Computer method for the analysis of evoked motor unit potentials

2. Duchenne, limb-girdle, facioscapulohumeral and myotonic muscular dystrophies

JOHN P. BALLANTYNE¹ AND STIG HANSEN

From the University Department of Neurology, Institute of Neurological Sciences and the Department of Clinical Physics and Bio-engineering, Glasgow

SYNOPSIS Single motor unit potentials recorded from surface electrodes over the extensor digitorum brevis muscle and evoked by stimulation of the anterior tibial nerve at the ankle were obtained by a computer subtraction method. Their latencies, durations, amplitudes, and areas were measured in control subjects and patients with Duchenne, limb-girdle, facioscapulohumeral, and myotonic muscular dystrophy. Lateral popliteal motor nerve conduction velocities were also recorded. In the muscular dystrophies there was a significant increase in both the latencies and durations of motor unit potentials, the latter in notable contrast with the findings of conventional needle electromyography. Fastest motor conduction velocities were significantly reduced in the limb-girdle, facioscapulohumeral, and myotonic muscular dystrophy patients, while the shortest distal motor latencies were significantly prolonged in these patients and those with Duchenne muscular dystrophy. The results support the presence of a definitive neurogenic influence in the muscular dystrophies.

In an earlier study we described a computer subtraction technique for the isolation and measurement in man of motor unit action potentials (MUP) recorded from surface electrodes over the extensor digitorum brevis muscle (EDB) and evoked by stimulation of the anterior tibial nerve at the ankle (Ballantyne and Hansen, 1974b). The area, amplitude, duration, and latency of each MUP can be measured, providing indices of the electrophysiological activity in the motor unit and of the functional integrity of the innervating axon and/or neuromuscular junction. We have stated our preference for surface rather than concentric needle electrode recording in this situation (Ballantyne and Hansen, 1974b) as the action potential obtained more accurately reflects the number of muscle fibres in the motor unit and is relatively uninfluenced by muscle fibre density.

The purpose of this paper is to present the results obtained from the application of this technique to patients with Duchenne, limb-girdle, and facioscapulohumeral myotonic muscular dystrophies.

METHODS

All values are expressed as mean $\pm$ one standard deviation (SD). Mean values were compared using Student's *t* test.

SUBJECTS 1. *Controls* Thirty-three subjects, members and relatives of the staff of the Institute of Neurological Sciences, were investigated. None had evidence of neurological disease. Twelve of these subjects aged 10.7 ± 2.2 years were used as controls for the Duchenne study, while the other 21 normal subjects aged 38 ± 14 years formed a control group for the limb-girdle, facioscapulohumeral, and myotonic dystrophies.

2. *Duchenne muscular dystrophy* Twelve boys aged 10 ± 2.9 years were studied. In all cases, the primary

¹ Address for correspondence: University Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF.
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diagnosis had been made previously on the basis of clinical history, family history, clinical examination, serum creatinine kinase, and muscle biopsy. In four patients these investigations were supplemented by electromyography.

3. Limb-girdle and facioscapulohumeral muscular dystrophies Twelve patients aged 37 ± 17.4 years were studied, of whom three had facioscapulohumeral muscular dystrophy. The mean duration of symptoms was 14 ± 8.2 years. The diagnosis was reached on the basis of clinical examination, muscle biopsy (seven patients), and electromyography (EMG) (12 patients). Serum enzyme studies, performed on all patients, were normal to slightly elevated. Only those patients in whom the EMG appearances were considered myopathic were included in the study.

4. Myotonic muscular dystrophy Twelve patients aged 45 ± 14.0 years were studied. The duration of the symptoms was 16 ± 12.2 years. In all patients the clinical and electromyographic features were characteristic of myotonic muscular dystrophy. In only one patient was a muscle biopsy performed and this was reported to show myopathic changes.

Motor unit counts from the EDB muscles of these patients have been reported (Ballantyne and Hansen, 1974c).

TECHNIQUES The composition and placement of the surface recording electrode over the EDB muscle, the properties of the stimulating electrodes over the anterior tibial nerve at the ankle, and details of the rate and strength of stimulation used to evoke MUPs have been described previously (McComas *et al.*, 1971b; Ballantyne and Hansen, 1974a). The description of the amplification and display systems and of the computer handling of data for the isolation of individual MUPs has been presented (Ballantyne and Hansen, 1974b). The values for area and peak to peak amplitudes of MUPs were provided by the computer. The latency and duration of each MUP were measured manually from the computer print-out, the former from the time interval between the onset of the stimulus artefact and the initial deflection of the potential in the print-out, the latter from the initial deflection to the final return of the baseline to zero potential including positive and negative phases.

Fastest motor conduction velocities in the lateral popliteal nerve (knee to ankle segment) and shortest distal motor latencies (anterior tibial nerve at the ankle to the EDB muscle) were measured using an established technique (Hodes *et al.*, 1948). The

evoked muscle action potential was recorded from surface electrodes over the EDB muscle as above.

The limb temperatures were maintained at $33^\circ\text{C} \pm 1^\circ\text{C}$.

RESULTS

1. MOTOR UNIT PARAMETERS *Control subjects* Both the mean amplitude and area of the MUPs of adult controls are significantly greater than those of the young control group (Tables 1 and 2). The mean duration and mean latency are similar in the two groups (Tables 3 and 4).

TABLE 1
MOTOR UNIT POTENTIAL AMPLITUDES

	Number of potentials	Amplitude of potentials* (μV)	P
Controls	160	58.6 ± 28.5	—
Limb-girdle dystrophy	92	65.1 ± 37.0	NS
Myotonic dystrophy	107	69.7 ± 43.9	< 0.03
Controls	111	44.7 ± 23.5	—
Duchenne dystrophy	97	34.5 ± 19.9	< 0.003

* Mean $\pm$ SD.

TABLE 2
MOTOR UNIT POTENTIAL AREAS

	Number of potentials	Area of potentials*, area units	P
Controls	160	16.5 ± 7.6	—
Limb-girdle dystrophy	92	19.7 ± 11.4	< 0.02
Myotonic dystrophy	107	23.1 ± 12.5	< 0.001
Controls	111	13.2 ± 6.9	—
Duchenne dystrophy	97	12.1 ± 5.8	NS

* Mean $\pm$ SD.

Duchenne muscular dystrophy In these patients there is a significant reduction in the mean amplitude of MUPs (Fig. 1, Table 1) with an increase in the percentage of low amplitude MUPs but none with amplitudes less than the lower limit of the normal range. The mean area of the MUPs (Fig. 1, Table 2) is slightly but not significantly reduced in these patients but mean

TABLE 3
MOTOR UNIT POTENTIAL DURATIONS

	Number of potentials	Duration of potentials* (ms)	P
Controls	160	9.50 ± 1.70	—
Limb-girdle dystrophy	92	10.42 ± 1.63	< 0.001
Myotonic dystrophy	107	11.29 ± 2.23	< 0.001
Controls	111	9.32 ± 1.63	—
Duchenne dystrophy	97	10.32 ± 2.10	< 0.001

* Mean ± SD.

TABLE 4
MOTOR UNIT POTENTIAL LATENCIES

	Number of potentials	Latency of potentials* (ms)	P
Controls	160	4.49 ± 0.82	—
Limb-girdle dystrophy	92	5.65 ± 1.46	< 0.001
Myotonic dystrophy	107	6.43 ± 1.97	< 0.001
Controls	111	4.53 ± 1.48	—
Duchenne dystrophy	97	5.36 ± 1.34	< 0.001

* Mean ± SD.

duration (Fig. 2, Table 3) is significantly prolonged. The mean latency of MUPs is considerably prolonged (Fig. 2, Table 4) and many units have latencies greater than the upper limit of the control range.

Limb-girdle and facioscapulohumeral muscular dystrophies The mean value for MUP ampli-

tudes is not significantly greater than that of the control group (Fig. 3, Table 1) but mean area is significantly increased with a fall in the percentage of small area MUPs (Fig. 3, Table 2) and a rise in the percentage of large area MUPs. The mean duration of the MUPs (Fig. 4, Table 3) is significantly prolonged as is mean latency (Fig. 4, Table 4), with a considerable increase in the

FIG. 1 Histograms of MUP amplitudes and areas. Young control subjects and patients with Duchenne muscular dystrophy.

FIG. 2 Histograms of MUP durations and latencies. Young control subjects and patients with Duchenne muscular dystrophy.

FIG. 3 Histograms of MUP amplitudes and areas. Adult control subjects and patients with limb-girdle and facioscapulo-humeral muscular dystrophy.

FIG. 4 Histograms of MUP durations and latencies. Adult control subjects and patients with limb-girdle and facioscapulo-humeral muscular dystrophy.

percentage of long latency MUPs. Some of the latter are considerably longer than the upper limit of the normal range.

Myotonic muscular dystrophy The mean amplitude of MUPs is significantly increased (Fig. 5,

Table 1) as is mean area (Fig. 1, Table 2) with an increase in the percentage of large area MUPs. Mean MUP duration is also significantly increased, many have durations greater than the upper limit of the normal range (Fig. 6, Table 3) and the mean latency of MUPs is significantly

TABLE 5

FASTEST MOTOR CONDUCTION VELOCITIES AND SHORTEST DISTAL MOTOR LATENCIES IN LATERAL POPLITEAL NERVES

	No. of patients	Mean age (yr)	Fastest motor conduction velocity* (m/s)	P	Shortest distal latency* (ms)	P
Controls	20	38	51.7 ± 3.6	—	3.43 ± 0.46	—
Limb-girdle dystrophy	12	37	46.3 ± 5.7	< 0.01	4.22 ± 0.71	< 0.001
Myotonic dystrophy	10	45	42.6 ± 5.5	< 0.001	4.99 ± 0.87	< 0.001
Controls	12	11	53.7 ± 3.5	—	3.27 ± 0.61	—
Duchenne dystrophy	12	10	50.8 ± 5.5	NS	4.53 ± 0.74	< 0.001

* Mean ± SD.

FIG. 5 Histograms of MUP amplitudes and areas. Adult control subjects and patients with myotonic muscular dystrophy.

FIG. 6 Histograms of MUP durations and latencies. Adult control subjects and patients with myotonic muscular dystrophy.

prolonged, in some cases, to almost twice that of the upper limit of the normal range (Fig. 6, Table 4).

2. MOTOR CONDUCTION VELOCITIES AND DISTAL MOTOR LATENCIES (Table 5) The fastest motor conduction velocities in the lateral popliteal nerves are within the normal range in the Duchenne dystrophy patients, but significantly reduced in the limb-girdle, facioscapulohumeral, and myotonic muscular dystrophies. The shortest distal motor latencies are significantly prolonged in all three groups of patients with muscular dystrophy.

DISCUSSION

Sacco *et al.* (1962) reported that both the durations and amplitudes of voluntary MUPs increase from infancy to maturity. In our young control subjects we, too, have found that the amplitudes of the evoked MUPs are reduced but their durations are comparable with values in adult subjects. Examination of the data of Sacco *et al.* (1962) indicates that this parameter may have reached adult values by the age of 11 or 12 years, the mean age of our young controls.

DUCHENNE MUSCULAR DYSTROPHY Needle electrode studies show a preponderance of short duration, low amplitude often polyphasic MUPs in Duchenne muscular dystrophy (Kugelberg, 1947; Buchthal and Rosenfalck, 1963). The reduction in duration of the potentials is a consequence of the reduced muscle fibre density in the motor units whereby the early and late components of the action potential are lost (Buchthal *et al.*, 1960). In the normal individual these components are produced by volume conduction to the relatively small recording surface of the concentric needle electrode of action potentials of distant muscle fibres (Buchthal *et al.*, 1960) and these are reduced in numbers in Duchenne muscular dystrophy. The potential recorded with the much larger surface electrode is more dependent on the number of muscle fibres in the unit than on their spatial distribution (Kaeser, 1970), so that the circumstances leading to the shortening of the MUPs found in needle studies do not occur.

We have noted a significant increase in the

duration of the MUPs in these patients. Prolongation of the duration of the MUP may be attributed to a reduction in the propagation velocity of the action potential in individual muscle fibres which would cause an increase in dispersion of these potentials. This explanation is unlikely, as Buchthal *et al.* (1960) and Buchthal and Rosenfalck (1963) reported normal conduction velocities in dystrophic muscle fibres despite the known variation in muscle fibre diameter in this condition. In the normal individual the duration of the MUP is almost exclusively determined by the degree of dispersion of the innervation zone of the motor unit (Buchthal *et al.*, 1955, 1957). In a primary myopathy general thinning out of muscle fibres in the motor unit (Buchthal *et al.*, 1960) cannot lead to an increase in the dispersion of the innervation zone. In the normal subject Buchthal *et al.* (1957) have reported that differences in the conduction time in the intramuscular nerve fibres contribute no more than 0.5 ms to the duration of the motor unit potential. However, in the presence of a slowing of conduction in these fibres this factor will become of increasing importance. We have found a significant increase in both the shortest distal motor latencies (Table 5) and in the latencies of individual MUPs (Fig. 2, Table 4) in Duchenne dystrophy patients. As the conduction velocity in the knee to ankle segment of the motor nerve was normal (Table 5), we submit that prolongation of the distal latency is a consequence of slowing of conduction in intramuscular nerve twigs and/or an increased delay at the neuromuscular junction. Decrementing muscle action potential responses at fast tetanization rates have been reported in Duchenne dystrophy (McComas *et al.*, 1970). This need not indicate a disturbance in endplate function as Stålberg and Thiele (1972) have shown that decrementing responses may occur when there is blocking of transmission in intramuscular nerve fibres and that the degree of blocking increases with rising frequency of stimulation. They also reported the occurrence of 'paired blocking' of muscle fibre action potentials in cases of progressive muscular dystrophy indicating a disturbance of impulse conduction in the intramuscular nerve fibres. Furthermore, there is no evidence on light or electron microscopy of any anatomical abnormality of the motor endplate in Duchenne

muscular dystrophy (Jerusalem *et al.*, 1974), unlike the known association between the neuromuscular transmission defect and the morphological changes at the endplate in myasthenia gravis (Bickerstaff and Woolf, 1960; MacDermot, 1960; Cöers *et al.*, 1966; Desmedt, 1966; Simpson, 1971). While we cannot exclude the possibility that an increase in neuromuscular delay contributes to the prolongation both of MUP latencies and of distal motor latencies, the evidence would support the additional occurrence of slowing of conduction in the intramuscular nerve fibres. The differences in conduction time in these fibres will lead to a reduction in synchronization of individual muscle fibre potentials and an increase in the durations of MUPs. The small increase in duration of the muscle fibre action potential noted during intracellular recording in dystrophic muscles (Ludin, 1973) is insufficiently large to contribute significantly to the duration of the MUP.

The amplitude of the surface recorded MUP depends on the total number of muscle fibres in the unit and the temporal summation of their action potentials. Histological studies (Buchthal *et al.*, 1960; Adams, 1974) indicate a reduction in the number of muscle fibres in the muscles in Duchenne dystrophy. We have reported normal numbers of motor units in the EDB muscles of these patients (Ballantyne and Hansen, 1974c). There is therefore a reduction in the number of muscle fibres in each motor unit. The amplitude of the muscle fibre action potential is reduced in dystrophies (Ludin, 1973). Both these factors contribute to the reduction in the amplitude of the MUP noted in this study.

While the mean area of the MUPs in Duchenne dystrophy is reduced compared with the control values, this is less marked than we would have anticipated in view of the reduction in the number of muscle fibres noted histologically in dystrophic muscles. The explanation for this finding is not clear but there are several possible interpretations. Examination of Ludin's data (1973) shows that, despite the reduction in amplitude of the spike potential in dystrophic muscle fibres, the area under the potential is moderately increased due to the prolongation of the potential duration. This will militate against a reduction in MUP area despite a loss of muscle fibres. Secondly, as the MUP area is

composed of the summated biphasic or polyphasic potentials of individual muscle fibres, the increased temporal dispersion of these potentials which alters their phase relationships may lead to a disproportionate change in the area of the MUP. Finally, should polyneuronal innervation occur in dystrophic muscle such that some fibres are common to several motor units, the mean population of fibres in individual units would not fall in proportion to the total reduction in muscle fibres in the whole muscle. Woolf and Cöers (1974) have noted that multiterminal innervation may occur in muscular dystrophies and Hunt and Kuffler (1954) have claimed that polyneuronal innervation is present in normal muscles of the cat. Recently, Tate and Westerman (1973) reported multiple innervation of muscle fibres in the soleus muscle of the cat during reinnervation. Buller (1974) considers the question of polyneuronal innervation of skeletal muscle 'is not yet settled'. Which if any of these hypotheses are pertinent to the problem cannot be answered at this stage, but we hope to pursue this further.

MYOTONIC MUSCULAR DYSTROPHY In this group of patients there is significant increase in all parameters of the MUP and this is associated with reduction in the number of motor units in the muscle (McComas *et al.*, 1971a; Ballantyne and Hansen, 1974c). These are not the expected findings in a primary myopathy. Larger than normal units should not occur. Our results support the conclusion of McComas *et al.* (1971a) that some of the surviving motor units in this condition have enlarged by collateral reinnervation of muscle fibres which have lost their primary innervation as the disease progresses. This will lead to an increase in both the amplitude and area of the MUP but without effect on its duration (Buchthal *et al.*, 1960). Prolongation of the latencies of the MUPs and of the distal motor latencies may be in part due to a disturbance of neuromuscular transmission. Histological studies (MacDermot, 1961) have demonstrated abnormalities of the motor endplates and decrementing responses to tetanization are known to occur in myotonic dystrophy (McComas *et al.*, 1971a). The site of this dysfunction could, however, lie in intramuscular nerve fibres rather than at the endplates. We

have already referred to the studies of Stålberg and Thiele (1972) in this context. Histological abnormalities of intramuscular nerve twigs have been reported (Allen *et al.*, 1969; Kito *et al.*, 1973). The reduction in conduction velocity in the proximal segment of the motor nerve and the prolonged distal latency which we have found in this condition (Table 5) support the presence of a disturbance of function in the motor axons and intramuscular nerves. As in the Duchenne dystrophy patients, the prolongation of the distal motor latencies and the latencies of individual motor unit potentials must in part be due to reduced conduction velocity in the intramuscular nerve fibres leading in turn to a prolongation of MUP durations.

LIMB-GIRDLE AND FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHIES The changes in dimensions of the MUPs are intermediate between those noted in the Duchenne and myotonic muscular dystrophy groups. There is a rise in the percentage of MUPs of increased duration (Fig. 4) and area (Fig. 3) but the mean amplitude remains little changed. Figure 3 does, however, show that there has been a very small increase in the percentage of low and high amplitude MUPs. We have reported normal motor unit numbers in these patients (Ballantyne and Hansen, 1974c). This alteration in MUP parameters is probably the electrophysiological reflection of a pathological remodelling of the motor units. In this group of patients there is also a significant reduction in the fastest motor conduction velocities and an increase in distal motor latencies. We consider that the explanations for these changes are similar to those discussed above for Duchenne and myotonic muscular dystrophies.

If, as we have postulated above, slowing of conduction velocity in the intramuscular nerve fibres is mainly responsible for both the prolonged distal latencies and increased durations of the MUPs in these conditions, then we should expect to demonstrate a relationship between these two parameters. That such is indeed present is shown in Fig. 7 where there is a highly significant correlation ($r=0.992$) between mean MUP durations and latencies.

It should be emphasized that MUP amplitudes quoted in this paper are (under our recording conditions) absolute and are not equivalent to the

FIG. 7 The relationship between mean MUP durations and latencies. YC: Young controls. OC: Older controls. DD: Duchenne muscular dystrophy. L-GD: Limb-girdle and facioscapulohumeral muscular dystrophy. MD: Myotonic muscular dystrophy.

values quoted by McComas *et al.* (1971a, b, c), Sica and McComas (1971), and Panayiotopolos *et al.* (1974). These authors measured the increments in amplitude of the muscle action potentials on the addition of each newly recruited MUP and assumed that these values were proportional to the absolute amplitudes of the contributing MUPs. This assumption is correct only if each MUP is of identical latency, duration, and shape with temporal coincidence of the potential maxima. Alternatively, the potential maxima of incrementing MUPs must always coincide irrespective of their latencies or durations. The results of the present study do not substantiate these assumptions. We have found a considerable variation in the latencies and durations of individual MUPs obtained by computer subtraction in both control subjects and patients with muscular dystrophy. Furthermore, during motor conduction velocity studies electromyographers are familiar with the increase in potential duration and the shortening of the latency to the initial deflection and peak amplitude of the muscle compound action potential that occurs as the intensity of stimulation to the

TABLE 6
SUMMATION FACTOR FOR MUP AMPLITUDES

	No. of patients	Mean value of MUP amplitudes		Summation factor Mean $\frac{I}{P}$
		From individual units* Mean I (μV)	From increments to muscle compound action potential† Mean P (μV)	
Controls	21	61.2 $\pm$ 13.6	42.1 $\pm$ 12.2	1.48 $\pm$ 0.23
Limb-girdle dystrophy	11	64.9 $\pm$ 13.2	31.2 $\pm$ 9.5	2.17 $\pm$ 0.44
Myotonic dystrophy	12	69.8 $\pm$ 27.2	38.4 $\pm$ 12.5	1.82 $\pm$ 0.40
Controls	12	45.0 $\pm$ 14.1	27.4 $\pm$ 9.5	1.68 $\pm$ 0.32
Duchenne dystrophy	12	36.6 $\pm$ 10.8	16.1 $\pm$ 8.0	2.75 $\pm$ 1.68

* Individual MUPs obtained by computer subtraction of stored templates (see Method). I is the mean motor unit amplitude in each patient.

† P is the mean potential increment in each patient calculated from the formula $P = (A^n/n)$ where n is the number of motor unit potentials summated to give a muscle compound action potential of amplitude A^n .

motor nerve is increased. These appearances are due to the recruitment of MUPs of different initial and peak amplitude latencies. The summation factor (Table 6) calculated from the mean amplitude of individual MUPs obtained by computer subtraction, and that obtained from MUP increments to the compound muscle action potential, is an index of the lack of coincidence of the potential maxima of the recruited MUPs. While this factor is comparable in the two control groups, it is increased in the muscular dystrophies (Table 6), indicating that the temporal relationships of the potential maxima of the MUPs do not conform in these pathological states to the pattern found in control subjects. The amplitudes of the MUP increments are not proportional to absolute MUP amplitudes when comparisons are made between control subjects and patients with neuromuscular disease.

CONDUCTION VELOCITY STUDIES (Table 5)

The responses in the EDB muscle evoked by stimulation of the anterior tibial nerve at the ankle were recorded in control subjects and patients from surface electrodes over that muscle. When concentric needle electrode recording is used the shortest latency motor units may lie outwith the pick-up zone of the electrode (Simpson, 1964; Kaeser, 1970), producing spurious prolongation of the distal motor

latencies by up to 1 ms (Simpson, 1964). In a group of our subjects in whom the distal motor latency was simultaneously recorded by both methods the latency to the needle electrode was never less than, and in most cases greater than, that to the surface electrode. Since the needle electrode may not record from the motor units of shortest latency, it may not record from the motor units whose axons have the fastest motor conduction velocities. This will lead to an underestimation of the fastest motor conduction velocities in the proximal segment of the nerve. For the measurement of shortest distal motor latencies and fastest motor conduction velocities surface recording electrodes must be used (Kaeser, 1970).

In the Duchenne patients and their controls the values we have obtained for fastest motor conduction velocities and shortest distal motor latencies (Table 5) are similar to those reported by McComas *et al.* (1971c). However Nakao *et al.* (1968) reported slowing of conduction in the proximal segments of median and tibial nerves but they did not measure distal motor latencies.

Kito *et al.* (1973) noted histological abnormalities in peripheral nerves in myotonic patients and stated that conduction velocities were depressed. Although McComas *et al.* (1971a) found a reduction in the mean value for motor conduction velocity in their myotonic dystrophy patients, it was not significantly different from control values. In the limb-girdle dystrophy group Sica

and McComas (1971) noted normal values for both these parameters. The discrepancies between our results and those of McComas *et al.* (1971a) and Sica and McComas (1971) may be partly explained by the different methods used to record the evoked muscle action potential. In the myotonic dystrophy patients McComas *et al.* (1971a) used either needle or surface recording, but in neither the limb-girdle nor Duchenne dystrophy group of patients did they state the method of recording. It is particularly important in the statistical analysis of conduction velocity values between two populations that the technique of recording is consistent. This may explain the significantly higher mean values for motor conduction velocity ($P < 0.01$) and shorter mean distal motor latencies ($P < 0.001$) which we have noted in our adult control subjects compared with those of Sica and McComas (1971).

In conclusion, we have presented evidence from measurements of the parameters of electrically evoked MUPs obtained by computer subtraction and from studies of motor conduction velocities and distal motor latencies which would support the presence of a neurogenic influence in the aetiology of Duchenne, limb-girdle, and facioscapulohumeral and myotonic muscular dystrophies.

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