defect is likely to be of primary importance. Experimental models of myositis have been established in rats[10] and guinea-pigs[11] and used to study possible lymphocyte dysfunction. Kakulas provided good evidence for this in a series of experiments[12,13] in which lymphocytes from rats with 'experimental polymyositis' were shown to be cytotoxic to normal rat muscle in culture. Cytotoxicity of human lymphocytes, from patients with polymyositis, against human fetal muscle preparations has also been demonstrated. Johnson *et al.*[14] produced a lymphotoxin active against human fetal muscle monolayers by incubating lymphocytes with autologous muscle from patients with polymyositis. Experimental allergic myositis, reviewed by Sloper *et al.*[15], differs, however, in several respects from human polymyositis and dermatomyositis. The evidence from *in vitro* and animal studies is of considerable interest but its relevance to human polymyositis has to be interpreted with caution.

The cause of polymyositis and dermatomyositis is unknown but there are a number of possible precipitating factors including viral infection, drugs and neoplasia.

Benign post-infection polymyositis has been described after 'flu-like' illness[16]. Virus-like particles have been observed with electron microscopy in muscle biopsies by many workers[17-20]. The isolation of viruses from muscle specimens has proved to be very difficult. So far a Coxsackie A9 virus[21] and an influenza A, Texas/1/77[22] have been successfully cultured. Viral antibody titres are worth measuring especially when the disease is of sudden onset or associated with a 'flu-like' illness. Bradley[23] has suggested that viruses might infect skeletal muscle, causing release of cellular constituents. The muscle may then be destroyed by the body's immunological response directed at the hitherto confined intracellular components.

Drug-induced myopathies are well recognised[24], but it is rare for a true inflammatory myopathy to follow drug administration. D-penicillamine-induced myositis is perhaps the best example[25], though myositis has been associated with administration of penicillin and sulphonamides[26].

Since 1916, when Sterz[27] described a case of dermatomyositis accompanying a carcinoma of the stomach, there has been much discussion as to whether polymyositis and dermatomyositis are really associated with malignancy. It is probably fair to say that most observers accept that an association does exist, and that it is stronger in men over the age of forty. Long-term follow-up of cases is important, as occult neoplasms may declare themselves many months after the onset of the muscle disorder[8]. The tumours most commonly associated with dermatomyositis are those of the breast, ovary, stomach and lung[28].

Investigations

Apart from the usual haematological and biochemical tests to confirm a general inflammatory disorder there are more specific ways of investigating polymyositis and dermatomyositis.

Electrical Studies

Electromyographic abnormalities have been found in up to 89 per cent of cases of polymyositis[1]. The principal abnormalities seen are fibrillation potentials, positive sharp waves and myopathic changes, and, occasionally, evidence of a myasthenic syndrome. There is no good evidence that the severity of the clinical condition correlates with the EMG findings. Electromyography is therefore of limited value in prognosis or in guiding treatment.

Force Measurements

A simple and practical method of measuring quadriceps muscle strength is available[29]. The subject sits, with knees flexed and feet above the ground, in a straight-backed chair. The pelvis is secured by a seat belt and the subject then attempts to push away a strap which is looped around one ankle. The force generated by the quadriceps is an isometric contraction which is transmitted to a strain gauge, the force signal being recorded with an oscillograph. The technique is useful in guiding steroid therapy, the dose being reduced as strength increases. The same technique was most useful in assessing the course of one of our patients, previously reported[3] who continued to get weaker when her

prednisolone dose was 120 mg daily. It was considered that this high dose of corticosteroids was contributing to her increasing weakness and the dose was reduced to 15 mg daily. Only after this did her strength gradually begin to return to normal. Muscle strength in the quadriceps and other muscles can also be measured with a hand-held dynamometer[30].

Needle Biopsy

The value of needle biopsy as opposed to 'open' muscle biopsy has been discussed recently[31]. The size of specimen obtained is small (30-50 mg) but adequate for most histochemical studies. Biopsies may be taken from multiple sites and repeated several times, with minimal complications. One of our patients had a total of six needle biopsies over a two-year period. The first biopsy showed marked pathological changes. In the succeeding biopsies the pattern slowly improved, the sixth biopsy showing virtually normal muscle tissue. Although it can be argued that needle biopsy could have missed an affected area, the persistent improvement seen in the fourth, fifth and sixth biopsies persuaded us that a genuine improvement had taken place. Eighteen months after her discharge from hospital her quadriceps muscle strength was within the normal range.

A recent study of sequential needle biopsies has been reported by Schwarz and colleagues[32]. They noted that failure to respond to corticosteroids (up to 60 mg prednisolone/day) was associated with a high percentage of fibres with internal nuclei found in the initial biopsy. Repeated biopsies, in steroid-treated patients who do not seem to be improving clinically, may be useful in determining whether a steroid myopathy has developed. Steroid myopathy is usually associated with a simple pattern of type II fibre atrophy[33] without the fibre necrosis, phagocytosis and cellular infiltration characteristic of active myositis.

Metabolic Studies

Vernon Young[34] first suggested that 3-methyl histidine excretion might be used to measure the breakdown of myofibrillar protein. This suggestion has been examined by several groups of workers[35-37]. Originally 3-methyl histidine excretion was thought to reflect muscle breakdown. However, a very high excretion may persist even when there is net synthesis of muscle[4]. Muscle repair may thus be associated for a limited period with increased degradation. This is illustrated in the patient described above (Fig. 2), on whom metabolic balance studies were carried out while she was being treated with steroids. Her nitrogen balance became positive when prednisolone was reduced to 30 mg/day, but her 3-methyl histidine excretion remained elevated for some time afterwards. As the muscle repair process takes time to be completed, the results should be interpreted with caution, particularly if used as evidence for the success or failure of different treatment regimes.

Urinary creatine excretion[38] has been described as a useful and sensitive laboratory method for detecting the

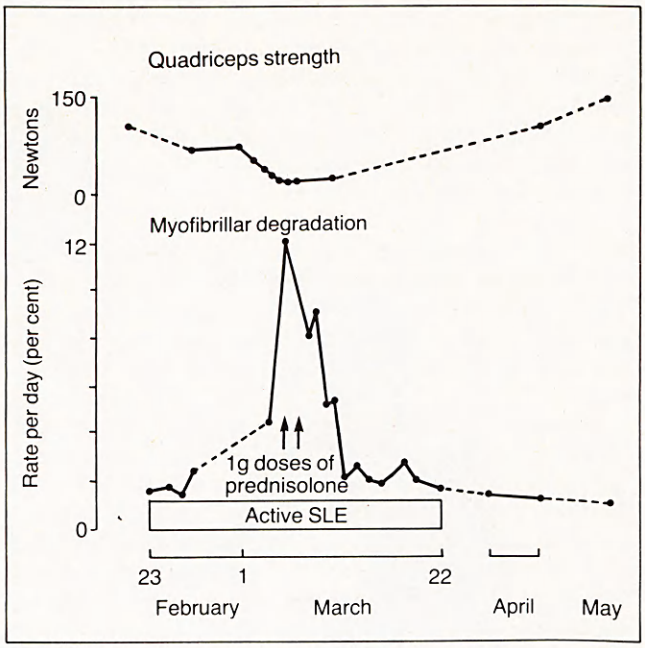

Fig. 2. *Changes in myofibrillar degradation rate (determined as in Fig. 1) in a patient with systemic lupus erythematosus in whom a remission followed intravenous administration of two 1 g doses of methyl prednisolone. Note that clinical deterioration was accompanied by reduced quadriceps strength and increased myofibrillar degradation, both of which were reversed once remission had occurred. (Courtesy Ellis Horwood (Publishers) Ltd, Chichester[4].)*

onset of steroid myopathy. The results of the methods used were reported as per cent creatinuria (creatine/[creatine + creatinine]). This was found to be more reliable than absolute creatine excretion values. It was also found to correlate with the degree of muscle weakness as judged clinically. It may thus prove a useful non-invasive method of following patient progress, though attended by the problems of ensuring complete 24-hour urine collections and the fact that creatinine excretion is reduced as muscle bulk diminishes.

Increased urinary zinc excretion has been described as an indicator of muscle catabolism[39]. Faecal zinc excretion may also be a marker of muscle breakdown, as zinc is mainly excreted into the intestine[40].

Myoglobin

Increased serum and urinary concentrations of myoglobin in polymyositis indicate leakage from striated muscle cells. However, the urinary threshold for myoglobin is comparatively high[41], so that searching for myoglobinuria is of little value. But with a quantitative microcomplement fixation technique, Kagen reported[42,43] myoglobinaemia in 14 of 21 patients with dermatomyositis and 11 of 21 with polymyositis. Serum myoglobin concentrations fell rapidly when steroid therapy was started in 6 patients followed by serial

estimations. In addition, Nishikai and Reichlin[44] found that changes in serum myoglobin were a more sensitive indicator of inflammatory muscle disease than the CPK level.

Immunological Studies

Cell-mediated cytotoxicity to muscle in polymyositis was demonstrated several years ago[45] but there has been difficulty in measuring muscle specific damage *in vitro* because of the mixed cell nature of monolayer cultures. The recent development, by Cambridge and Stern[46], of a lymphocyte myotoxicity assay utilising the selective uptake of tritium-labelled carnitine by myotubes in monolayer cultures of human fetal muscle promises to overcome these problems. With this technique human fetal muscle monolayers previously incubated with tritium-labelled carnitine are cultured with the peripheral blood lymphocytes from patients with polymyositis. Any consequent damage to the myotubes results in the release of the small soluble carnitine molecules. After washing and dissolving with sodium dodecylsulphate, the muscle monolayers are placed in a scintillation counter. The emission from the remaining carnitine is measured and compared with values obtained before the lymphocytes were added.

Using this technique Cambridge and Stern have demonstrated myotoxicity in a number of cases of active polymyositis but none in patients in whom the disease was in remission or in normal controls. In a longitudinal study of a patient with polymyositis the degree of cytotoxicity rose sharply just before the patient experienced a clinical relapse.

Treatment

To our knowledge no double-blind, properly controlled trial of corticosteroids has ever been performed in polymyositis or dermatomyositis. In consequence, the literature contains contradictory statements about corticosteroids, with widely varying reports of their efficacy. While some authors[8,47,48] have claimed considerable success, others[49,50] found very little benefit. Carpenter and his colleagues[51] could find no benefit in giving high doses of steroids (20 mg or more of prednisolone daily for at least eight weeks) compared with low doses (10 mg prednisolone or less for the same period). Corticosteroids even if successful in inducing a remission may produce substantial muscle breakdown (*see* Fig. 2).

Other immunosuppressive drugs such as azathioprine, methotrexate and cyclophosphamide are often prescribed for their 'steroid sparing' effect. However, a prospective, double-blind trial[52] of azathioprine given concomitantly with prednisone showed no benefit in the group taking the azathioprine compared with the group taking a placebo.

Prospects

De Vere and Bradley[1] indicated that the risk of mortality to patients with polymyositis is four times that of the general population. This is partly due to the presence of accompanying neoplasms, but also related to the adverse effects of corticosteroids. The immunosuppressive regime therefore requires careful management, as drug therapy may be required for several months or years.

Several questions about polymyositis remain unanswered. For example, does the degree of muscle breakdown at the time of diagnosis affect the outcome, and if so, how may this best be measured? To what extent might corticosteroids affect muscle regeneration? Is there a role for physiotherapy in building muscle strength and bulk after the acute inflammation has subsided?

The investigations described in this article offer an opportunity to re-examine the diagnostic criteria, monitor progress of disease and assess the effects of treatment in inflammatory myopathy.

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Book Review

Clinical Hypertension by J. D. Swales. Chapman & Hall Ltd, Andover, Hants, 1979. Price £10.50 (hardback), £6.50 (paperback).

This book is a remarkable achievement, for in less than 200 pages of text, Professor Swales presents an astonishing amount of information. Throughout, in order to ensure continuity of text, only essential references are given, but each chapter includes a list of recommended publications for further reading, from which sources of reference can be identified.

The initial chapters on blood pressure control, baroreceptors and the central nervous system and, in particular, the renin-angiotensin-aldosterone system take the reader logically and with great clarity through what often seems a confused and confusing field.

When discussing controversial issues, Professor Swales presents the conflicting views, assessing the work of each and giving his own formed opinion on their merits and relevance, an approach of particular value in the chapters on pathogenesis and epidemiology, when considering issues such as the role of sodium, fluid volume, renin and neurogenic control in the pathogenesis of raised arterial pressure.

Although secondary hypertension is fully covered, it is unfortunate that the short chapter entitled 'Essential Hypertension' can, and probably will cause confusion to some, by attempting to delineate various subgroups—borderline, labile, hyperdynamic β-adrenergic states, renin sub-groups and the malignant phase—as if these were manifestations of one specific disease, a concept made untenable 25 years ago by Pickering.

The clinical assessment and management of the hypertensive patient are well and sensibly presented, the drugs in current use are logically grouped according to their mode of action, and the combinations likely to be effective in the various situations encountered in patient care recommended. Unfortunately, the use of intravenous diazoxide is recommended several times for the treatment of various hypertensive emergencies, without sufficiently emphasising the considerable dangers associated with this preparation when administered intravenously.

The final chapter on obstetric and surgical aspects of hypertension includes sensible and practical advice on the management of the hypertensive patient having to undergo surgery. However, there are many anaesthetists who would not accept the statement that 'unless target organ damage is present, anti-hypertensive treatment can be delayed until convalescence'.

Overall, this is an extraordinarily good book, which will be read with benefit and pleasure by all interested in hypertension and those responsible for the care of hypertensive patients. At a cost of £10.50 for the hardback edition, it also represents very good value for money.

MICHAEL HAMILTON