Myopathy Associated with Amyloid Angiopathy

JOSEPH BRUNI, JUAN M. BILBAO, KENNETH P H. PRITZKER

SUMMARY: *A 38-year-old patient with the clinical picture of a progressive myopathy resembling limb girdle muscular dystrophy is presented. Muscle biopsy showed amyloid deposits in the walls of small endomysial blood vessels. There was no clinical or physiological evidence of peripheral nerve involvement, no plasma cell dyscrasia and no generalized amyloidosis. There was no muscle fiber hypertrophy, inflammation or neurogenic change. There was no response to steroid therapy.*

The etiopathogenesis of this amyloid angiopathy is undetermined. The extensive vessel involvement with amyloid deposition and the absence of changes indicative of muscular dystrophy or inflammatory myopathy leads us to favor an ischemic basis for this patient's myopathy.

RÉSUMÉ: *Le cas d'un patient de 38 ans avec une myopathie progressive ressemblant à une dystrophie des ceintures est présenté. Une biopsie du muscle montra des dépôts amyloïdiens sur les parois de petits vaisseaux sanguins de l'endomètre. Il n'y avait pas d'évidence clinique ou physiologique d'atteinte du nerf périphérique, pas de dyscrasie des cellules plasmatiques et pas d'amyloïdose généralisée. Il n'y avait pas d'hypertrophie des fibres musculaires, ni d'inflammation ou de changement neurogénique. Il n'y eut pas de réponse au traitement aux stéroïdes.*

L'étiopathogénèse de cette angiopathie amyloïde n'est pas déterminée. L'implication du vaisseau avec dépôt amyloïde et l'absence de changements indicatifs d'une dystrophie musculaire ou d'une myopathie inflammatoire nous amène à croire en une raison ischémique pour la myopathie de ce patient.

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INTRODUCTION

The muscular dystrophies are a group of heritable degenerative myopathies, but the pathogenesis is controversial (Rowland, 1976). Three theories are favored: 1. The vascular theory (Demos, 1961, Cazzato, 1968, and Hathaway et al., 1970). 2. The neurogenic theory (McComas et al., 1971 and McComas et al., 1974). 3. The membrane theory (Brown et al., 1967, Matheson, 1974, Lumb and Emery, 1975, Miller et al., 1975, Sha'afi et al., 1975, Mawatari et al., 1976). None of these can explain all the features of this group of diseases.

The vascular theory states that the muscle damage is secondary to changes in the vessels supplying striated muscle. The following is a case report of a patient with a progressive myopathy who, on muscle biopsy, was found to have amyloid deposits in the walls of small blood vessels, suggesting that an intramuscular ischemic mechanism may have led to a progressive myopathy. The clinical picture was compatible with limb girdle dystrophy.

CASE REPORT

This 38-year-old male presented to St. Michael's Hospital in October 1975 because of progressive muscle weakness. He had been well until the age of 20 when he began to notice easy fatiguability. He developed leg pain, not associated with exercise, followed by loss of muscle bulk in his calves. By the age of 22 he had difficulty climbing stairs and getting up from a seated position. By the age of 24 he had weakness of his arms and loss of bulk in his biceps and shoulder muscles.

He has had progressive deterioration and has been confined to a wheelchair for the past year. The masticatory, facial, pharyngeal and neck muscles are not involved. There have been no sensory symptoms or other neurologic complaints. The patient has a brother aged 55 who has a similar illness and a first maternal female cousin who developed difficulty walking at the age of 20.

Neurological examination revealed normal cranial nerves. There was marked bilateral wasting and weakness of the shoulder girdle musculature with winging of the scapulae. Biceps and triceps were similarly involved. There was mild weakness and atrophy of wrist and finger extensors and intrinsic hand muscles. Abdominal and paraspinal muscles were weak. In the lower extremities there was marked pelvic girdle, quadriceps, and hamstrings wasting and weakness and bilateral foot drop. There was also mild weakness of plantar flexion, eversion and inversion with moderate atrophy of the calf muscles (Fig. 1). There was no myotonia. Deep tendon reflexes were absent or markedly depressed. Sensation was normal.

Thyroid function was normal. CPK on admission was 1749 international units. Renal function was normal. A collagen screen was negative (ESR, ANA, LE cell screen, rheumatoid factor). Urine for myoglobin was negative. Serum protein electrophoresis was normal. Serum kappa and lambda light chains were the same as in controls and there were no free light chains in the urine. An ECG was normal. Left and right lateral and medial popliteal nerve conduction values were within normal limits and left median and ulnar nerve sensory-motor conduction

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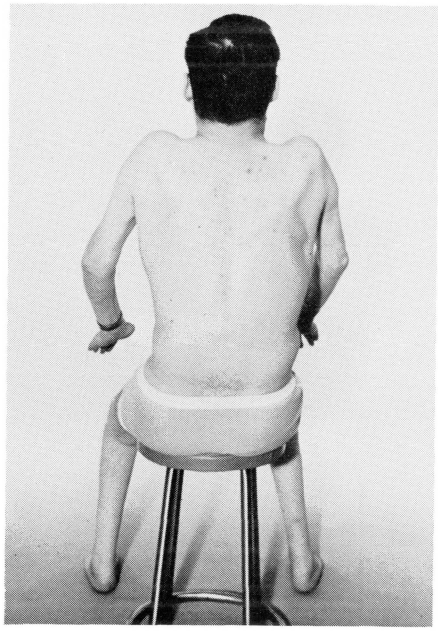

Figure 1—Patient is attempting to elevate his arms. Note marked weakness and atrophy of proximal shoulder muscles and atrophy of calf muscles bilaterally.

values were normal. The electromyogram was abnormal showing considerable increase in polyphasic activity with no after contraction or increased muscle irritability. The EMG was in keeping with a myopathy.

A biopsy of the left vastus medialis muscle was performed, the tissue was embedded in paraffin and the following stains were done: Hematoxylin - Phloxine - Saffron. Congo-Red, Gomori's Trichrome and Thioflavin T. There were areas of marked atrophy of muscle fibers and focal moderate increase in connective tissue and occasional angular elements (Fig. 2). The atrophy was not uniform with some fascicles showing a greater involvement. Occasional muscle fibers were undergoing active phagocytosis; there was no fiber hypertrophy and regenerating fibers were occasionally seen. Blood vessels of medium and small caliber, arterioles as well as venules, exhibited acidophilic homogeneous changes in their walls which, by Congo Red staining, polarization microscopy and Thioflavin T, proved to be amyloid (Figs. 3 and 4). Amyloid was not seen in the nerve bundles contained in the muscle, and there was no significant deposition of amyloid anywhere outside the vessel wall. There was no evidence of a necrotizing vasculitis. A biopsy of the right biceps was also carried out and histochemical reactions with ATPase (pH 9.4, 4.6, 4.2), NADH, and PAS showed atrophy of all fiber types and no fiber hypertrophy (Fig. 5). In this specimen there was fiber type 1 predominance. There were a number of ring fibers and over 20% of the muscle fibers contained inter-

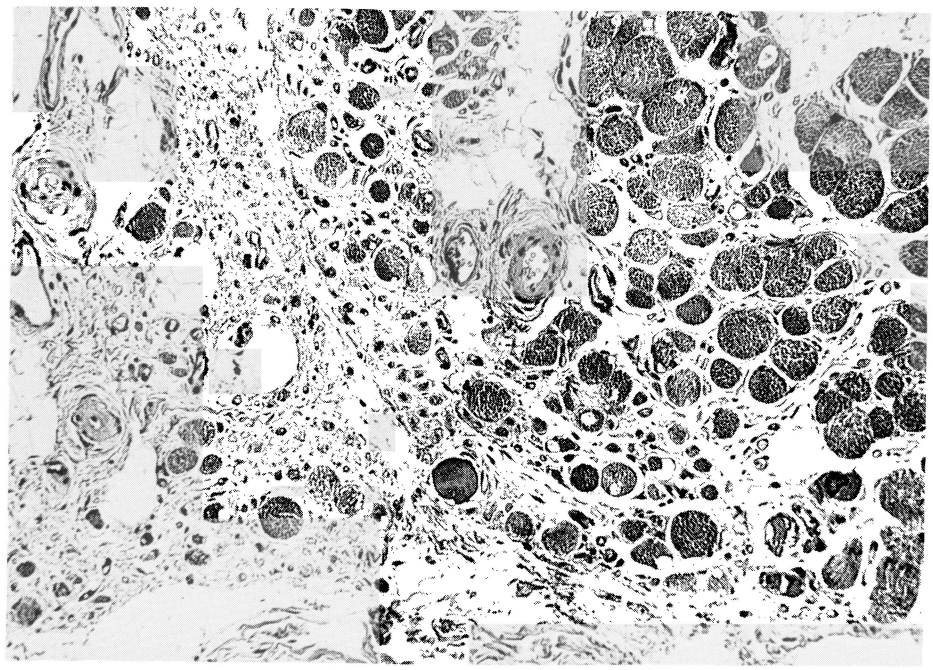

Figure 2—Note marked atrophy of muscle fibers and thickened blood vessel wall (Hematoxylin-phloxine-saffron, original magnification x 100).

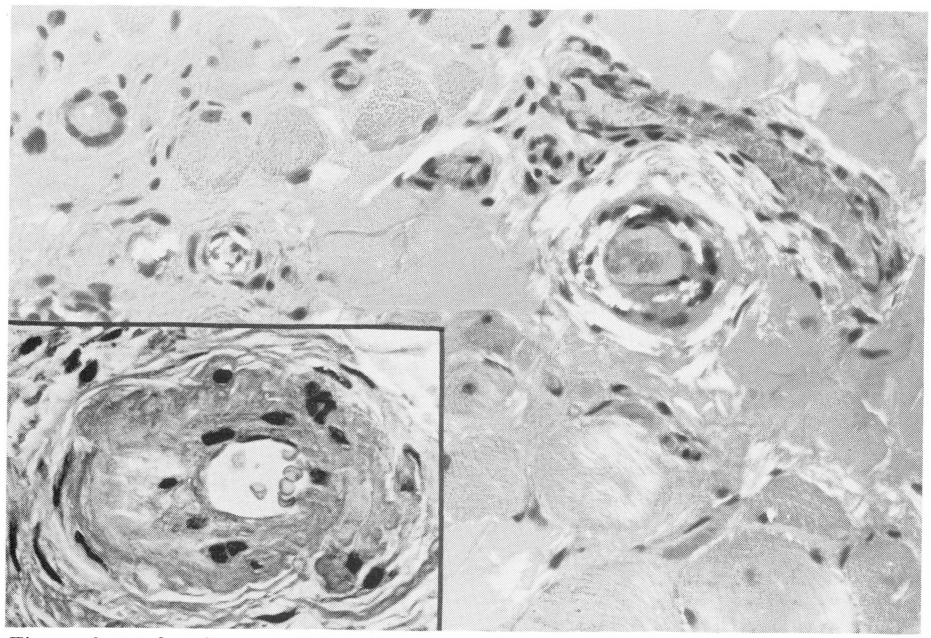

Figure 3—Refractile material exhibiting green-yellow dichromism was seen in the vessel wall (Congo red, original magnification x 180. Photographed under half-crossed polarizing filters). Insert, marked infiltration of vessel wall with amorphous acidophilic material (Hematoxylin-phloxine-saffron, original magnification x 250).

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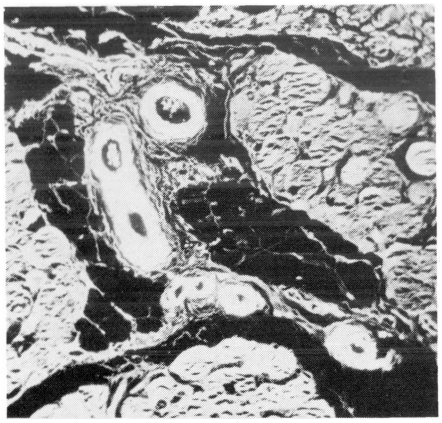

Figure 4—Fluorescent amyloid deposits infiltrating the wall of endomysial blood vessels (Thioflavin T, fluorescence microscopy, original magnification x 250).

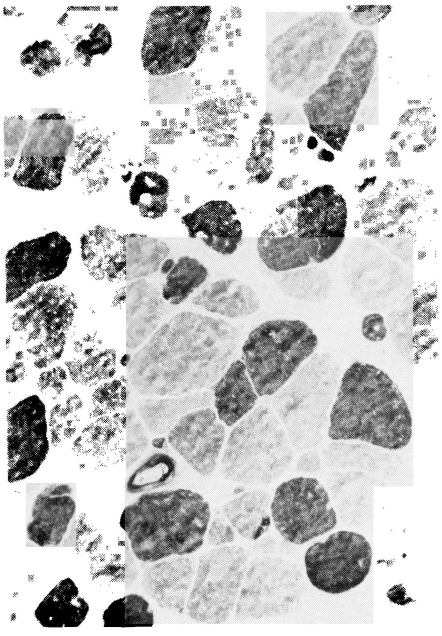

Figure 5—Atrophy of both fiber types with no fiber hypertrophy (ATPase, original magnification x 180).

nal nuclei. Rectal mucosa and skin biopsies were negative for amyloid.

The patient was discharged on a course of cortico-steroid therapy (80 mg/day) with no change in his clinical status. While in hospital there was a transient drop in the CPK to 658 international units within six weeks of treatment. The medication was slowly tapered and the CPK again rose to 1,481 international units while he was on 15 mg of steroid daily. A repeat muscle biopsy of the right vastus medialis performed in July, 1976 showed similar changes to the previous two muscle biopsies except that there was type II fiber predominance.

There was no hypertrophy of muscle fibers. The difference in fiber type predominance in the biopsies is difficult to interpret but may be due not only to the muscle biopsy site but also to progression of the disease in that muscle. We did not think that this was due to re-innervation as there was no evidence of nerve involvement.

DISCUSSION

Although this patient's clinical features were compatible with limb girdle muscular dystrophy, the histological findings of amyloid angiopathy in the small blood vessels of striated muscle is evidence that this patient had a distinct disease process. The absence of clinical and physiological evidence of peripheral nerve involvement, the absence of amyloid in other tissues such as skin and rectal mucosa, and the absence of any evidence of plasma cell dyscrasia argues against a myopathy related to any known generalized or specific forms of amyloidosis.

We were able to find only one report in the literature (Engel, 1973) of a myopathy associated with "amyloid angiopathy". This differs from the better known amyloid myopathy associated with generalized amyloidosis in which amyloid deposits in the muscle are found in the interstitial tissues (Martin et al., 1970 and Harriman, 1976). Clinically, these patients showed general enlargement of muscles, whereas our patient showed progressive loss of muscle bulk.

The question was raised whether the involvement of the medium and small caliber vessels could have caused the chronic ischemia of the muscles leading to atrophy. The second possibility is that the amyloid deposits are merely secondary to primary limb girdle muscular dystrophy, taking into account that certain muscular dystrophies (facio-scapulo-humeral) may be a heterogeneous group. Amyloidosis, with muscular dystrophy is not often reported (Reichenmiller et al., 1968 and Engel, 1973). This patient's family history is compatible with an autosomal recessive disorder, but the rest of the family members were not available for assessment.

The histology of ischemic myopathy is not well defined. There are experimental models of ischemic myopathy, but there are completely opposing viewpoints, as shown by Engel and Karpati, as to whether the results support an ischemic theory for the causation of muscular dystrophy (Engel, 1973 and Karpati et al., 1974). More recent studies of muscle blood flow in patients with muscular dystrophy using Xenon 133 clearance showed no difference from controls (Paulson et al., 1974 and Bradley et al., 1975). We did not see the great variation in the size of the muscle fibers with hypertrophy, the one feature most characteristic of a dystrophic process. The high CPK levels are indicative of an active process, but do not distinguish inflammation from a dystrophy or ischemia.

The question as to whether this patient could have chronic polymyositis was raised. Clinically, there were features compatible with this diagnosis. However, dysphagia and neck flexor weakness, common in polymyositis, were not present and cine studies of swallowing were normal. Also the marked muscle atrophy was more than one commonly sees in polymyositis. Histologically, there was no evidence of an inflammatory reaction and steroid therapy did not influence the clinical course.

The extensive vessel involvement with amyloid deposition and the absence of changes indicative of muscular dystrophy leads us to favor an ischemic basis for this patient's myopathy. The etiopathogenesis of this amyloid angiopathy remains undetermined.

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