The motor unit in psychotic patients: a single fibre EMG study

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SUMMARY Single fibre EMG recording from extensor digitorum communis muscle is described in patients with psychotic illness. The fibre density, or average number of single muscle fibre action potentials belonging to the same motor unit within the uptake area of the electrode, was higher in the patient group than in normal controls. Increased jitter was occasionally seen. Motor and sensory nerve conduction velocity values were within the normal range. The results indicate that psychosis is associated with denervation and reinnervation by collateral sprouting.

Recent studies of muscle biopsies from patients with schizophrenia and manic depressive psychosis have indicated that some patients have structural abnormalities of the neuromuscular system (Meltzer and Crayton, 1974, 1975; Crayton and Meltzer, 1976). The most common finding was scattered atrophy of individual muscle fibres, suggestive of a denervation process. When the distribution of intramuscular nerve twigs was studied, an increase in the terminal branching was demonstrated (Fig. 1). In methylene blue stained material, the terminal innervation ratio (TIR) as defined by Coërs and Woolf (1959) was increased in a significant number of psychotic patients. The ratio was in the range of 1.4–1.5 in psychotic patients whereas the normal value is 1.1. Further studies of the morphology of the terminal bulbs at the motor endplate suggested that there were significant alterations in their structure (Crayton and Meltzer, 1976). Preliminary conventional EMG studies have shown slight changes suggestive of a process of denervation and reinnervation.

However, in nearly all cases of psychosis, the abnormalities are not apparent as clinically obvious motor dysfunction. Functional changes are subtle and only seen when special studies of neuromuscular coordination are done. Psychotic patients show a higher incidence of 'soft' neurological signs (Rochford *et al.*, 1970), and their capacity to perform refined psychomotor tasks is impaired (Holzman, 1972; Holzman *et al.*, 1973).

The present study, using single fibre electromyographic methods, was undertaken to explore the physiology of the motor unit in such patients in a more refined way than has been done previously. One aim of our investigation was to determine whether the single fibre EMG method could provide some electrophysiological correlate of the structural alterations of the intramuscular nerve distribution previously described. We also sought to determine whether the altered structure of the individual endplates has resulted in a failure to conduct impulses adequately by measuring the neuromuscular jitter (Ekstedt and Stålberg, 1973). In addition, since jitter and blocking of neuromuscular transmission are characteristics of active processes of reinnervation, we explored the relationship of these parameters to the clinical course of the psychotic disease process.

Patients and methods

Seventeen inpatients at Ulleråker Hospital in Uppsala volunteered for the study (Table 1). The patients ranged in age from 20 to 73 years. Ten were men and seven were women. The following diagnoses were represented: schizophrenia 10; probable schizophrenia 2; acute schizophreniform psychosis 1; manic-depressive psychosis 2; acute psychosis 1; alcoholic psychosis 1. Duration of recognised disease ranged from four months to 41 years. Diagnosis was made on the basis of clinical evaluation by the psychiatrists at the hospital. All patients in the study had received some type of psychotropic medication (Table 1). Patients received various phenothiazine and butyrophenone neuroleptic drugs

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Fig. 1 Drawings of methylene blue stained intramuscular nerve endings from biopsy samples of *peroneus brevis*. (A) Array of endings from normal control subject. (B) Single intramuscular nerve twig from schizophrenic patient (Crayton and Meltzer, unpublished).

such as chlorpromazine, thioridazine, and haloperidol. Dosage was roughly estimated and classified as low (up to 100 mg of chlorpromazine or equivalent per day), medium (100–500 mg per day), or high (more than 500 mg per day). Patients also received drugs other than neuroleptics, some of which are listed in Table 1.

Single fibre EMG studies were performed in the voluntarily activated extensor digitorum communis muscle of the right arm. The fibre density value was calculated by determining the average number of fibres belonging to the same motor unit within the uptake radius of the electrode (about 275 μm), based on measurements from 20 separate recording positions (Stålberg and Thiele, 1975). The neuromuscular jitter (Ekstedt and Stålberg, 1973) was assessed visually on the oscilloscope, and recorded as (a) normal, (b) increased without blocking, or (c) increased with blocking (Fig. 2). As in previous studies, the normal jitter was defined to be between 5 and 50 microseconds when expressed as the mean value of consecutive differences (MCD) of the interpotential intervals. When there was a question about whether the jitter was normal or abnormal, the action potential complex was recorded on magnetic tape (TEAC-A 3340S), and subsequently analysed by a computer (PDP-11/40).

Electroneurographic recordings were made on a DISA 1500 EMG apparatus with filter settings 2–16,000 Hz. In the right ulnar nerve, velocity was measured using a surface stimulating electrode (DISA 13K62) over the nerve at the wrist and elbow, and surface recording electrodes, one over the belly of the abductor digiti minimi muscle, and one over the metacarpophalangeal joint of the fifth digit. Distal latency, amplitude of the surface motor response, and F-response latency were also measured. Right median nerve sensory conduction time

from the palm to the wrist and the amplitude of the response were measured, using surface stimulating and recording electrodes (DISA 13K62) according to the technique described by Eklund (1975). The antidromic conduction velocity along the right sural nerve and the response amplitude were measured while stimulating at a point between the two heads of the gastrocnemius muscle and recording over the lateral malleolus.

Results

MOTOR AND SENSORY NEUROGRAPHY

Nerve conduction velocity and distal latencies were all in the normal range for the patients studied (Table 2). In particular, ulnar nerve distal latencies, motor conduction velocity (MCV), and response amplitudes in the right forearm in which the fibre density measurements were made were all normal, except in one case (K-EH) of possible alcoholic polyneuropathy with a response amplitude of 4 mV. In order to determine whether there was evidence for a widespread neuropathy, 15 median and 16 sural sensory nerve conduction were also measured. In two subjects we were unable to elicit a sural response, and in one the median was not elicitable, probably for technical reasons. In others, responses were normal. F responses were studied in 11 patients. All values were normal with the two highest values occurring in two tall subjects (186 and 195 cm tall).

MOTOR UNIT FIBRE DENSITY

The fibre density (FD) values (Table 2) ranged from 1.35 to 2.35 in the patient population. One patient had a value of 3.35 in the right arm probably due to radial nerve palsy; in this case the value for FD was taken in the left arm. The mean value was 1.78 ± 0.26 SD, while a normal age-matched control

Table 1 Clinical data

Patient	Age (yr)	Sex	Diagnosis	Family history	Somatic diseases	Age on admission to hospital	In hospital		Neuroleptics		Comments
							Years	Times	Dose	Years	Current
HE	20	F	S?	Mother	SI ↑ liver ft	20	1	1	High	1	Low
MJ	20	F	Par. psych.	Father, alcohol	No	17	1	2	Low	1	Med.
FG	23	M	S	Father	No	17	4	2	M/high	4	Med.
HJ	27	F	S?	Mother	No	27	1	1	M/high	1	Med.
SN	28	M	Sf	Aunt	No	25	1	6	Med.	3	Low
LL	30	F	S	Father	No	22	1	6	M/high	8	High
JK	39	M	S	Mother and father	No	36	1	2	Low	3	Low
LT	39	M	S	Brother	No	28	1	5	Med.	10	Med.
BP	40	M	S	Mother	No	26	1	13	Med.	13	None
RK	45	F	MD	Mother	No	41	1	3	Low	4	Low
TJ	47	M	S	Mother	No	22	22	1	Med.	22	High
K-EH	51	M	CA	Mother	AN, TD	46	5	1	Med.	5	Low
M-LA	54	F	S	Mother	No	28	1	4	Low	15	Low
BL	55	M	S	Aunt, Mother	TD	19	35	1	Med.	25	Low
GV	62	M	S	Mother	TD	21	14	1	Med.	25	Low
GF	67	M	S	Cousins	TD	38	25	1	Low	25	None
EJ	73	F	MD	Mother	No	45	20	10	Low	15	Low

S? = probable schizophrenia. Par. psych. = paranoid psychosis. S = schizophrenia. Sf = schizophreniform psychosis. MD = manic-depressive psychosis. SI = chronic alcoholic. SI ↑ liver ft = slightly abnormal liver function tests. AN = alcoholic neuropathy. TD = tardive dyskinesia. ECT = electroconvulsive therapy. LSD = lysergic acid diethylamide. Li. carb. = lithium carbonate. For classification of neuroleptic dose, see text.

Fig. 2 Examples of the three categories of jitter used for classifying the single fibre EMG recordings. (A) Normal ($< 50 \mu\text{s}$, here $13 \mu\text{s}$). (B) Increased jitter ($> 50 \mu\text{s}$, here $82 \mu\text{s}$). (C) Increased jitter ($> 50 \mu\text{s}$, here $140 \mu\text{s}$) and intermittent impulse blocking.

group (ages 20–73 years) had a mean FD of 1.49 ± 0.17 . The mean values differ significantly (t -test, $t=4.16$, $P<0.001$). Seven of the 17 patients' FDs exceeded two standard deviations above the normal mean, while only three of 129 controls did ($\chi^2>100$, $P<0.001$). In previous studies it was found that the fibre density increases in subjects over the age of 70 years and shows greater interindividual variability. If the 73 year old patient is excluded from data analysis, six of 16 patients and none of 119 controls between 20 and 70 years of age had FD values exceeding the normal mean by more than two standard deviations. In Fig. 3 the patient data are plotted against normal values for the extensor digitorum communis muscle previously published (Stålberg and Thiele, 1975). The pattern of increased FD in the psychotic patients was usually characterised by an increase in the number of motor unit potential complexes with two or three elements (Fig. 4). In only 23 of 340 recordings were there complexes with more than three components. Ten of these occurred in one subject, TJ, in whom neurological examination revealed a slight right radial nerve palsy. There was no significant correlation between FD values and the neurographic findings, including motor and sensory conduction parameters and evoked response amplitudes (Fig. 5).

JITTER AND BLOCKING IN SINGLE FIBRE EMG STUDIES

Most patients showed little evidence of increased jitter, although eight of 17 patients had at least one motor unit potential complex with increased jitter. The jitter was never great, however, with computer

analysed MCD values being in the range of 60 to 120. Impulse blocking was seen in two recordings in one patient (K-EH) and in one complex from another (TJ) in the arm with the slight radial palsy.

RELATIONSHIP OF NEUROLOGICAL FINDINGS TO CLINICAL DATA

There was no significant correlation between any of the clinical parameters listed in Table 1 and any of the neurophysiological measures. The series is undoubtedly too small to control for variance associated with all the factors. We only emphasise here the lack of correlation between the neurophysiological findings and such non-disease-related factors as estimated total medication, amount of current medication, and duration of hospitalisation.

Discussion

Psychotic patients in this study showed an increase in the average fibre density of the motor unit (FD) when compared with normal control material. Most of the increases were modest, with values in a range of 1.7–2.35. The increase in FD is interpreted as a sign of fibre grouping due to reinnervation by collateral sprouting after preceding denervation. It is consistent with the previously described morphological studies in muscle biopsy samples (Meltzer and Crayton, 1974, 1975; Crayton and Meltzer, 1976) which showed increased branching of intramuscular nerve endings reflected in increased terminal innervation ratios (TIR). It is tempting to compare the FD

Table 2 Neurophysiological data

Patient	Age (yr)	Sex	Diagnosis	FD	Jitter		Ulnar motor			Sural		Median sensory			
					bl	↑j (No.)	n	dist. lat. (ms)	CV (m/s)	ampl. (mV)	F (ms)	CV (m/s)	ampl. (μV)	lat. (ms)	ampl. (μV)
HE	20	F	S?	1.75	0	1	10	3.0	56	15	28.5	42	10	1.9	150
MJ	20	F	Par. psych.	1.60	0	0	7	1.9	66	11		46	20	1.2	220
FG	23	M	S	1.90	0	1	13	2.8	54	10	32.0	49	10	1.6	75
HJ	27	F	S?	1.53	0	0	24	2.7	60	15	27.0	50	20	1.1	75
SN	28	M	Sf	1.85	0	2	11	2.4	52	15	25.6	43	10	1.5	100
LL	30	F	S	1.60	0	2	7	2.1	50	13		50	20	1.4	150
JK	39	M	S	1.55	0	0	11	3.8	57	14	30.5	46	10	1.8	30
LT	39	M	S	1.80	0	2	9	3.0	58	15	29.0	42	10	1.6	25
BP	40	M	S	1.55	0	0	10	2.6	53	12		44	50	1.0	20
RK	45	F	MD	1.35	0	0	7	2.8	60	7	28.0			1.5	100
TJ	47	M	S	1.85	0	3	11	3.0	58	10	29.0	49	10	1.5	50
				*3.35	1	6	13								
K-EH	51	M	CA	1.75	2	1	7	3.0	67	4		44.5	10		
M-LA	54	F	S	1.85	0	0	12	2.5	57	10	24.0	54	15	1.5	100
BL	55	M	S	1.70	0	0	12	2.5	58	5		50	10	1.3	50
GV	62	M	S	2.05	0	0	13	3.8	54	12	35.6		0		
GF	67	M	S	2.25	0	2	14	2.9	60	8			0	1.5	50
EJ	73	F	MD	2.35	0	0	15	2.7	58	12	27.9	55	10		0

Jitter classification: bl = impulse blocking. ↑j = increased jitter. n = normal jitter. * = recording obtained from right extensor digitorum communis with signs of slight radial palsy. (These values not included in the statistics). FD = fibre density. dist. lat. = motor response latency at distal stimulation (wrist). CV = nerve conduction velocity. ampl. = amplitude of surface recorded response. F = latency of recurrent response at distal nerve stimulation (F response). lat. = latency between stimulus and surface recorded response.

values with the TIR values. A pattern indicating moderate but significant elevations in the amount of branching was obtained with both methods, with an increase in the mean from the usual 1.1 to approximately 1.4 (27%) in the TIR, and from 1.49 to 1.78 (19%) in the FD. The difference between the normal mean values obtained with the two methods is due

Fig. 3 Fibre density vs age (years) in patients (*) and normal subjects (●).

mainly to inherent methodological factors. In this investigation, however, no rigorous correlation between the two values can be made since the data were obtained from two different populations of patients in Chicago and Uppsala, and on two different muscles (peroneus brevis and extensor digitorum communis of the upper limb).

Examples of strikingly branched individual intra-muscular nerves were rare in both studies. The fibre density values found in this study are similar to those found in mild to moderately severe peripheral neuropathies, such as alcoholic polyneuropathy (Thiele and Stålberg, 1975), and are considerably less than the values in severe progressive clinically apparent diseases of the motor neurone, such as amyotrophic lateral sclerosis, progressive spinal muscular atrophy, and syringomyelia (Stålberg *et al.*, 1975). Only one of our patients (K-EH) had a probably significant medical basis for his increased fibre density. This patient had a history of chronic alcoholism and Korsakov's psychosis. His fibre

Fig. 4 Single fibre EMG recordings from psychotic patients, 10 sweeps superimposed. (A) Normal potential pair (jitter = 12 μ s). (B) Complex action potential with four single fibre components and normal jitter (jitter = 19, 21, and 20 μ s to 2nd, 3rd, and 4th component). (C) Potential pair with increased jitter (65 μ s). (D) Action potential complex with high but normal jitter in the second component (48 μ s), and increased jitter (134 μ s) and blocking (arrows) of the third component.

Fig. 5 Plots of fibre density (FD) vs electroneurographic parameters (distal latency and motor conduction velocity (ulnar), F wave latency, sensory conduction velocity (sural)). The correlation coefficients (r) are not statistically significant for any of the relationships.

density value was at the mean for the group. This patient, and the one with signs of radial palsy, showed intermittent impulse blocking in a few recordings in contrast to the other psychotic patients who showed no blocking.

The aetiology of the denervation process in psychotic patients is not clear. A dropout of whole motor units due to involvement of the anterior horn cell is not very likely since the patients have no fasciculations, and no reduction of the EMG interference pattern (Crayton, unpublished data). Furthermore, repeated loss of motor neurones should tend to increase FD considerably more than found in this study. The lesion seems to be localised peripherally in the motor unit. A general polyneuropathy could give this picture, but the normal sensory and motor nerve conduction velocities and distal latencies argue against this aetiology. The most likely site of the lesion is, therefore, in the peripheral part of the intramuscular nerve or at the motor endplate. Such a process may be related to an increased vulnerability of the endplate to degeneration followed by 'dying-back' (Cavanagh, 1964). Compensatory sprouting may mainly prevent loss of muscle fibres within the

motor unit, indicated by the generally normal amplitude of the surface EMG response. Patients did not show increased distal motor latencies, but in these measurements only the fastest components contribute to the measured shortest distal latency values, thus masking a subpopulation of possibly slower conducting twigs. The possibility of a primary myogenic lesion or a shrinkage of the motor unit due to fibre atrophy to account for the increased FD (Stålberg, 1977) is not supported by the histochemical and histological investigation showing neurogenic abnormalities (Meltzer and Crayton, 1975).

The study of jitter has suggested that, in general, psychotic patients have stable neuromuscular transmission. However, in seven of the 17 patients there was increased jitter. The degree of jitter indicates the functional capacity of the terminal nerves, motor endplates and muscle fibres. During an active period of reinnervation, newly formed nerve twigs and motor endplates will show increased jitter and blocking for the first three months (Hakelius and Stålberg, 1974). The proportion of abnormal jitter recordings is, therefore, an indication of the dynamics of the

reinnervation process. In the case of active denervation-reinnervation, a high number of recordings should show impairment of impulse transmission. In our material only a few recordings showed increased jitter. This finding indicates that although reinnervation has taken place it appears to have restored function successfully in most cases. The denervation could have occurred in one active period during the disease process, or, alternatively, could follow a more slowly progressive course. In our study there was no detectable correlation between the duration of the disease (when age factors were excluded) and the electrophysiological data.

As with all studies of psychotic patients, the importance of non-specific factors such as age, duration of hospitalisation, and medication effects must be considered. In our sample there was an expected increased FD in older patients. However, since younger patients also showed increased values, age cannot be the only factor in increasing FD. Furthermore, the fact that older patients showed increase in FD indicates that the capacity to reinnervate by collateral sprouting remains intact in older psychotic patients. Hospitalisation may suggest a change in physical activity and diet of the patients. Inactivity *per se* does not induce denervation, and none of the patients had a history of nerve trauma at the hospital. There was no correlation between time of hospitalisation and fibre density. A failure to find a relationship between the duration or severity of illness and the amount of the fibre density increase may suggest that the fibre density measurements are not strictly related to an acute psychotic episode, but may be reflective of a factor predisposing to the development of a psychosis. In that case, the branching may be related to the putative genetic defect in patients who become psychotic. Study of family members of patients with psychosis, by muscle biopsy and EMG methods, may clarify this point. There was no correlation between fibre density or jitter values and the amount or duration of medication. The effects of medication must be studied further in a larger number of patients. We know of no evidence suggesting that commonly used anti-psychotic agents would cause a peripheral denervation. Furthermore, in studies of muscle morphology in psychotic patients, young patients in hospital only briefly, with little or no medication, showed significant abnormalities (Meltzer and Crayton, 1974).

This study adds to the accumulating evidence for a neuromuscular dysfunction in psychotic patients. The relationship of these findings to increased serum creatine phosphokinase during an acute psychosis, impairments of psychomotor function as reflected in eye-tracking disability (Holzman *et al.*, 1973), or to

studies of alteration of alpha motor neurone excitability in psychotic patients (Crayton *et al.*, 1977) remain to be elucidated. A wide variety of toxic and metabolic disorders have been implicated in the aetiology of schizophrenia including viral infections (Torrey and Peterson, 1973), circulating toxins (Dohan and Grasberger, 1973), and disorders of central neuronal function (Snyder *et al.*, 1974). The finding of increased FD and jitter abnormalities in this study suggest that single fibre EMG methods may provide an additional means of studying neurophysiological disturbances in functional psychosis.

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