Muscle changes in acromegaly

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Summary

Muscle biopsy specimens were obtained from 18 patients with acromegaly of varying degrees of severity. Half the specimens showed hypertrophy of type 1 fibres, while atrophy was most often seen in type 2 fibres. A direct correlation between muscle appearances and growth hormone levels was not observed. The needle biopsy technique is particularly suitable for determining the natural history of acromegalic myopathy.

Introduction

The presence of enlarged muscles associated with weakness is a well-recognised clinical observation in patients with acromegaly. Greenbaum and Young[1] produced an increase in muscle bulk by giving growth hormone to rats, and Brigland and Jehring[2] later showed that the hypertrophied muscles had no functional advantage; indeed, their contractile strength was lower than that of normal muscle.

Despite these observations there have been relatively few detailed studies on the myopathy of acromegaly. Recent developments in the methods for studying muscle by needle biopsy[3 4] have made it easier to obtain samples, and histochemical techniques have categorised skeletal muscle into separate types, with the result that muscle disorders can be more clearly differentiated.

Using these methods we studied the abnormalities of muscle in a series of patients with acromegaly of varying degrees of severity and attempted to correlate the results with the plasma levels of growth hormone.

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Patients and methods

Eighteen patients with acromegaly were studied (see table). There were 10 men and eight women, whose ages ranged from 36 to 79 years. The probable duration of disease ranged from 1 to 27 years. All but two (cases 7 and 10) were severely acromegalic, and all were fully ambulant except for one patient with osteoarthritis (case 17) and another, who, though ambulant, was restricted by heart failure (case 4). Only one patient (case 17) had clinical diabetes. In all except cases 7 and 13 growth hormone levels were greatly increased at the time of diagnosis. Two patients (cases 5 and 15) were untreated, and seven patients had normal growth hormone levels after treatment, which they had received for one to six years before biopsy.

Growth hormone concentrations were assessed by double antibody radioimmunassay.[5] Specimens were obtained from the lateral aspect of the quadriceps muscle by a needle muscle biopsy technique.[3] The sample was immediately frozen in isopentane at the temperature of liquid nitrogen and serial sections were cut at 6 μm on a cryostat. A histochemical technique was used similar to that of Dubowitz and Brooke,[6] and in normal controls matched for age and sex the distribution of muscle fibres into three types (1, 2A, and 2B) was similar to that observed by Dubowitz and Brooke.

The degree of abnormality in the muscle fibres was measured by calculating the atrophy and hypertrophy factors—the number of abnormally small or large fibres in the specimen—according to the method of Dubowitz and Brooke.[6] For convenience, the atrophy and hypertrophy factors are given as multiples of normal in the table. Fibres were regarded as deficient when they constituted less than 10% of the sample. Any abnormal degree of variance of the fibre size within each type was also recorded.

Results

Abnormalities were found in all except two patients (cases 7 and 10).

Hypertrophy—Nine patients showed hypertrophy of type 1 fibres and three also showed hypertrophy of type 2A and one showed hypertrophy of type 2B fibres. In one untreated patient (case 15) hypertrophy was confined to type 2B although the size of type 1 fibres varied considerably.

Atrophy was commonest in type 2A (seven patients) and type 2B fibres (six patients), and in only two cases were type 1 fibres atrophied.

Clinical details and biopsy findings in 18 patients with acromegaly

Patient	Age (years)	Sex	Probable duration of disease (years)	Growth hormone concentration (μg/l)							Changes in muscle appearance		
				At diagnosis	After treatment, before biopsy (years)						Type 1	Type 2A	Type 2B
					1	2	3	4	5	6			
1	47	F	10	150	36	31	18				Variance	Normal	A × 4, variance
2	47	F	12	76			10	25	29		H × 7	A × 9, variance	A × 9, variance, deficient
3	48	F	3	114	24	4	5				H × 2	Normal	Deficient
4	55	F	6	66	55	61					Variance	A × 3	A × 3, deficient
5	56	F	15	125							H × 2	H × 2	Normal
6	57	F	6	24	27						Normal	Normal	A × 6.
7	58	F	8	11		6	5	2	6		Normal	Normal	Normal
8	66	F	9	60	18				30	20	H × 1·5	A × 3, variance	A × 3, variance
9	36	M	9	44	16	17	10	6	9	9	Normal	A × 2	Normal
10	40	M	1	60	2						Normal	Normal	Normal
11	45	M	11	100	10	37					H × 3	H × 3	H × 3
12	48	M	9	37	2	1					H × 2	H × 4	Deficient
13	50	M	11	12	5						H × 4	Normal	Normal
14	54	M	7	290	10	10		4	5		H × 4	Normal	Normal
15	64	M	8	128	34	43		37			A × 4, variance	A × 2	H × 6
16	65	M	27	256	41	46	93	17			Normal	A × 2, variance	Normal
17	66	M	14	160	51	30		17	20	60	H × 4	Variance	Deficient
18	79	M	5	34	50	20					A × 2	A × 6, variance	A × 8, variance

H = Hypertrophy. A = Atrophy.

Variance—Abnormal variance of fibre size within muscle types was found in eight cases.

Discussion

The few studies on skeletal muscle in acromegaly have presented conflicting results. Lundberg *et al*[7] found no significant changes in any patient whom they investigated. In another series[8] clinical and electromyographic evidence of myopathy was found in five patients, but the muscle biopsy specimens were reported as normal. Using a histochemical technique closer to our own, Mastaglia *et al*[9 10] found type 1 hypertrophy and type 2 atrophy, but they did not attempt to correlate the results with individual growth hormone levels.

Our commonest finding was hypertrophy of type 1 fibres and atrophy of type 2 fibres, particularly type 2A. Atrophy was not that of simple disuse, which affects predominantly type 1 fibres,[11] while the hypertrophy was not that seen after exercise, which is most often present in type 2 fibres.[6] Hypertrophy also did not seem to be due to compensation for the loss of function in the smaller atrophic fibres, since in seven of the 10 patients with hypertrophy there was no atrophy of the other fibre types. In view of the experimental findings of Greenbaum and Young[1] hypertrophy is probably a direct result of excess growth hormone secretion.

Whether increased growth hormone levels are also directly responsible for the atrophic appearances is not clear. Although atrophy probably follows hypertrophy, in six patients the picture was that of atrophy only. It is perhaps significant that of the two patients with normal biopsy findings one had only slightly raised hormone concentrations and the other was clinically little affected by the disease, which appeared to be of recent onset. The duration of the disease would seem to be more important than the actual height of the growth hormone concentrations, which did not correlate directly with the muscle appearances. Mastaglia[10] has suggested that a fall in growth hormone levels produced by treatment may be responsible for the atrophic changes, but our findings do not support this view since hypertrophy was maintained in four patients despite a prolonged period during which normal levels had been restored.

The possible relation of the skeletal muscle changes to acromegalic cardiomyopathy is important and requires further study. In the only patient in our series who died from heart failure due to cardiomyopathy (case 4) the skeletal muscle changes shortly before death were those of atrophy with considerable variation in type 1 fibres. An earlier biopsy specimen from this patient had shown considerable phagocytosis of individual muscle fibres indicative of severe myopathy. We have no evidence that restoring normal growth hormone concentrations can reverse the muscle abnormalities, since even a prolonged period of normal hormone concentration was still associated with considerable changes. Nevertheless, the history of the condition can be ascertained only by serial sampling, and the relatively atraumatic needle biopsy technique is particularly suitable for this purpose.

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SHORT REPORTS

Aortic incompetence in systemic lupus erythematosus

Aortic incompetence as a sole manifestation of endocarditis is uncommon in patients with systemic lupus erythematosus (SLE).[1] We report a case where this developed in a patient with SLE treated with corticosteroids.

Case report

An obese 28-year-old woman with a previous history of polyarthralgia was seen by a psychiatrist in 1969 when she complained of depression. She was treated with amitriptyline and diazepam. Two months later she developed fever, polyarthralgia, a butterfly rash, diffuse alopecia, and pericarditis. Her blood pressure was 120/80 mm Hg. Investigation showed haemoglobin 10 g/dl, erythrocyte sedimentation rate 100 mm in first hour, LE cells positive, and antinuclear antibody and Rose-Waaler tests both positive. She was given 60 mg prednisone orally per day. Her illness subsided, and the prednisone was gradually reduced to a maintenance dose of 10 mg daily. A minor exacerbation of her articular symptoms in July 1971 necessitated increase of prednisone to 15 mg daily for one month.

In September 1973 she was asymptomatic, but a high pitched early diastolic murmur behind the left sternal edge in the third and fourth intercostal spaces was heard, and the blood pressure was 195/60 mm Hg. The haemoglobin level was 11·9 g/dl, the Wasserman reaction was negative, and blood cultures were negative. In October 1975 exertional dyspnoea developed, the diastolic murmur was found to have persisted, and electrocardiography showed left ventricular hypertrophy. In December 1975 the exertional dyspnoea was increasing, and an ejection systolic murmur in addition to the diastolic murmur was heard at the left sternal edge. Cardiac catheterisation confirmed the presence of aortic incompetence without stenosis. Cardiac cineangiography showed moderately severe aortic regurgitation with satisfactory left ventricular function, good movement of the aortic valve cusps, and some dilatation of the ascending aorta. Treatment with 10 mg prednisone and a diuretic was continued. When reviewed in March 1976 she continued to do well.

Discussion

This 28-year-old patient developed SLE in 1969 and was treated with corticosteroids. Four years later despite apparent reasonable control of the disease she developed aortic incompetence with no other demonstrable valvular defect. Aortic incompetence was not explicable on the grounds of cardiac failure secondary to anaemia, nor were the length of the subsequent history or the results of investigations compatible with a diagnosis of subacute bacterial endocarditis. The patient did not have ankylosing spondylitis, and rheumatic heart disease seems a less likely diagnosis with neither evidence of other valvular involvement nor history of acute rheumatic fever previously. It seems most likely that this patient developed aortic incompetence as a complication of her SLE. When endocardial involvement by SLE occurs it most commonly effects the mitral valve,[1 2] and aortic incompetence without mitral valve disease in SLE is extremely rare. Bernhard *et al*[3] reported three such patients, while Schulman and Christian[4] described three cases with aortic incompetence and mitral valve disease. Aortic incompetence in our patient developed despite apparent control of other features of SLE and underlines the suggestion[3] that corticosteroid therapy may play a part in the development