The syndrome of myosclerosis

W. G. BRADLEY, P. HUDGSON, D. GARDNER-MEDWIN, AND J. N. WALTON

From the Muscular Dystrophy Group Research Laboratories, Newcastle General Hospital, Newcastle upon Tyne

SUMMARY Three cases are described presenting with progressive contractures in whom the muscles felt firm and ‘woody’ and a clinical diagnosis of myosclerosis was made in each case. A patient and his young sister were shown to be suffering from spinal muscular atrophy with superimposed, excessive proliferative activity of fibroblasts, and in these cases a beneficial effect of penicillamine was demonstrated. The third case with a clinical picture of myosclerosis was found on muscle biopsy to have extensive inflammatory infiltration of the connective tissue, and responded temporarily at least to high doses of corticosteroids. It is emphasized that several different disease entities can give rise to this clinical picture.

The classical paper on X-linked recessive muscular dystrophy by Duchenne in 1868 was entitled ‘Recherches sur la paralysis musculaire pseudo-hypertrophique ou paralysis myo-sclerosique’. In this work Duchenne pointed out the extensive fibrosis surrounding individual muscle fibres as well as muscle fasciculi, although he also emphasized the primary degenerative change seen in the muscle fibres themselves. It is now widely recognized that fibrosis as well as fat replacement is a non-specific response to many forms of muscle damage. However, since that time occasional cases have been published, some under the title of ‘fibrosing myositis’ or ‘myosclerosis’, the suggestion being that the fibrosis of the muscle was the primary pathogenetic event. The familial occurrence of this phenomenon has been reported (Cordier, Löwenthal, Radermecker, and van Bogaert, 1952; Löwenthal, 1954). Walton and Adams (1958) suggested that ‘chronic myositis fibrosa’ represents simply a chronic phase of polymyositis. The characteristic clinical feature of these cases has been the hard, woody texture of the muscles to palpation due to fibrosis.

In recent years we have encountered three such cases and in this report we describe the results of our investigations in these patients. The status of ‘myosclerosis’ as a disease entity is reviewed.

METHODS

Muscle biopsies were taken under general anaesthesia from the left quadriceps muscle in case 1, the left quadriceps and biceps in case 2, and the left biceps in case 3. These were all fixed in formol-calcium and embedded in paraffin wax, 5 µ sections then being cut and stained with haematoxylin-eosin and by the picro-Mallory and Mallory’s phosphotungstic acid-haematoxylin methods. A portion of the second biopsy specimen from case 2 was rapidly frozen in Arcton at -150°C at the time of removal. Ten µ sections were cut from this at -30°C in a Dittes cryostat and a battery of histochemical preparations were made including myofibrillar ATPase and NADH tetrazolium reductase activities. Material from all three biopsies was prepared for electron-microscopy and preliminary sections were examined. No unexpected ultrastructural abnormalities were found.

CASE 1

G.W. was 23 years old when first investigated in 1967. He developed difficulty in walking at the age of 4 years, when he began walking on his toes because of progressive contractures of the calf muscles. He also had difficulty in climbing stairs and in rising from a low chair, he fell frequently and had great difficulty in getting up from the floor. Several orthopaedic operations were performed on his feet but, in spite of these, the contractures spread to involve the knee-flexors. At the age of 15, diffuse upper limb weakness began with contractures at the elbows but
at no time was there muscle pain or tenderness, dysphagia, Raynaud's phenomenon, or other skin disorder. His younger sister (case 2) had a similar condition, but three other sisters were normal. There was no involvement of other members of the family and no consanguinity. All the muscles of the body were slender, including those of the face, and muscle power was reduced to a mild degree. The most striking feature was the firm, woody consistency of all the muscles, and the restriction of movement of many joints apparently due to fibrous contracture of the muscles (Figs 1 and 2). The elbows could be extended only to about 130° (right 124°, left 134°), and the knees only to about 140° (right 134°, left 140°). There was also a flexion deformity of both hip joints, and of the right ankle joint due to contracture of the respective flexor muscles. The tendon reflexes were present, although depressed. No fasciculation was seen. His face had a somewhat pinched appearance but the skin was of normal thickness and mobility.

INVESTIGATIONS. A blood count was normal and the erythrocyte sedimentation rate (ESR) was 7 mm/1 hr. Plasma proteins were 6·3 g/100 ml.; albumin 5·4 g/100 ml., globulin 0·9 g/100 ml. Electrophoresis showed a slight decrease in gamma-globulin. Serum glutamic oxaloacetic transaminase (SGOT) estimations were 20 and 41 u./ml. (normal less than 35 u./ml.). Serum creatine kinase activity was 63 i.u. (normal less than 75 i.u.). Urinary amino acid chromatography was normal. Radiographs of the muscle showed no calcification. Electrocardiogram (ECG)
The syndrome of myosclerosis

The syndrome of myosclerosis was normal. Electromyography of the right quadriceps and right biceps muscles (D.G.-M.) showed no spontaneous activity. There was an interference pattern of normal amplitude but reduced density, and individual motor unit action potentials of long duration (12–20 msec) and high amplitude (1.5–8 mV), with many polyphasic potentials. Maximal motor conduction velocity of several nerves was normal (right lateral popliteal nerve 51 m/sec, terminal latency 4–5 msec; right ulnar nerve 67 m/sec, terminal latency 2.5 msec; right median nerve 64 m/sec, terminal latency 4–0 msec). The findings were those of chronic denervation with reinnervation. A biopsy was obtained from the left quadriceps muscle (see below).

After this biopsy he was treated with penicillamine hydrochloride 450 mg three times daily. Within two weeks, extension of the joints had improved, particularly at the knee (right knee 153°, left knee 163°; right elbow 125°, left elbow 138°). The patient felt more mobile, and his gait improved. At three months, extension of the right knee was 172°, the left knee 175°, the right elbow 124°, and the left elbow 148°. The legs felt much stronger, and he was able to get out of a bath, which previously he had been unable to do. Unfortunately, penicillamine

**FIG. 3.** Case 1. Transverse section from the quadriceps muscle biopsy showing several apparently normal fasciculi in one half of the field and several broad, interlacing bands of mature collagen with a few fat cells in the other. H and E x 160.

**FIG. 4.** Case 1. Transverse section from the same quadriceps muscle biopsy showing moderately severe chronic myopathic degeneration with considerable variation in fibre diameter, fibre splitting, and significant endomysial fibrosis. Van Giesen, x 60.
FIG. 5. Case 2. Transverse section from the biceps biopsy showing numerous small 'groups' of atrophied fibres, all approximately the same size. Some of the atrophied fibres contain clumped, dark nuclear material. Picro-Mallory, ×180.

FIG. 6. Case 2. Cryostat section from the quadriceps biopsy showing randomly distributed atrophic fibres of various sizes. There are two prominent nuclear clumps in the centre of the field and some of the larger fibres contain internal nuclei. H and E, ×125.
caused nausea and vomiting so the dosage was reduced to 300 mg per day for three months, after which he occasionally took up to 600 mg per day. He insisted that 300 mg taken in the morning was sufficient to relieve him of stiffness during the day, though he still felt nauseated. Gradually the contractures returned, but they again remitted after the institution of therapy with enteric-coated penicillamine in a dose of 750 mg of base per day.

PATHOLOGICAL FINDINGS In this case there were occasional broad bands of perimysial collagen surrounding substantially normal fasciculi with normal individual fibres (Fig. 3). In other areas there was abnormal variation in fibre diameter with occasional atrophic fibres, frequent examples of fibre splitting, and moderately severe endomysial fibrosis (Fig. 4). No evidence of ‘grouped’ atrophy or of active myopathic degeneration was found in this material and no histochemical preparations were available for study. These findings were interpreted as being those of a rather indolent primary myopathy with the fibrosis as the most striking abnormality, although, in retrospect, the presence of large areas of apparently normal muscle is perhaps suspicious of a denervating process (see below).

CASE 2

J.W., the younger sister of case 1, was aged 4 years when first investigated in 1967. At the age of 2 years she began having occasional falls, with difficulty in getting up again off the floor. At the age of 4 years, she had slender muscles with mild weakness of proximal limb girdle muscles and lesser involvement of the distal musculature. The muscles felt slightly firm, particularly proximally. The tendon reflexes were normal, and there was no myotonia or fasciculation.

INVESTIGATIONS (1967) Electromyography of the right quadriceps muscle (D.G.-M.) showed there was firm fibrous resistance to needling of the muscle; the findings otherwise were of a mild, patchy myopathy. A biopsy was obtained from the left quadriceps muscle (see below). No therapy was given, and at about the age of 8 years she began falling more frequently due to a slight increase in the muscle weakness. All the muscles felt rather more firm, though by no means as hard as those of her brother (case 1).

INVESTIGATIONS (1971) Blood count, plasma aldolase, and urinary amino-acid chromatography were normal. The SGOT level was 38 u./ml. Barium swallow and barium meal showed no abnormality and an ECG was normal. Electromyography of the right extensor digitorum brevis (EDB) and right abductor pollicis brevis (APB) (Dr. A. Upton) showed a reduced interference pattern on maximal voluntary contraction with single motor unit action potentials of very large amplitude (up to 5 mV in APB and 15 mV in EDB). No spontaneous activity was recorded. Maximum motor conduction velocity of several nerves was normal (left lateral popliteal nerve 55 m/sec, terminal latency 3-0 msec; right median nerve 67 m/sec, terminal latency 2-8 msec). Orthodromic sensory nerve action potentials at the wrist from stimuli to the fingers were conducted to a normal velocity (right median nerve 60 mV, conduction velocity 56 m/sec; right ulnar nerve 30 mV, conduc-

![FIG. 7. Case 2. Cryostat section from the quadriceps biopsy showing impressive 'grouping' of normal-sized type 1 fibres. NADH tetrazolium reductase. × 100.](http://jnnp.bmj.com/content/jnnp/51/6/649)
A biopsy was obtained from the left biceps muscle (see below). In view of her brother's response to therapy, she was given penicillamine hydrochloride 600 mg per day. After one month there was definite improvement in the power of the limbs, both objectively and on timed performance.

**PATHOLOGICAL FINDINGS** In the first biopsy from this girl there was only moderate interstitial fibrosis, largely confined to one fascicle, and the most impressive feature was the presence of several large foci of 'grouped' atrophy. In these areas the atrophic fibres were all roughly the same size and many contained clumped, dark, pyknotic nuclei (Fig. 5). In
The syndrome of myosclerosis

657

the second biopsy from this case the haematoxylin-eosin stained cryostat section showed the atrophic process to be more randomly distributed, although occasional dark clumps of pyknotic nuclei were seen again (Fig. 6). The myofibrillar ATPase and NADH tetrazolium reductase preparations showed aggregates of large numbers of roughly normal sized fibres of uniform histochemical type, usually type I (Fig. 7). The histological and histochemical findings in this case strongly suggest the presence of a chronic denervating process, probably central in origin.

CASE 3

K.H. was aged 6 years when first investigated in 1966. His mother noticed that for four months he had been unable to straighten his fingers, which had progressively become clenched. For three weeks he had complained of slight pain and swelling of one ankle. There was no family history of rheumatoid arthritis or other disease, and he had two normal sibs. There was no muscle pain or symptoms of constitutional illness, though he was found to have intermittent low grade fever rising up to 38.3°F (101°F). All movements of the wrists and ankles, and to a lesser extent the knees, elbows, and shoulders, were restricted by about 10–15°, apparently due to contracture of the muscles moving the joints. The muscles themselves were of normal strength, though they felt extremely firm to palpation.

INVESTIGATIONS (JUNE 1966) Examination of the blood showed haemoglobin, 10.5 g/100 ml., white cell count 12,000/cu. mm, ESR 30 and 55 mm/1 hr. Rose-Waaler and latex fixation tests were negative and no LE cells were found. Blood urea and electrolytes were normal. Plasma protein level was 7.1 g/100 ml. Electrophoresis showed a slight increase in gamma-globulin. Anti-streptolysin titre (ASOT) was 1:125 (normal). Serum creatine kinase activity was 13 i.u. Radiographs of the elbows, wrists, and ankles were normal. An ECG showed sinus tachycardia only.

A provisional diagnosis of rheumatoid arthritis was made and he was treated with aspirin and prednisone 30 mg per day for a week, reducing to 20 mg/day. The ESR remained raised for a week, and then fell progressively to 2 mm/1 hr but without improvement in the restriction of joint movement. The corticosteroid therapy was therefore reduced progressively, and a biopsy obtained from the left biceps muscle (see below). As a result of the changes in this biopsy he was treated with prednisone in high doses starting with 60 mg per day for three weeks, reducing over the next nine months to 15 mg per day, and gradually over the next 15 months to 2.5 mg per day. The ESR remained normal for most of this period, and there was a gradual diminution in the woody firmness of the muscles and restriction of movement of the joints, almost to the stage of normality. From August 1968, however, the woody firmness of the muscles and restriction of movement of the joints returned almost to the state when he was first seen, despite the continuation of prednisone at low dosage. In January 1971 a trial of penicillamine therapy (600 mg thrice daily) was given for seven months without benefit.

PATHOLOGICAL FINDINGS In the biopsy sample from the third patient there was gross perimysial fibrosis with only slight to moderate endomysial fibrosis. However, the striking feature in this biopsy specimen was the presence of quite dense small round cell infiltrates in the broader perimysial collagen bands (Fig. 8) which sometimes extended between apparently normal muscle fasciculi. High power examination of these infiltrates showed that most of the cells were lymphocytes which sometimes were concentrated around small vessels (Fig. 9). No other histological abnormalities were found. These changes were regarded as being those of an indolent inflammatory polymyopathy with the inflammatory process virtually confined to the interstitium of the muscle ('interstitial myositis').

DISCUSSION

The first and third cases in this report presented with progressive contractures of many muscles causing limitation of movement of the joints and a firm, 'woody' consistency of the muscles on palpation. Case 2, the sister of the first patient, had only mild weakness with slight firmness of the muscles. Clinically, the condition in each case was diagnosed as a form of myosclerosis, which in cases 1 and 2 was regarded as familial. However, the investigations demonstrated that this pattern resulted from different disease entities.

There is little doubt that the first two cases suffer from a familial form of spinal muscular atrophy. This conclusion rests upon the electromyographic evidence of denervation and reinnervation in case 1 and the results of the second electromyogram,2 the presence of grouped atrophy and fibre type grouping in the biopsy material from case 2. The severe interstitial fibro-

2 The findings in the first electromyogram are difficult to explain but may have been due to early secondary myopathic degeneration.
sis in case 1, and the moderate fibrosis in one fascicle of the first biopsy from case 2 were perhaps unusual for material obtained from patients with spinal muscular atrophy, and suggested the possibility of a primary, proliferative disorder of the fibroblasts in addition to the disease of the motor neurones. Indeed, the most surprising aspect of case 1 was the presentation with contractures without weakness after what was clearly a prolonged period of denervation. In case 1 it is possible that denervation was secondary to strangulation of intramuscular nerves by connective tissue, but the finding of similar evidence of denervation and reinnervation in case 2 with relatively little fibrosis makes this explanation highly unlikely.

The response to penicillamine in cases 1 and 2 is most interesting. This drug, which owes its action to its thiol groups, has been used in scleroderma, its action presumably being to inhibit the formation of the cross bands which lead to the formation of insoluble collagen (Harris and Sjoerdsm, 1966). The drug clearly benefited case 1, presumably by this mechanism. It is too early to be certain that the initial beneficial effect in his sister (case 2), who had only mild fibrosis, will be maintained.

In case 3, the same clinical picture resulted from an unusual inflammatory disorder affecting only the intramuscular connective tissue. Bernheim, Mouriquand, Lanternier, and Perrin (1954) reported a case with a somewhat different clinical and pathological picture, but emphasized the rare occurrence of fibrosing polymyositis with inflammatory oedema restricted to the connective tissue. The mild fever, raised ESR, and anaemia in this patient were pointers to an underlying inflammatory disease. The initial diagnosis was juvenile rheumatoid arthritis. Inflammatory cell infiltration of skeletal muscle may occur in rheumatoid arthritis, though the changes are not usually as extensive as those which were seen here (Sokoloff, Wilens, Bunim, and McEwan, 1950). The patient showed a satisfactory response to a prolonged high dosage of prednisone, but relapsed when the drug was progressively withdrawn after two years. In more typical cases of polymyositis, corticosteroid therapy may have to be prolonged, and it will be interesting to follow the course of this patient to see whether the contractures will again resolve with reinstitution of corticosteroid therapy. In striking contrast to the first two cases, penicillamine was entirely without effect in this patient.

Fibrosis of muscle causing a ‘woody’ sensation to palpation is not unusual in polymyositis, and from the histological picture and description of several of the early cases described as ‘myosclerosis’ it seems likely that this was the condition underlying the syndrome—for instance, the cases described by Burton, Cowan, and Miller (1923). The commonest cause of a fibrosed contracted muscle is muscular dystrophy in its late stages, a finding first emphasized by Duchenne (1868). Usually there is no difficulty in diagnosing these cases. Indeed, it is probable from the little histological evidence and clinical details of some of the early cases described as myositis fibrosa or myosclerosis that these patients were suffering from the late stages of a muscular dystrophy—for example, the cases of Hauptmann and Thannhauser (1941) and Stewart and Macgregor (1951).

Not all cases in the literature under this title can clearly be ascribed to a muscular dystrophy, polymyositis, or spinal muscular atrophy, although, in many cases previously reported, modern diagnostic techniques of electrophysiology, histochemistry, and electron microscopy were not available. This applies to the two families reported by Cordier et al. (1952), one with a father and son affected with a mild, progressive weakness and contracture of proximal musculature and minimal signs of central nervous system involvement, and the other family with four sibs suffering from predominantly distal muscle involvement. In the former case, however, the presence of neurological signs must suggest a diagnosis of spinal muscular atrophy. Similarly, results of modern investigative procedures were not available in two families described by Löwenthal (1954), in one of which four sibs in one generation and in the second four individuals in three generations were affected. The patient described by Altman and Davidson (1939) had prominent ptosis with normal extraocular movements and normal fundi, and may have suffered from centronuclear myopathy (Bradley, Price, and Watanabe, 1970) or spinal muscular atrophy. The two cases described by Whalen, Combs, and Deiss (1959) and Ricker, Seitz, and Trostdorf (1970) appear to be similar, though both resisted...
The syndrome of myosclerosis

659

attempts to elucidate the underlying nature of the disease. In these two patients there was progressive hardening and contracture of the muscles of the shoulders, neck, and back causing striking flexion and abduction deformities of the shoulders. Both showed marked interstitial fibrosis on muscle biopsy but there was no evidence of myositis ossificans. The family described by Hauptmann and Thanhauser (1941) showed rather similar contracture of neck and shoulder muscles, though with more evidence of a proximal myopathy. Primary amyloidosis has also been recorded as a cause of ‘pseudo-myopathy’ with a ‘woody’ sensation on palpation of skeletal muscles (Martin, van Bogaert, van Damme, and Peremans, 1970).

Other conditions causing fibrous overgrowth in muscle are usually focal in distribution. The fibrous contracture of extensive ischaemic damage to muscle is well known. The interesting conditions of focal proliferative myositis (Kern, 1960; Enzinger and Dulcey, 1967; MacKenzie, 1970) and fasciitis (MacKenzie, 1970) usually present as a rapidly growing tumour often thought to be a sarcoma before biopsy. Myositis ossificans initially may present with simple fibrosis of muscle (Eaton, Conkling, and Daeschner, 1957), rather than the classical features of painful swellings of muscles which rapidly ossify causing deformity, often with associated intermittent fever (Mair, 1932; McKusick, 1966). Skeletal muscle is not involved in either plantar or palmar fibromatosis but is the characteristic site of development of desmoid fibromatosis (Shuman, 1971). It is not involved in either mediastinal or retroperitoneal fibrosis (MacKenzie, 1970), though involvement of skeletal muscle in the collagen vascular diseases, including systemic sclerosis (scleroderma) is well known.

The question must be asked whether the terms fibrosing myositis or myosclerosis are of any value in the study of muscle disease. The clinical picture indicated by the terms results from many different disease processes, some of which may be elucidated by current methods of investigation and some of which are susceptible to therapy. Many of the earlier cases reported still defy accurate classification, and many of them did not have the benefit of modern investigative techniques. As a descriptive term ‘excessive fibrosis’ is preferable, since it highlights the unusual overgrowth of fibroblasts and collagen without suggesting that the fibrosis is necessarily of primary importance. It points to the need for further investigation, which may, for instance, show a primary inflammatory disease of connective tissue requiring corticosteroid or other immunosuppressive therapy. It does appear, however, that, in rare cases such as the first two described in this report, the overgrowth of collagen, though secondary, is playing a major part in producing disability. In these instances, penicillamine or some other therapy aimed at inhibiting collagen formation is worthy of trial.

The authors wish to acknowledge with thanks the technical assistance of Mr. J. J. Fulthorpe, Mr. G. Henderson, Mrs. V. Giles, and Mrs. D. Hargreaves. They are also grateful to Mrs. E. Mooney who typed the manuscript.

REFERENCES


The syndrome of myosclerosis

W. G. Bradley, P. Hudgson, D. Gardner-Medwin and J. N. Walton

*J Neurol Neurosurg Psychiatry* 1973 36: 651-660
doi: 10.1136/jnnp.36.4.651

Updated information and services can be found at:
[http://jnnp.bmj.com/content/36/4/651](http://jnnp.bmj.com/content/36/4/651)

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)