Haemophilic neuromyopathy

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SUMMARY Twenty haemophilic patients were examined neurologically and found to have varying degrees of muscle atrophy. The pathogenesis of the atrophy was investigated by electromyography, serum muscle enzyme levels, and muscle biopsies. In most cases the EMG showed such abnormalities as reduced numbers of functioning motor units and "myopathic" motor unit potentials. Serum enzyme levels were frequently raised, and type 2 fibre atrophy was found in the three patients who underwent muscle biopsy. These findings suggest the presence of neuromyopathic involvement in haemophilic patients.

Muscle atrophy is a well-known finding in haemophilic patients and has been attributed to disuse or to fibrosis after intramuscular haemorrhage (Ikkala, 1960; Wilkinson *et al.*, 1961; Williams *et al.*, 1972). However, neither explanation could account for the severe muscle wasting which we have observed in some patients with normal physical activities and no history of intramuscular bleeding. This puzzling observation has prompted the present study in which neuromuscular function in 20 unselected patients with haemophilia has been investigated by means of electromyography, serum enzymology, and muscle biopsy. No similar study appears to have been undertaken previously.

Patients and methods

Twenty male patients with haemophilia were studied. They were aged 2-30 years (mean 12.45 ± 7.40 years). The disease was of the A type in 19 patients and of the B type in one. It was of the severe form with the exception of a single patient with A type who had a moderate form. All patients gave informed consent to the various procedures. None of the patients had serological evidence of Chagas' disease which would be an important cause of neuromuscular involvement in Brasil (DeFaria *et al.*, 1977).

ELECTROMYOGRAPHY

Electromyographic examinations were performed in all cases. Measurements were made directly

from a variable persistence storage oscilloscope (Tektronix type 5403) which permitted a maximum signal amplification of $10 \mu\text{V}/\text{cm}$. Electrical stimuli to motor and sensory nerves consisted of rectangular voltage pulses, $50 \mu\text{s}$ in duration, delivered from a Devices Ltd stimulator, type 3072; this instrument and the oscilloscope time base were triggered from a mini-digitimer (Devices Ltd model D-100). The EMG examination involved motor unit counting, determination of impulse conduction velocities in motor and sensory nerves fibres, and measurement of sensory nerve action potential amplitudes. For stimulating and recording from nerves, pairs of chlorided silver discs were used, each disc being 5 mm in diameter and separated from its neighbour by 30 mm. Evoked muscle responses were recorded with silver strips (McComas *et al.*, 1971) and for the intramuscular examination concentric needles (Disa type 9013L0501) were used.

ENZYME STUDIES

Serum levels of five enzymes—alanine transaminase, aspartate transaminase, creatine kinase, aldolase and lactic dehydrogenase—were studied.

MUSCLE HISTOLOGY

"Open" biopsies were performed under local anaesthesia on the vastus medialis muscles of three patients. The patients were treated immediately beforehand with antihemophilic globulin intravenously. There was clinical evidence of relatively minor intramuscular bleeding subsequently in one case. Paraffin sections were stained with haematoxylin and eosin while frozen sections were treated for activity of the following

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enzyme systems: myosin ATP-ase at pH 9.4; aldolase; naftol-esterase-acetate; phosphofructokinase; NADH₂-tetrazolium reductase; phosphorylase.

Results

CLINICAL FINDINGS

The most common clinical findings were arthropathy and muscle wasting. The arthropathy was usually evident in the knee and elbow joints followed, in order of frequency, by the ankles, shoulders, and hips. Fifteen patients had more than one joint involved. Atrophy was evident in muscles next to the affected joints both proximally and distally. However, most of the patients exhibited a very interesting general picture: they were slim with slender limbs and reduced muscle bulk even when the relevant joints appeared normal. The overall picture was of symmetrical, mainly proximal, muscle wasting. The shoulder girdle muscles were particularly involved, and some winging of the scapulae could be seen in the

Table 1 Clinical findings in haemophilia. Joints: k=knee; a=ankle; e=elbow; h=hip; s=shoulder; w=wrists. Muscles: q=quadriceps; c=calf; f=forearm; a=arm. Capitals denote bilateral involvement

Patients	Age (yr)	Arthropathy	Muscle wasting	
			General	Focal
ABS	8	K,e	+	Q,c
ALB	16	K,h,s	+	
ASMM	6	k,e,a	+	q,c
DOF	10	e,a,k	+	f,a,c
EJD	9	k,e,a		q
IAS	8	k,e	+	q,c,a
IBG	10	K	+	q,c
JCJ	17	K,e	+	Q,C
JCJ	11	K,e	+	q,c
JCJ	8			
OBF	30	e,k,s	+	q
VONG	20	A,k		q
ABN	11	K,E,W	+	Q,C
CRJ	4	K,E,h	+	q
JPP	11	k,A,E,s	+	q
AJJ	2			
MRS	24	k	+	q,c
AJ	4	k	+	
JBS	24	K,H,e,s,A	+	Q,C
CAR	17	k	+	q,c

Fig. 1 Atrophy of the shoulder girdle muscles in two haemophilic patients without any clinical evidence of shoulder joint lesions; both patients had been observed for two years. Note the winging of the scapula in the 17 year old patient (left); patient JCJ (right) was aged 8 years.

majority of patients (Fig. 1). Muscles with mild or moderate atrophy and remote from affected joints, retained relatively good power in contrast to those with severe atrophy adjacent to arthropathic lesions. Hypotonia was a common finding but deep reflexes were almost always normal, except for muscles with severe atrophy. The cranial nerves were not affected. There was no clinical evidence of peripheral sensory nerve involvement.

ELECTROMYOGRAPHIC FINDINGS

Electromyographic abnormalities were a common finding, both on motor unit counting and concentric needle examination. Thus, reduced motor unit counts were found in some intrinsic muscles of hands and feet as follows: in 10 out of 17

extensor digitorum brevis muscles, in nine of 18 thenar muscle groups, and in four of 14 hypothenar muscle groups (Table 2). Widespread fibrillations and positive sharp wave activity were found in only one patient by concentric needle electromyography. Five patients had reduced interference patterns in at least one of the muscles examined (Fig. 2, top). The distal muscles examined, abductor pollicis brevis and extensor digitorum brevis, presented high voltage and long duration potentials in eight out of 13 patients. However, the most frequent EMG abnormality observed was small brief motor unit potentials, sometimes mixed with longer complex potentials, during weak contraction in the larger muscles of the limbs (vastus medialis, biceps brachialis, and tibialis anterior) (Fig. 2, bottom). These "myopathic" motor unit potentials were found in at least one muscle in 12 of 19 patients (Table 3). Four patients were examined on two occasions and it was our impression that myopathic motor unit potentials were more frequent when the haemophilia was least well controlled. Motor nerve conduction velocities were normal in the median, ulnar, and peroneal nerves of all patients. Sensory nerve conduction velocities were normal in the median and ulnar nerves of 16 patients, and were reduced in four cases. Sensory nerve action potential amplitudes were always normal in the radial, median, and ulnar nerves after digital stimulation.

Table 2 Motor unit number in haemophilic patients. Each letter corresponds to the same patient, dotted line is the lower normal limit

Table 3 Needle electromyographic findings. Muscles: EDB=extensor digitorum brevis; VM=vastus medialis; TA=tibialis anterior; APB=abductor pollicis brevis; B=biceps. Voluntary potentials: N=neuropathic; n=normal; M=myopathic

Patients	Muscles				
	EDB	VM	TA	APB	B
ABS	N	n	—	—	—
ALB	n	n	—	n	M
ASMM	N	n	—	—	—
DBF	—	—	—	—	M
EJD	—	M	n	—	—
IAS	—	M	M	N	n
IBG	M	M	M	—	—
JCJ	N	M	M	N	M
JCJ	—	M	M	—	M
JCJ	—	M	M	—	N
OBF	N	n	M	n	M
VONG	N	n	n	—	—
ABN	n	n	M	—	—
CRJ	—	—	—	—	—
JPP	—	n	n	—	—
AJJ	—	M	—	—	—
MRS	n	n	n	—	—
AJ	—	n	—	—	—
JBS	N	n	n	N	M
CAR	—	n	n	N	—

Fig. 2 (Top) Reduced interference pattern in extensor digitorum brevis muscle of patient ALB, aged 15 years; the muscle action potentials shown are of normal amplitude. (Bottom) Small brief ("myopathic") motor unit potentials in vastus medialis muscle of patient DBF, aged 10 years, during moderately strong contraction.

BIOPSY FINDINGS

Specimens were taken from the vastus medialis muscles of three patients with no signs of hip or knee arthropathies. The results were qualitatively similar but differed in severity. Some fibres were observed to have undergone complete degeneration while others had changes restricted to the periphery (Fig. 3, right). Attempts at regeneration were also seen. Staining for myosin ATP-ase at

pH 9.4 and for NADH revealed moderate atrophy of type 2 fibres. No evidence of recent or previous haemorrhage was observed in any of the specimens.

SERUM ENZYME STUDIES

A battery of muscle enzyme tests was performed on sera from 16 patients, and in 12 patients the studies were repeated six to eight months later.

Fig. 3 Vastus medialis biopsy specimens of patient JCJ (8 years old). The specimen on the right has been stained with haematoxylin and eosin and shows fibres undergoing degenerative changes, the earliest of which appear to occur in the fibre peripheries; there are also attempts at regeneration. The specimen on the left has been stained for NADH₂-TR activity and shows marked atrophy of type 2 fibres (pale fibres).

Fig. 4 Serum enzyme levels in haemophilic patients; the interrupted lines mark the upper limits of the normal ranges. See text.
SGPT=alanine transaminase,
SGOT=aspartate transaminase,
CPK=creatine kinase,
LDH=lactate dehydrogenase.

From Fig. 4 it can be seen that more than half of the examinations were abnormal, the most sensitive tests being those for aldolase and aspartate transaminase activities. In some patients marked fluctuations of the titres were observed, especially for creatine kinase and aldolase (Fig. 4). Some of these enzymes (particularly the transaminases) were reported raised in haemophilia because of hepatitis by Mosley and Galambos (1975).

Discussion

The results of the present study, comprising clinical, EMG, serum enzyme, and muscle biopsy investigations, leave little doubt that muscle abnormalities are to be found in nearly all cases of haemophilia. On the basis of electromyography the general form of these abnormalities is for "myopathic" features to predominate in proximal limb muscles and for "neuropathic" ones to occur distally. Among the possible explanations for these findings must be considered haemorrhage into nerves and muscles, and also the effects of disuse in muscles associated with arthropathic lesions, themselves the consequence of previous bleeding into the joint cavities. So far as haemorrhage into the muscle belly is concerned, none of the patients had reported episodes of painful swelling suggestive of haematoma. Although the possibility of repeated minor bleeding remains,

there was no evidence for this in the three muscle biopsies undertaken. In relation to intraneural haemorrhage, this may undoubtedly complicate haemophilia, and can cause a variety of peripheral nerve syndromes (Silverstein, 1964; Brower and Wilde, 1966). Again, however, there was no history of an acute nerve palsy in any of our patients and it is relevant that sensory nerve responses were of normal amplitude in all the radial, median, and ulnar nerves examined. In four of the patients, however, slowed impulse conduction could be demonstrated in sensory fibres of the median or ulnar nerves, and was most likely the result of nerve entrapment by hypertrophic joints. Apart from the fact that impulse conduction was normal in most patients it would be difficult to account for the generalised and symmetrical muscle atrophy on a neuropathic basis, and the greater involvement of proximal muscles is also against such an explanation. So far as disuse is concerned, pronounced wasting and weakness were found in muscle around severely affected joints, and it seems likely that disuse was the major pathogenic factor. Nevertheless, it was frequently possible to observe less severe atrophy in muscles operating joints with normal structure and mobility, and some of the patients led reasonably active lives. It, therefore, seems likely that a significant neuromuscular disorder may exist in haemophilia which is not directly related to the

haemorrhagic diathesis. It is certainly interesting, and quite possibly of pathogenetic significance, that haemophilia resembles the Duchenne and Becker types of muscular dystrophy in being inherited as a sex-linked recessive trait. Furthermore, the same mixture of "myopathic" features in proximal muscles and of "neuropathic" features in distal ones is observed in the muscular dystrophies (McComas, 1977) as in haemophilia. Since the gene loci for haemophilia and Becker type muscular dystrophy are close to each other on the X-chromosome, both being part of the colour-blindness group (McKusick, 1974; Emery, 1977), it is possible that in haemophilic patients a small region of the chromosome, rather than a single gene, may be abnormal. Clearly, genetic studies would be of value in exploring this point and further speculation at the present time is unwarranted.

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