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Hemiplegic Atrophy

Morphological Findings in the Anterior Tibial Muscle of Patients with Cerebral Vascular Accidents

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Summary. Anterior tibial muscle biopsies of the hemiplegic side of 16 patients with a cerebrovascular accident in the middle cerebral artery region were analyzed qualitatively and quantitatively by enzyme histochemistry and electron microscopy.

Patients grouped according to the time lapsed as from the occurrence of the accident (1–17 months) demonstrated a progressive decrease in the fiber diameter and changes in fiber type distribution with predominant type II atrophy and type I predominance. Nuclear internalization, myopathic alterations, and perifascicular fatty infiltrations were observed constantly.

In the affected fibers the ultrastructural findings were myofibrillar alterations with the formation of rods and cytoplasmic bodies. There was accumulation of lipofuscin, glycogen, and lipid droplets. Microvascular changes were observed frequently.

Biopsies from the asymptomatic legs were either normal or showed age-related muscle alterations.

Correlation was noted between the clinical and functional status of the patients and the morphological aspects seen in muscle biopsies.

Key words: Human skeletal muscle – Hemiplegia – Cerebral vascular disease – Histopathology – Electron microscopy – Rehabilitation

Introduction

Morphological studies of skeletal muscle fibers of patients with hemiplegia secondary to various cerebral diseases, stressed a muscle fiber atrophy indicated as "central" atrophy or "disuse" atrophy (Silverstein 1955; Fenichel et al. 1964; Edström 1969; Brooke and Engel 1969).

These observations have been mainly concerned with muscle biopsies from patients in advanced stages following the onset of the disease.

There are no recent reports on the changes occurring in the muscle fibers of patients with spastic hemiplegia at successive stages following cerebral vascular accidents.

In the present study we report the histological and ultrastructural findings and the fiber type composition in anterior tibial muscle biopsies from hemiplegic patients at different stages (1–17 months) after the occurrence of a cerebrovascular accident.

Muscle biopsies from both legs of selected patients have also been studied for a comparative study of hemiparetic and normal contralateral side.

Particular attention was paid to the selection of patients regarding the site and extent of the cerebral lesion and the type of rehabilitation therapy.

Material and Methods

Patients

Sixteen patients (nine men and seven women), aged 42–75 years, with hemiplegia due to a cerebrovascular accident volunteered for the study.

They had cerebral infarctions in the middle cerebral artery region due to arterial occlusion. The diagnosis was verified by TAC and cerebral angiography. Cortical somatosensory evoked potentials obtained by stimulation of the posterior tibial nerve at the ankle, performed at the time of the biopsy, showed no responses or SEPs with minimum amplitude.

In no instance we noted previously suspected neuromuscular diseases.

The subjects were arranged in four groups (four patients per group) on the basis of the interval between the cerebrovascular accident and the muscle biopsy. Patient groups and clinical information pertinent to the study, such as spasticity evaluation, sensory deficit, and difference in leg measurement, are summarized in Table 1. One patient from each group had bilateral muscle biopsies for

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Table 1. Physical and clinical data of hemiplegic patients at the time of biopsy

Group (duration)	Patient (age and sex)	Hemiplegic side	Duration in days	Gait	Difference in leg measurement	Spasticity		Sensory deficit
						Stretching reflex[a] (increase)	Inversion of paralysed foot evocable	
1	BS (67 F)	Right	50	none	none	moderate	sitting	marked
(1–2 months)	SM (74 F)	Right	38	none	none	reduction	absent	marked
	PE (42 M)	Right	57	none	none	reduction	absent	marked
	GA (74 M)	Right	58	none	none	moderate	absent	marked
2	AL (60 F	Left	97	yes	0.4 cm	strong	sitting	moderate
(3–4 months)	RZ (52 F)	Left	99	yes	0.5 cm	moderate	sitting	moderate
	CL (74 F)	Left	69	yes	none	strong	standing up	moderate
	CA (72 M)	Left	80	yes	0.3 cm	strong	sitting	moderate
3	CD (68 M)	Left	122	yes	0.5 cm	strong	sitting	slight
(5–7 months)	RD (57 M)	Right	124	yes	0.9 cm	moderate	standing up	slight
	GC (59 M)	Left	130	yes	0.4 cm	moderate	walking	moderate
	EA (61 M)	Left	207	yes	0.4 cm	moderate	walking	slight
4	TG (58 M)	Left	300	yes	0.5 cm	strong	walking	slight
(8–17 months)	NG (70 M)	Right	360	yes	0.8 cm	strong	walking	slight
	SM (75 F)	Right	250	yes	0.5 cm	strong	walking	absent
	BS (68 F)	Right	270	yes	0.4 cm	moderate	walking	slight

[a] In comparison with non-paralyzed side

morphological comparison with the contralateral normal muscle. These patients (PE, RZ, CD, NG) were aged 42, 52, 68, and 70 years, respectively.

Muscle Biopsy

The muscle biopsy was performed under local anesthesia using open surgical technique. The anterior tibial muscle was chosen because it can show different degrees of spasticity in the hemiplegic patients.

Specimens taken from the anterior tibial muscle were fixed in 10% neutral formalin for histology, in Karnovsky fluid for electron microscopy, and cooled in isopentane chilled with liquid nitrogen for enzyme histochemistry.

Resin-embedded longitudinal and transverse sections were stained with Dominici' stain and impregnated according to Gomori' silver technique for reticulin. Transverse cryostat sections were stained by Giemsa, hematoxylin and eosin (HE), Gomori' modified trichrome stain, and by Sudan black and Oil red O for lipids and PAS reaction for glycogen.

Fiber typing was performed with reactions for ATP-ase, pH 9.4 and 4.2, and for DPNH-diaphorase according to the methods described by Dubowitz and Brooke (1973).

For determination of the muscle fiber diameter, an ocular micrometer scale was used; 75 fibers were measured per fiber type and specimen. The mean of two orthogonal diameters was taken as the muscle fiber diameter (Schmitt 1976). The fiber atrophy was graded according to the classification suggested by Jennekens et al. (1971). Histograms of type I and type II fibers were made for each patient, and the number of type I and type II fibers was calculated (Brooke and Engel 1969).

For electron-microscopic studies, ultrathin sections cut by a Porter Blum microtome were stained with uranyl acetate and lead citrate. Observations were performed using a Zeiss EM 109 electron microscope under direct magnification from ×1,800 to ×40,000. The method proposed by Siperstein et al. (1973) was used to quantify the capillary basement membrane width.

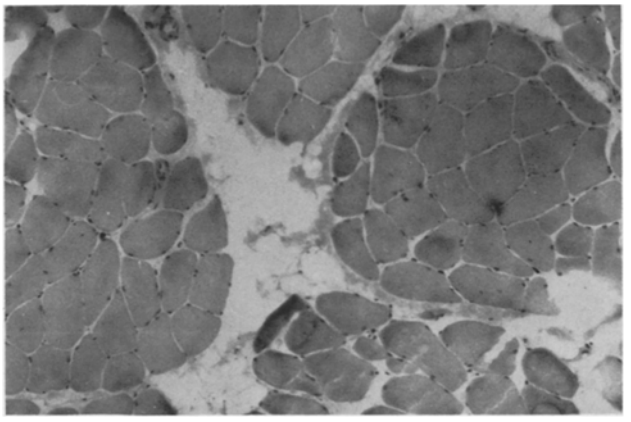

Fig. 1. The recent lesion shows variability in the fiber diameters, nuclear internalization, and perifascicular fatty infiltrations. Case SM, 1 month after the cerebral accident. HE, ×170

Results

Histopathology

Muscle from Hemiparetic Side. In all the muscle specimens morphological changes were found but their degree and character varied in the different groups (Table 3).

In group 1 the muscle fibers are generally polygonal, and the fascicles are interspersed by perimysial tissue showing fatty infiltrations. Separation of the fibers by interstitial edema is often associated with capillary

Table 2. Mean fibre occurrence and diameter (range in parentheses) in anterior tibial muscle of hemiplegic patients at different times after cerebral vascular accident

	Groups			
	1 (1–2 months)	2 (3–4 months)	3 (5–7 months)	4 (8–17 months)
Fiber occurrence (%)				
Type I	66.0 (64–68)	78.5 (68–84)	76.5 (68–84)	75.5 (66–80)
Type II	34.0 (32–36)	21.5 (16–32)	23.5 (16–32)	24.5 (22–34)
Fiber diameter (μm)				
Type I	56 (46–68)	44 (36–55)	40 (30–56)	40 (28–52)
Type II	46 (40–55)	36 (25–48)	34 (24–41)	28 (22–40)

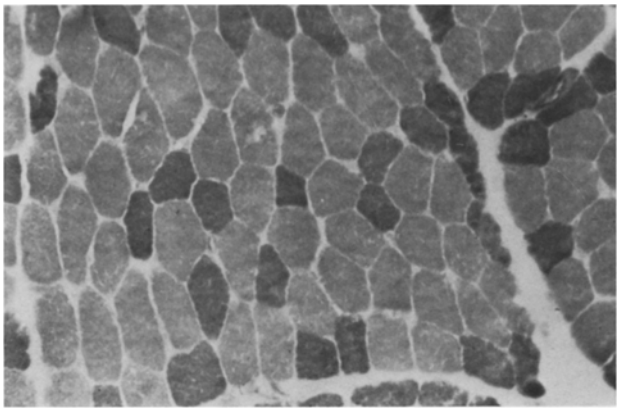

Fig. 2. The recent lesion shows preferential type II fiber atrophy. Case PE, 2 months after the cerebral accident. mATP-ase, pH 9.4, × 275

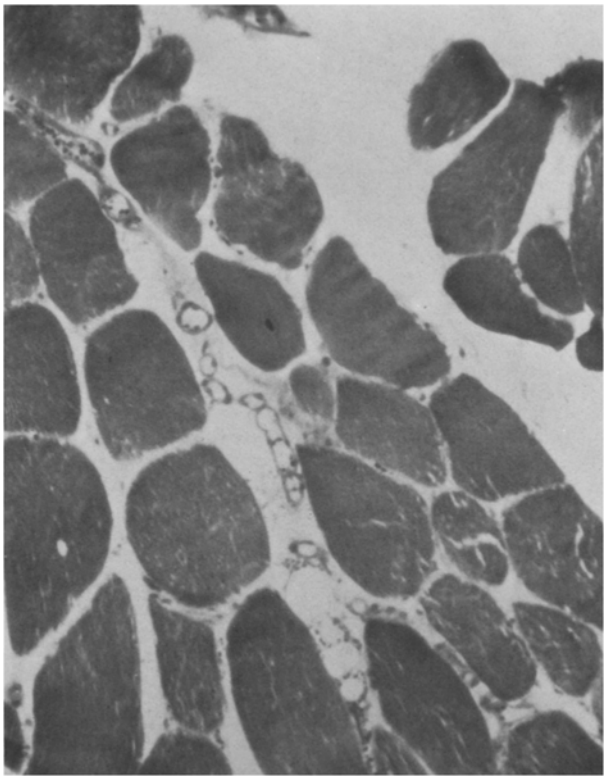

Fig. 3. Fascicular atrophy with variation in the fiber profiles and capillary dilatation. Case NG, 12 months after accident. HE, × 600

enlargement. Centrally localized nuclei and single fibers undergoing degenerative changes are seen sometimes (Fig. 1). As summarized in Table 2, the fiber diameter is reduced and the type II fibers are more often atrophied than type I fibers (Fig. 2). The fiber type ratio is normal and some type I fibers are hypertrophied.

In groups 2, 3, and 4, the muscle fibers are numerically reduced and packed into atrophic fascicles interspersed by fatty infiltrations (Fig. 3). The degree of fiber atrophy varied in the various patients, but is generally marked in groups 3 and 4.

The fiber type composition is altered in almost all patients of groups 2, 3, and 4 with atrophy and numerical reduction of type II fibers and with a predominance of type I fibers (Fig. 4a, b). In most patients of all groups, centrally localized nuclei are a common feature, and single fibers show degenerative-myopathic changes. Splitting of some fibers was also found. Neither basophilic regenerating fibers nor endomysial fibrosis are observed.

As seen in Table 3, in groups 2, 3, and 4, respectively, one patient (AL, EA, SM) revealed a fiber type composition similar to the contralateral normal muscle, with a moderate degree of atrophy and without important ultrastructural changes. A study of clinical and physiologic data obtained in successive stages after biopsy reveal a good functional recovery in these patients.

Contralateral Normal Muscle. A small number of morphological deviations are seen in these biopsies, particularly in the 68- and 70-year-old patients. They consist of scattered angular atrophic type II fibers. The mean fiber diameter for type I fibers ranges from 58 to 76 μm (mean 62 μm, $n = 4$) and for type II fibers, 62–78 μm (mean 65 μm).

Fiber typing on sections treated for mATP-ase, pH 9.4, demonstrate a type I predominance (66%).

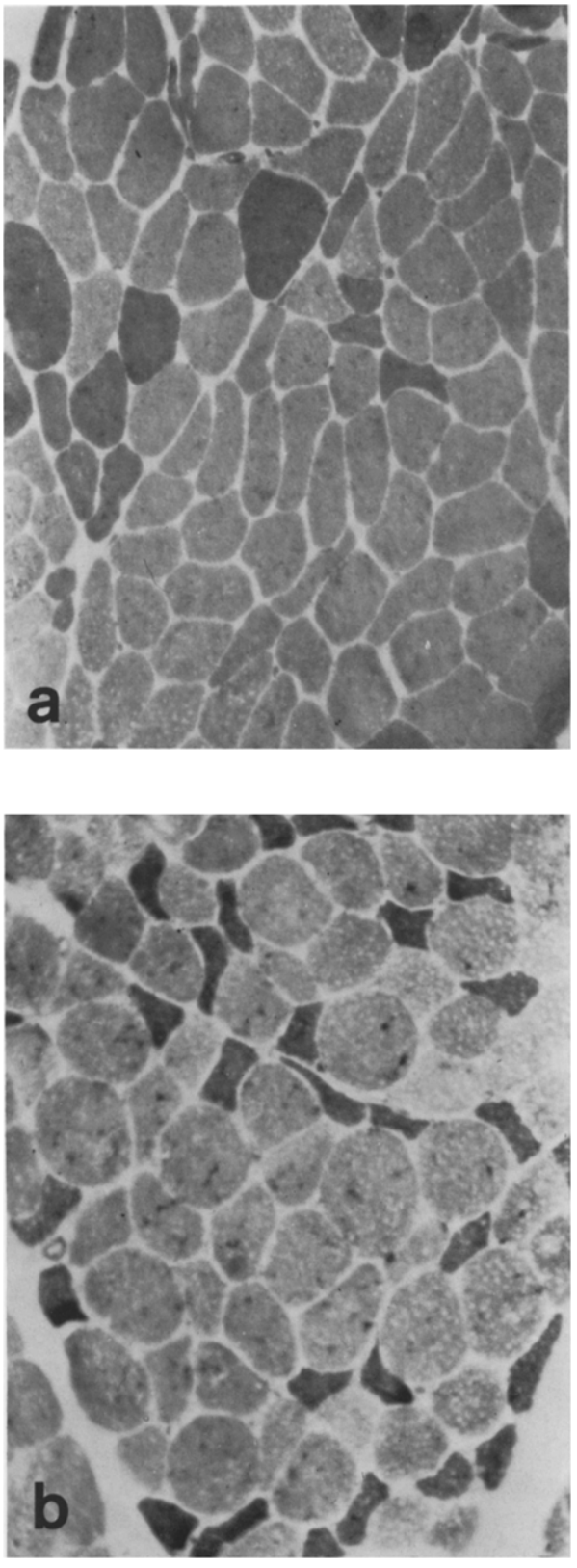

Fig. 4. Type I fiber predominance and type II fiber atrophy. **a** Case RD, 4 months after accident. mATP-ase, pH 9.4, × 400. **b** Case SM, 8 months after accident. mATP-ase, pH 9.4, × 400

Ultrastructural Findings

Muscle from Hemiparetic Side. The main ultrastructural findings observed in muscle fibers of the patients are reported in Table 4.

Group 1. The fine structure of fibers is generally well preserved. The main changes are the anomalous amount of lipid droplets and glycogen granules in the subsarcolemmal region and polymorphous lipofuscin bodies. Scattered fibers show nuclear internalization. The myofibrillar apparatus, mitochondria, and components of the sarcoplasmic reticulum are normal.

Group 2. The sarcoplasmic lipid and glycogen accumulation and the lipofuscin presence are generally very evident and accompained by changes in the myofibrillar components. In a variable number of fibers (40–70%), disorganized myofilaments in restricted myofibrillar areas are seen. The mitochondria and components of sarcoplasmic reticulum are generally normal. In a number of fibers nuclear internalization is seen.

Groups 3 and 4. Numerous fibers show myofibrillar disorganization, loss, and disruption, with streaming of Z line and frequent rod formation.

In half of the patients, characteristic cytoplasmic bodies with an amorphous osmiophilic core and lighter halo composed of thin filaments are seen in grouped fibers. In various sections of our material, the core shows structural continuity with the Z disk. Frequent internalization of nuclei with a vesicular appearance occurs. In rare instances mitochondria show swelling or bizarre shaping near the areas of myofibrillar disorganization. Lipofuscin, lipid, and glycogen storage are constantly observed. Microvascular alterations are present in groups 2–4 and consist of a thickening of the basement membrane of the capillaries and a thickening of the media with perivascular fibrosis of small arteries. In group 1, an evident capillary enlargement with inconstant basement membrane thickening is seen. In some cases, peripheral nerve fascicles are present in the interstitium of the muscle specimens. In all istances they show a normal appearance with preservation of large and small myelinated fiber component.

Contralateral Normal Side. No frequently occurring abnormalities of the muscle fibers are seen. Mitochondria and sarcoplasmic reticulum are generally normal and interspersed between densely packed myofibrils with normal sarcomeric banding. In the two older patients, some atrophic fibers show structural abnormalities, i.e., disarrayed myofilaments and dilated sarcoplasmic reticulum vesicles. In the same subjects microvascular alterations are seen that consist of perivascular fibrosis, with a thickening of the media

Table 3. Histological and enzyme-histochemical changes in the anterior tibial muscle of hemiplegic patients

Groups	Cases	Histology				Enzyme histochemistry		
		Degeneration	Internal nuclei	Fibrosis	Fatty infiltrations	Type I fibers (%)	Fiber atrophy grade (0 – 1 – 2 – 3)	Atrophy type
1	BS	–	–	–	moderate	64	1	–
	SM	+	+	–	moderate	66	1	II
	PE	–	+	–	moderate	66	1	II
	GA	+	+	–	evident	68	1	II
2	AL	–	–	–	evident	68	1	II
	RZ	+	–	–	evident	84	2	II
	CL	–	–	–	evident	78	2	II
	CA	+	+	–	evident	84	2	II
3	CD	+	+	–	evident	76	2	II
	RD	+	++	–	evident	78	3	II
	GC	+	+	–	marked	84	2	II
	EA	–	+	–	marked	68	1	II
4	TG	+	++	–	evident	80	2	II
	NG	+	+	+	evident	78	3	II
	SM	–	–	–	evident	66	2	II
	BS	+	+	–	marked	78	2	II

– = no alteration
+ = 1–5% of the fibers
++ = 5–10% of the fibers

Table 4. Ultrastructural findings in biopsies of hemiplegic patients

Groups	Patients	Fibers with changes (%)	Myofibrils				Sarcoplasmic masses	Mitchondrial changes	Lipid	Glycogen	Lipofuscin
			Disorganized	Streaming	Rods	Cytoplasmic bodies					
1	BS	–	–	–	–	–	–	–	+	+	+
	SM	15	–	–	–	–	+	–	+	+	++
	PE	–	–	–	–	–	–	–	+	+	++
	GA	40	++	–	–	–	+	+	++	++	++
2	AL	–	–	–	–	–	–	–	+	+	++
	RZ	70	++	–	+	–	+	–	++	–	+
	CL	40	+	+	+	–	+	–	+	+	+
	CA	70	++	–	–	–	+	+	++	+	++
3	CD	30	++	+	+	+	+	+	++	+	++
	RD	70	++	+	+	++	+	–	++	+	++
	GC	15	+	–	–	–	–	–	+	–	+
	EA	–	–	–	–	–	–	–	+	–	++
4	TG	60	+	+	+	++	–	+	++	+	++
	NG	50	+	+	+	++	–	–	++	+	++
	SM	–	–	–	–	–	+	–	+	+	++
	BS	38	+	–	–	+	+	–	++	+	++

of small arteries. These muscular and microvascular changes are considered as age-related alterations.

Discussion

There are only few reports on the alterations of human skeletal muscle in hemiplegia.

Histological studies on quadriceps muscle biopsies from eight patients with spastic hemiplegia following cerebrovascular accidents revealed a simple muscle atrophy, with minimal nuclear internalization in the wasted muscles (Fenichel et al. 1964). The histograms of muscle fiber types of patients with miscellaneous upper motor neuron diseases revealed a preferential

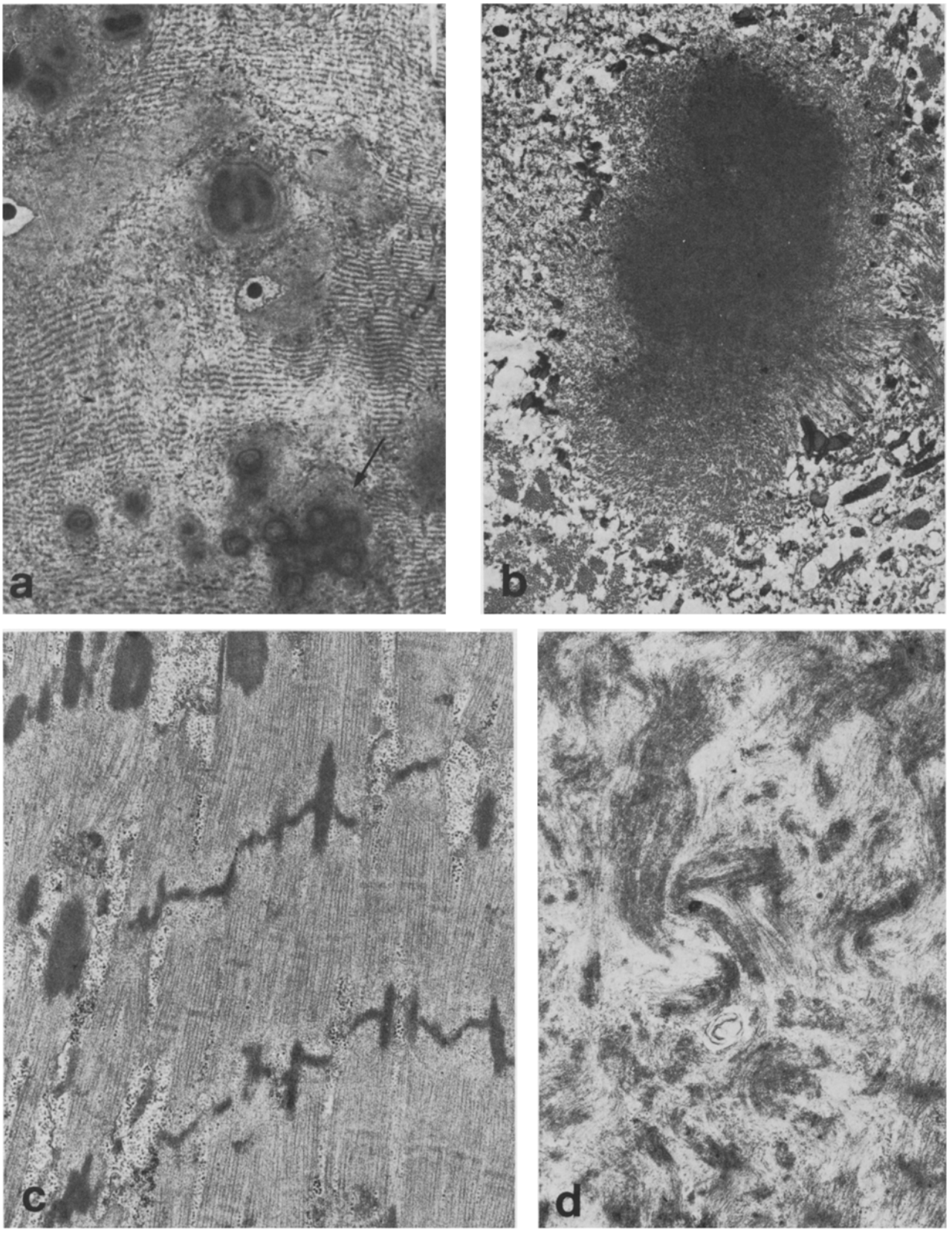

Fig. 5. **a** Cytoplasmic bodies (*arrow*) in a degenerating muscle fiber. Semithin section. Toluidine blue, × 1,835. **b** Thin filaments radiate from a central electron-dense core of a cytoplasmic body. × 13,220. **c** Myofibrillar disorganization, streaming of Z line and rod formation. × 23.410. **d** Packed disarrayed myofilaments in a degenerating fiber. × 26,165

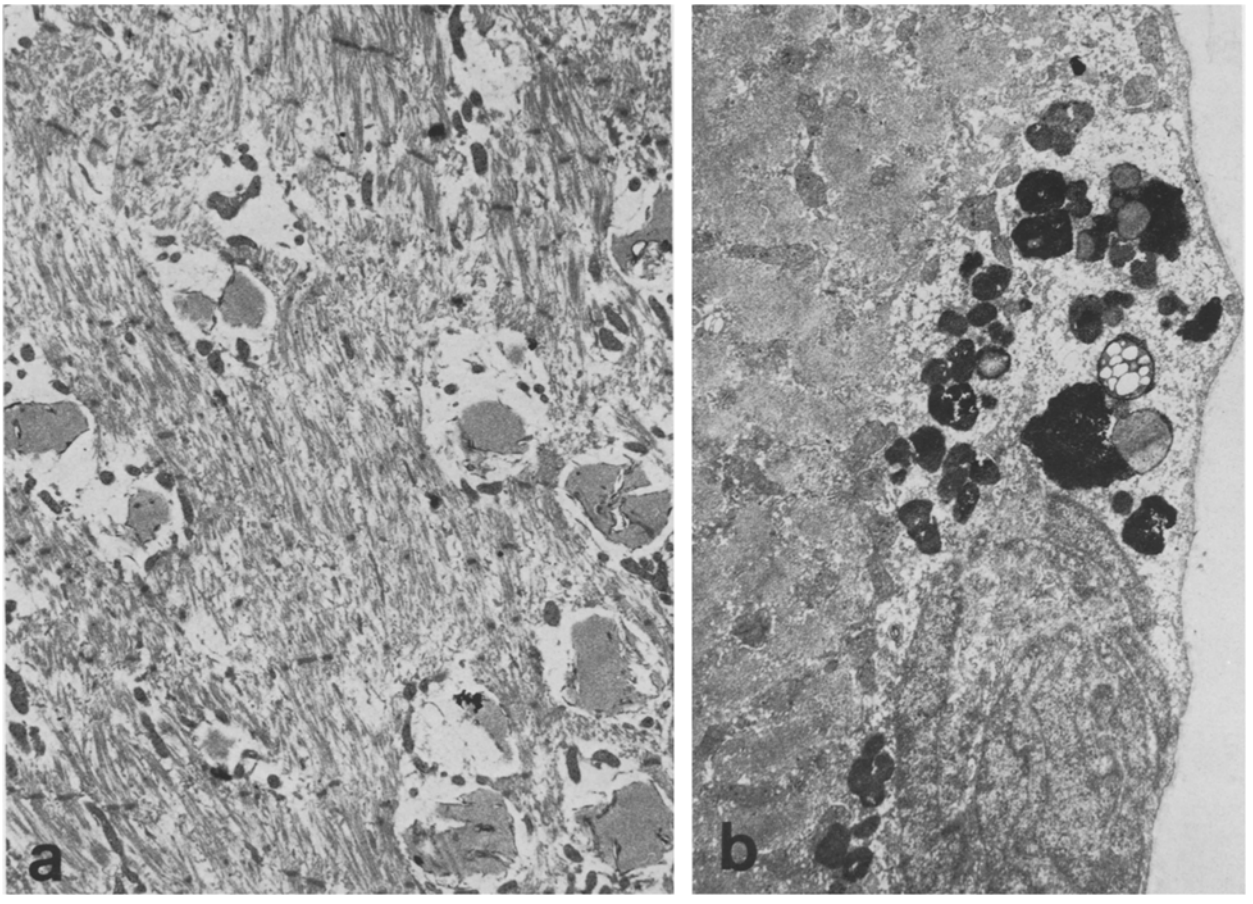

Fig. 6. a Numerous lipid bodies between disrupted myofibrils. × 30,000. **b** Multiple lipofuscin bodies variously shaped in subsarcolemmal areas. × 11,400

reduction of type II fibers as compared to the normal fibers (Brooke and Engel 1969).

The qualitative and quantitative morphological findings described here reveal that leg muscle of hemiplegic patients with cerebrovascular accidents suffer from an ingravescent muscle fiber atrophy with variable structural damage.

Patients with a recent cerebrovascular accident show reduction of the fiber diameters with discrete preservation of the fiber type ratio and of the fine fiber structure.

In the successive stages from the occurrence of the accident (3 – 17 months) the main modifications concern the progressive atrophy of the type II fibers and their progressive numeric reduction, with a predominance of type I fibers.

The changes are accompained by frequent nuclear internalization and perifascicular fatty infiltrations. These alterations are different from the age-related structural abnormalities seen in the asymptomatic leg of some patients, which are similar to those occurring in muscle fibers of middle or old-aged sedentary subjects (Sjöström et al. 1980; Scelsi et al. 1980).

Preferential or selective atrophy of type II fibers is a common abnormality seen in inactive muscle, in muscle disuse (Dubowitz and Brooke 1973), in immobilized muscle (Patel et al. 1969), and in paraplegic patients with spinal cord lesions (Scelsi et al. 1982).

At ultrastructural levels, myofibrillar changes, lipofuscin accumulation, and enhanged lipid-glycogen storage in muscle fibers were found.

Lipofuscin accumulation in fiber sarcoplasm of all studied subjects is regarded as a consequence of fiber degeneration: in fact, this material may well possess lysosomal activity and may have an action similar to autophagic vacuoles (Dubowitz and Brooke 1973).

The enhanced lipid storage is evident in the numerically predominant type I fibers in almost all patients of groups 2 – 4; lipid storage seems indicative of an increased reliance on lipid as an energy source in the contraction of tibialis paretic muscle. This metabolic fiber adaptation seems to be similar to that demonstrated in the muscle fiber of distance runners and in

endurance activity (Essen 1977; Lithell et al. 1979; Prince et al. 1981).

Another frequent finding is the presence of cytoplasmic bodies in atrophic muscle fibers of half the cases of groups 3 and 4. These bodies have been described in various neuromuscular diseases and are considered as nonspecific structures (Dubowitz and Brooke 1973; Poloni et al. 1979). We considered the observation of Engel (1962) who stressed the presence of cytoplasmic bodies in denervated human muscle and in experimental denervation studies. This observation and the finding in our cases of type II fiber preferential atrophy, similar to those seen in paraplegic patients with traumatic cord lesions (Scelsi et al. 1982), may be suggestive of a denervation process.

Nevertheless, the normal appearance of intramuscular peripheral nerve fascicles and the absence of morphological patterns of denervation suggest that in hemiplegic subjects denervation phenomena are inconsistent and, if present, are due to concomitant preexistent pathology.

Since contradictory findings are reported concerning the existence of vasomotor disturbances in hemiplegia and specifically regarding its relation to muscular atrophy (Kennard et al. 1934; Sturup et al. 1935; Feudell and Fischer 1956; Fenichel et al. 1964), the microvascular changes seen in the present study represent the morphological aspects of vasomotor disturbances clinically evident in hemiparetic limbs of our patients. These alterations, similar to those observed in paraplegia (Scelsi et al. 1982), could probably explain the degenerative myopathic lesions of muscle fibers observed in numerous cases.

The loss of uniformity of the morphological findings in some patients at later stages after lesion seems to be related in part with the different extension and gravity of anatomo-pathologic cerebral lesion and in part with the evolution of the disease and with the functional recovery of the individual patient.

In fact, some subjects of groups 3 and 4 demonstrating a good functional recovery revealed at biopsy no significant structural changes of muscle fibers, with discrete preservation of fiber type composition. This finding seems to indicate that muscle biopsy may provide information of prognostic value of the possible recovery of these patients.

In our opinion, there is a great deal of information to be found in the muscle biopsies from hemiplegic patients, with particular regard to fiber type composition. From our results it should possible to choose a selected rehabilitation therapy that may exert its specific influence on the fiber type population (Edwards et al. 1980), mantaining in patients with recent cerebral lesion the type II fiber population that shows atrophic changes and numeric reduction.

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