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An electrophysiological investigation of limb-girdle and facioscapulohumeral dystrophy

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SUMMARY A detailed electrophysiological study has been made of the extensor digitorum brevis muscle and its motor innervation in 11 patients with limb-girdle or facioscapulohumeral dystrophy. In nine patients there were reductions in the populations of motor units and many surviving units appeared to be abnormally large. Most of the investigated muscles had slowed isometric twitches and decremental evoked potentials after repetitive nerve stimulation. The experimental observations have been interpreted in terms of a neuropathic process.

We wish to report the results of a detailed electrophysiological examination of muscle and motor nerve function in patients with limb-girdle or facioscapulohumeral dystrophy. It will be shown that in affected muscles there is evidence of a reduction in the number of operative motor units, a slowing of the isometric twitch, and decremental responses to repetitive nerve stimulation. The present study complements similar investigations of the myotonic and Duchenne types of dystrophy (McComas, Campbell, and Sica, 1971b; McComas, Sica, and Currie, 1970, 1971d); as in these other studies, a neurogenic explanation for the observed results will be postulated. A preliminary account of this work has already appeared (McComas and Sica, 1970).

METHODS

Eleven patients were studied; in Table 1 their ages are given, together with the duration of symptoms and the clinical diagnosis. All except the patient H.L. were able to walk, usually with the aid of sticks; none wore calipers. Table 1 also shows the results of muscle biopsy and serum creatine kinase estimations if these had been performed. All patients were studied electromyographically; for this investigation unipolar concentric needle electrodes (Medelec Ltd.) were used to sample the electrical activity induced in vastus lateralis (VL) and extensor digitorum brevis (EDB) muscles by volitional contraction. The densities of the interference patterns during maximum effort were analysed subjectively and any spontaneous discharges at rest were noted. The action potentials of fibres recruited during weak effort were fed through an amplifier with a frequency response which was 3dB down at 2Hz and 10 kHz. The potentials were then 'stored' on a Hewlett-Packard type 141A oscilloscope and their parameters measured. Potentials were regarded as probably 'neuropathic' if they possessed more than one of the following characteristics: long duration (> 15 msec in EDB; > 20 msec in VL), polyphasic configuration, and enlarged amplitude (> 5mV in EDB; > 2 mV in VL). Similarly potentials were considered 'myopathic' if they were abnormally brief—for example, 3-4 msec—or if they were polyphasic without any increase in amplitude or duration.

In each patient the maximum conduction velocities of impulses in motor fibres of the deep peroneal nerve were measured and the following special investigations were carried out:

1. Estimation of the number of motor units in the extensor digitorum brevis muscle (McComas, Fawcett, Campbell, and Sica, 1971a).

2. Measurement of isometric twitch parameters in the extensor hallucis brevis muscle (most medial subdivision of the extensor digitorum brevis; see Sica and McComas, 1971).

3. Responses of extensor digitorum brevis muscles to repetitive stimulation of deep peroneal nerves. One second trains of supramaximal stimuli were given at frequencies of 3/sec, 10/sec, 30/sec, and sometimes 50/sec. Stimulation was then repeated at 30/sec two minutes after the cessation of a maximal voluntary contraction, itself lasting two minutes (see also Fig. 13 in Desmedt, 1966). A reduction of 20% or more in response

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TABLE 1

Patient	Sex	Age (yr)	Duration weakness (yr)	Diagnosis	FH	Investigations			
						SCK (i.u.)	Biopsy	EMG	
								VL	EDB
H.C.	F	28	20	FSH	+			M	M
J.S.	F	41	24	FSH	+	40		M	Normal
E.P.	F	58	28	FSH	+	47	M	M*	N
L.C.	M	59	40	FSH	−			M	Normal
J.L.	F	36	25	LG	−		M	M*	Normal
J.P.	F	45	35	LG	−	17	M		Normal
H.L.	M	46	31	LG	−		M	*	M
E.M.	M	49	31	LG	−	101	M	M*	Normal
M.M.	F	55	22	LG	−	915	M	M*	Normal
W.F.	M	57	36	LG	−			M	Normal
G.G.	M	60	27	LG	−			M	Normal

M, result suggestive of myopathy; N, result suggestive of neuropathy; VL, vastus lateralis; EDB, extensor digitorum brevis; +, positive result; −, normal result; * Additional EMG performed previously by another investigator.
Serum creatine kinase (SCK) values are expressed in international units (i.u.)/litre. In this laboratory the upper limit of the normal range is 75 i.u./l.

amplitude, during stimulation at any frequency, was regarded as significant. A population of 50 healthy subjects aged 18 to 59 was drawn upon for control observations. Except where stated, mean values throughout the text have been given with their standard deviations; the significance of a difference between two means was calculated by the *t* test.

RESULTS

NUMBERS AND SIZES OF MOTOR UNITS IN EXTENSOR DIGITORUM BREVIS (EDB) MUSCLES In an earlier study it was reported that a healthy subject below the age of 60 can be expected to have more than 120 motor units in an EDB muscle, when an electrophysiological method of estimation is used (McComas *et al.*, 1971a). An example of the use of this method in a patient with limb-girdle dystrophy is shown in Fig. 1 (A, B). In the present investigation it was found that only two patients had normal numbers of units and in one of these the value was at the lower limit of the normal range (Table 2). The most severely denervated muscle was in a 55 year old woman who possessed only 10 units. There did not appear to be any correlation between the number of surviving units and the age of the patient, though this may have reflected the relatively small number of observations. Indeed it can be seen in Table 2

TABLE 2

RESULTS OF ELECTROPHYSIOLOGICAL STUDIES IN PATIENTS WITH LIMB-GIRDLE OR FACIOSCAPULOHUMERAL DYSTROPHY

Patient	EDB motor units		Isometric twitch			Nerve stimulation		
	No.	Mean potential amp. (μV)	AT (g)	CT (msec)	½RT (msec)	CV (m/sec)	TL (msec)	DR
H.C.	32	57	170	80	68	48	5·0	−
J.S.	120	37	270	88	85	45	4·2	−
E.P.	33	44	32	80	90	51	4·2	−
L.C.	53	39	280	84	80	49	4·9	+
J.L.	76	98	205	68	48	52	3·8	+
J.P.	62	30	290	84	92	44	4·8	+
H.L.	51	12	25	?	?	44	4·0	−
E.M.	36	150	220	92	100	52	4·4	+
M.M.	10	120	125	110	?	46	5·2	+
W.F.	96	28	330	94	90	53	3·6	+
G.G.	144	43	350	76	72	45	3·5	+
Control range	121 −414	14 −60	160 −560	50 −78	36 −76	40 −60	3·0 −5·0	

AT, active tension; CT, contraction time, ½RT, half-relaxation time; CV, conduction velocity; TL, terminal latency; DR, decremental responses to repetitive nerve stimulation.

TABLE 3

MEAN VALUES (± SD) OF POOLED ELECTROPHYSIOLOGICAL DATA FROM NORMAL AND DYSTROPHIC SUBJECTS, TOGETHER WITH SIGNIFICANCE OF DIFFERENCES

	EDB motor units		*Isometric twitch*			*Nerve stimulation*	
	No.	*Mean potential amp. (μV)*	*AT (g)*	*CT (msec)*	*½RT (msec)*	*CV (m/sec)*	*TL (msec)*
Patients	65	59·5	209	85	81	48·1	4·3
mean (± SD)	(41)	(73·0)	(111)	(9·7)	(16)	(3·5)	(0·6)
Controls	199	28·9	313	63	52	49·0	4·0
mean (± SD)	(60)	(27·1)	(90)	(7·3)	(9·7)	(4·0)	(0·6)
P	<0·001	<0·001	<0·01	<0·001	<0·001	>0·6	>0·2

Abbreviations as in Table 2.

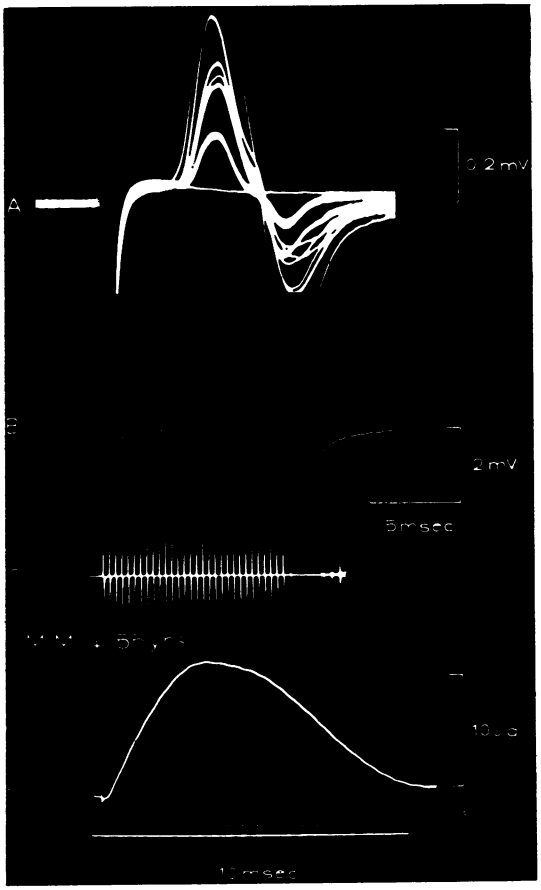

FIG. 1. *J.L., female, aged 36 years.* A. *EDB responses to juxtathreshold nerve stimulation.* B. *Maximal EDB response in same patient.* C. *Decremental EDB responses in same patient after indirect stimulation at 30 shocks/sec.* D. *EHB isometric twitch in patient M.M. Contraction time in this record was 130 msec, but repeated observations gave mean value of 110 msec.*

that the second most affected muscle occurred in the youngest patient of the series (H.C., aged 28). Table 2 also shows that the 'denervation' affected the patients with facioscapulohumeral dystrophy as well as those with the limb-girdle variety. In Table 3 it can be seen that, when the results from the 11 subjects were pooled, the mean number of units (65 ± 41) was significantly different from the control mean (199 ± 60 units).

In each patient the mean size of the motor unit potentials was calculated. In only one patient did this value fall below the normal range (14-60 μV) and in three the amplitudes were abnormally large (Table 2). A more detailed analysis of the sizes of the motor unit potentials was made by pooling the results from the patients and arranging them in a histogram (Fig. 2). In normal subjects very few potentials have amplitudes greater than 80 μV. In patients with limb-girdle or facioscapulohumeral dystrophy, however, 21 out of 115 potentials exceeded this value—for example, Fig. 1A. The mean amplitude for the patients was 59·5 ± 73·0 μV and was significantly larger than the control mean (Table 3).

ISOMETRIC TWITCH STUDIES In 50 control subjects the maximum isometric twitch tension of extensor hallucis brevis (EHB) muscles ranged from 160 to 560 g, with a mean of 313 ± 90 g. Although, as anticipated, the mean twitch tension for the population of dystrophic patients, 209 ± 111 g, was significantly lower than the control mean (Table 3), the values for individual patients were of considerable interest (Table 2). Thus, of the nine patients with denervation six had twitch tensions which were within the normal range. The relationship between the numbers of surviving units and the twitch tensions has been expressed graphically in Fig. 3. It can be seen that in these six patients the recorded tensions were actually abnormally large in relation

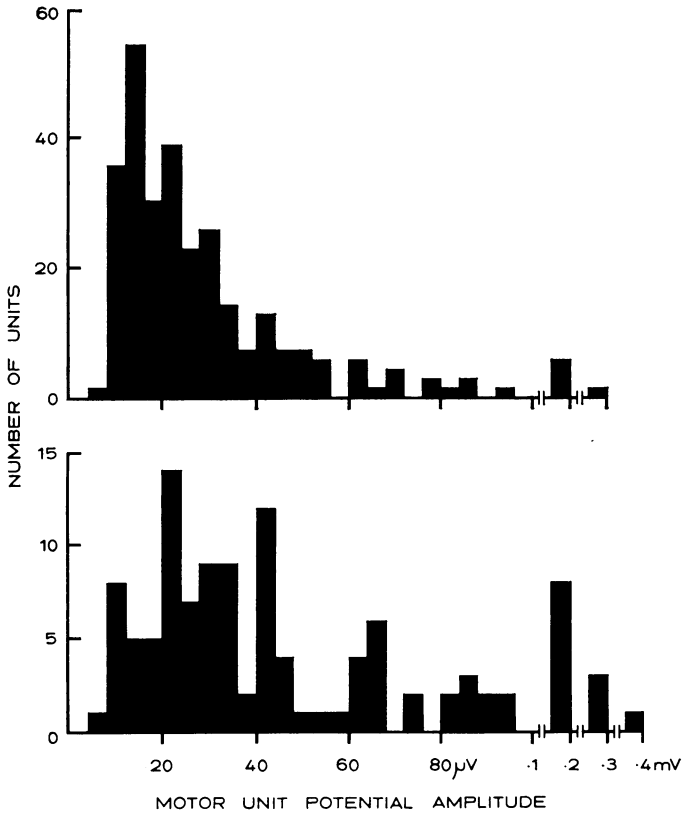

FIG. 2. *Amplitudes of motor unit potentials in controls (upper) and patients with limb-girdle and facioscapulohumeral dystrophy (lower). Control mean 28·9 ± 27·1 μV (n = 283); dystrophic mean 59·5 ± 73·0 μV (n = 115); difference between means significant (P = < 0·001).*

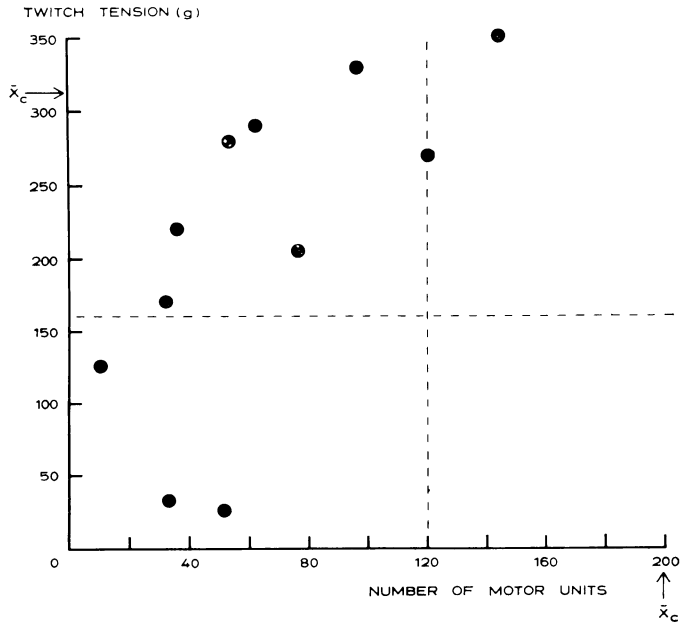

FIG. 3. *Isometric twitch tensions of dystrophic muscles with different amount of 'denervation'. Interrupted lines denotes lower limits of control results while $\bar{X}_c$ indicates respective mean control value.*

to the number of surviving units (see Discussion). Of the remaining three patients with denervation the weakest muscle was found in the most physically disabled subject (H.L.) who was the only one unable to walk. Table 2 shows that in this patient the maximum evoked muscle action potential was smallest, as was the mean motor unit potential amplitude. Finally, both of the patients with normal numbers of motor units had twitch tensions within the control range (Table 2), as would have been expected from the previous results.

The twitch speeds were also of interest for in all but two patients the contraction times fell outside the upper limit for normal subjects (78 msec; see Fig. 1d). The mean contraction and half-relaxation times for the patients were 85 ± 9·7 msec and 81 ± 16 msec respectively and were both significantly greater than the corresponding values in controls (63 ± 7·2 msec and 52 ± 9·7 msec; Table 3).

OTHER STUDIES In all patients the maximum conduction velocities of impulses in motor fibres of deep peroneal nerves were within the normal range for this laboratory (40-60 m/sec; see Table 2); furthermore the mean velocity, 48·1 ± 3·5 m/sec, was very close to the control value of 49·0 ± 4·0 m/sec and did not differ significantly from it ($P = > 0·6$). A comparison was also made of the terminal latencies in the control and dystrophic populations; this latency was measured as the time elapsing between stimulation of the deep peroneal nerve at the ankle and the onset of postsynaptic activity in EDB. Once again the control and dystrophic means were found to be in good agreement and did not differ significantly (Table 3). However, repetitive stimulation of deep peroneal nerves revealed one further abnormality in seven of the patients, including one (G.G.) in whom the estimated number of motor units was normal. In each of these patients the muscle action potentials declined appreciably (see Methods and Fig. 1c), resembling the responses obtained in myasthenia gravis.

The final investigation was to study with concentric needle electrodes the electrical activity induced in EDB and vastus lateralis muscles by voluntary contraction (see Methods). In all the *vastus lateralis muscles* examined electromyography was abnormal due to a high incidence of 'myopathic' potentials (Table 3). Although the densities of the interference patterns were reduced in three of these patients 'neuropathic' potentials were not encountered. The findings in *EDB muscles* were rather surprising, for in six patients electromyography was entirely normal. For example, the interference pattern appeared to have a normal density in the patient E.M. who was estimated to have only 36 units in EDB. In eight patients the majority of individual muscle action potentials were normal in all respects and in only one patient was a significant incidence of neuropathic discharges observed. The finding of 'myopathic' potentials in the weakest patient (H.L.) was of considerable interest and is discussed below. Fibrillation potentials and positive sharp waves were not recorded in any of the muscles examined.

DISCUSSION

One of the characteristic features of limb-girdle and facioscapulohumeral dystrophy is that the most severely affected muscles in the limbs are the proximal ones. For this reason the choice of a distal muscle, such as the extensor digitorum brevis (EDB), confers a special advantage, for it enables the degenerative process in muscle to be studied at a relatively early stage. Indeed, of the 11 patients studied, eight had EDB twitch tensions within the normal range. Of the various observations made in this study, the most significant one was that many motor units had completely ceased to function while others were abnormally large, as estimated by measurements of isometric twitch tension and motor unit potential amplitude. In an earlier study of dystrophia myotonica (McComas *et al.*, 1971b) it was argued that, in a primary myopathy, muscle fibres would be affected randomly within a muscle and that as the disease process continued individual motor units would become progressively smaller. In the Duchenne and myotonic dystrophies, it was found that the pattern of the disease did not conform to this prediction (McComas *et al.*, 1970, 1971b, c, d). Thus, while some motor units were entirely destroyed, others retained relatively normal sizes. Such findings were interpreted as indicating a neurogenic basis for these two types of dystrophy. If the same theoretical considerations are now applied to the present observations in limb-girdle and facioscapulohumeral dystrophy, then these conditions must also be regarded as neurogenic since both show selective involvement of motor units. However, in these last two disorders the enlarged sizes of many units have special significance, for they furnish perhaps the strongest evidence to date against a myopathic aetiology for dystrophy. Essentially such enlarged potentials could only have resulted if *potentially healthy* muscle fibres had lost their original (defective) innervation and had subsequently acquired a satisfactory nerve supply.

In an earlier paper (McComas, Sica, and Campbell, 1971) the size of a motor unit was used as an index of the functional normality of the corresponding motoneurone. It was argued that in

a partially denervated muscle healthy motoneurones should be able to 'annexe' denervated muscle fibres by axonal sprouting and thereby increase the sizes of their motor units. Conversely, those motor units which had not enlarged were considered to belong to dysfunctional ('sick') motoneurones; impaired neuromuscular transmission was thought to constitute a further sign of dysfunction. In the present study the twitch measurements and motor unit potential amplitudes both suggested that many motor units were enlarged. From the theoretical considerations presented above, it may therefore be inferred that some healthy motoneurones still remained in the spinal cords of patients with limb-girdle and facioscapulohumeral dystrophy. Similarly the occurrence of small or normal-sized units and the finding of myasthenic-like responses both indicate the additional existence of sick motoneurones.

If this interpretation of our results is correct, then the motoneurone pools in limb-girdle and facioscapulohumeral dystrophy differ from those in the myotonic and Duchenne types. In the former some healthy motoneurones are still present while in the latter nearly all neurones are sick. In the patient H.L. the small sizes of all the investigated motor units were of ominous significance, since they suggested that all the surviving motoneurones had entered the sick phase before cell death. In the paper of McComas *et al.* (1971c) an attempt was made to calculate the annual loss of functioning motoneurones and the duration of the sick phase in individual cells. It was estimated that, on average, three cells were lost each year from an EDB motoneurone pool in a patient with limb-girdle dystrophy and that the preceding sick phase had lasted 12 years.

The measurements of twitch speed were of interest, for they suggested that the 'slow twitch' motor units were less severely affected by the disease process. However, in a careful examination of isometric twitches in adductor pollicis muscles of patients with limb-girdle dystrophy, Desmedt (1967) reported that the contraction and half-relaxation times were within normal limits. We do not know the reason for this discrepancy between the two studies.

Finally, one important question remains to be answered. Did the patients have limb-girdle or facioscapulohumeral dystrophy, or should they have been diagnosed as suffering from the Kugelberg-Welander syndrome? There are two possible answers to this problem. The first is that, on the basis of the laboratory evidence available, a diagnosis of limb-girdle or facioscapulohumeral dystrophy was appropriate to each of the patients examined. We have given particular weight to the results of electromyography; in all of the vastus lateralis muscles studied the majority of the motor unit potentials were undoubtedly 'myopathic'. It should be added that a further seven patients, in whom a diagnosis of limb-girdle dystrophy had either been made previously or was currently under consideration, were rejected, since most of the potentials recorded from proximal muscles were 'neuropathic'.

However, the second approach to the diagnostic dilemma is, we believe, the more satisfactory one. As stated above, the present results suggest that the limb-girdle and facioscapulohumeral dystrophies are neuropathic processes and it is already known that the Kugelberg-Welander syndrome is a disorder of the motoneurone. Therefore, it seems to us illogical to force patients into one or other diagnostic category on the basis of clinical or laboratory findings; the two conditions are the same.

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