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Familial Focal Loss of Cross Striations*

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Summary. Two patients, a brother and sister, both suffering from congenital generalized muscle weakness with a progressive course are reported. Muscle biopsy revealed areas with loss of cross striations in the muscle fibers, electronmicroscopically presenting complete disorganization of the myofibrils with streaming of the Z discs and absence of mitochondria. Vesicular nuclei with prominent nucleoli were present in these areas. There was a type I fiber predominance in both cases. The mean diameter of the type I muscle fibers in one of the cases was too small. Motor endplate alterations in this patient gave no evidence of denervation but were suggestive of a delayed development of motor nerves.

Key words: Cross striations loss of – Myopathy congenital.

Zusammenfassung. Es werden zwei Patienten beschrieben, Bruder und Schwester, beide an einer kongenitalen, generalisierten, progressiven Muskelschwäche leidend. Die Muskelbiopsie zeigte Zonen mit Verlust der Querstreifung in den Muskelfasern, und bei elektronenmikroskopischer Untersuchung zeigte sich eine totale Unordnung der Myofibrillen mit Strömung der Z-Scheiben und Fehlen von Mitochondrien. In diesen Bezirken fanden sich blasige Kerne mit prominenten Nukleolen. In beiden Fällen zeigte sich ein starkes Überwiegen der Typ-I-Fasern. Der mittlere Durchmesser der Typ-I-Muskelfasern war in einem der Fälle zu gering. Veränderungen in der motorischen Endplatte in diesem Fall zeigten keine Denervierung, sondern deuteten auf eine verzögerte Entwicklung der motorischen Nerven.

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Introduction

In 1967 Engel [8, 9] described a 14 year old girl who, from birth, had flaccid, predominantly proximal muscular weakness which was only very slowly progressive. She had slight ptosis and impaired extraocular movements. The tendon reflexes were absent. The muscle biopsy revealed focal lesions with loss of cross striations but preservation of longitudinally arranged myofibrillar material. There were multiple vesicular nuclei in and closely around these abnormal regions. Enzyme activity and glycogen appeared to be reduced or absent in these areas on histochemical examination. Type I fibers were widespread, small and significantly predominant. Electron microscopy disclosed myofibrillar degeneration in the foci with smearing of Z disc-like substance and loss of mitochondria. This disorder was later referred to by the author as focal loss of cross striations. Two new familial cases with the same clinical and morphological abnormalities will be presented here.

Case Reports

Case 1 was a 6 year old boy who was born at term after a normal pregnancy. Fetal movements were said to have been normal. According to the mother, the baby was a floppy infant. He was too heavy (birthweight 5300 g) and too tall (length 0.62 m). His motor development was retarded. He stood at 17 months and walked when he was 24 months old. He never could run and was not able to stand up from a supine position without the support of his hands. He had a waggling gait. His arms were too weak. During the winter, he often had long periods of bronchitis. The intellectual development was normal. On examination, the patient showed severe paresis of the extraocular muscles without diplopia. There was no ptosis. Although the facial expression was poor, the isolated functions of the facial muscles seemed to be intact. There was a slight weakness of the masseter muscles. Speech was somewhat nasal and dysarthric. He had no dysphagia. The pharyngeal reflex was positive. There was generalized muscle weakness.

However, the flexors of the head, the proximal muscles and the dorsal flexors of the feet were involved to a greater extent. There was moderate atrophy of the paretic muscles. The calves were remarkably well developed. There was a clock-like thorax deformity and a marked hyperlordosis. The tendon reflexes were absent. There were no myotonia or fasciculations present.

On re-examination nearly two years later the patient had a normal development of length and weight for his age, but there was definite worsening of the symptoms, especially of the weakness of the proximal muscles.

Laboratory Findings

The serum CPK levels were normal on three occasions. Normal values were found for ESR, hemoglobin, sodium, potassium, magnesium, calcium, lactate, GOT, GPT, aldolase, LDH, alkaline phosphatase, urea and creatinine. The Wassermann reaction was negative. The PBI, T_3 and T_4 tests were normal. Urinalysis revealed no abnormalities. Amino acid chromatography and estimation of α-aminonitrogen in the urine were normal. The creatinine : creatine ratio in the urine was normal. The CSF, X-rays of the chest, EEG and ECG were normal. Pulmonary function was quantitatively disturbed (vital capacity 51%, expiratory one second value 52%, inspiratory one second value 56%).

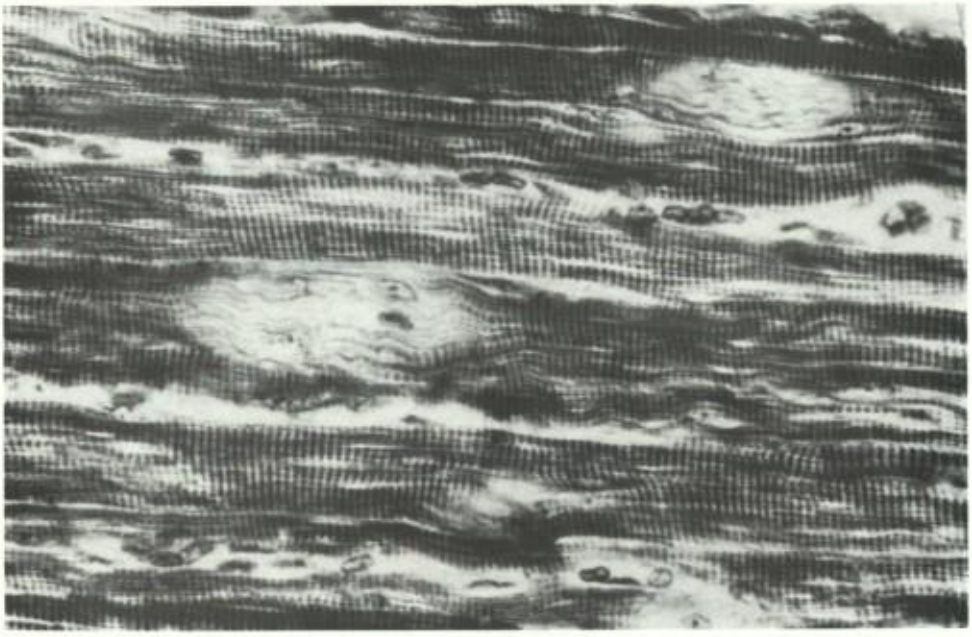

Fig. 1. Areas with loss of cross striations in longitudinal section. PTAH. ×600

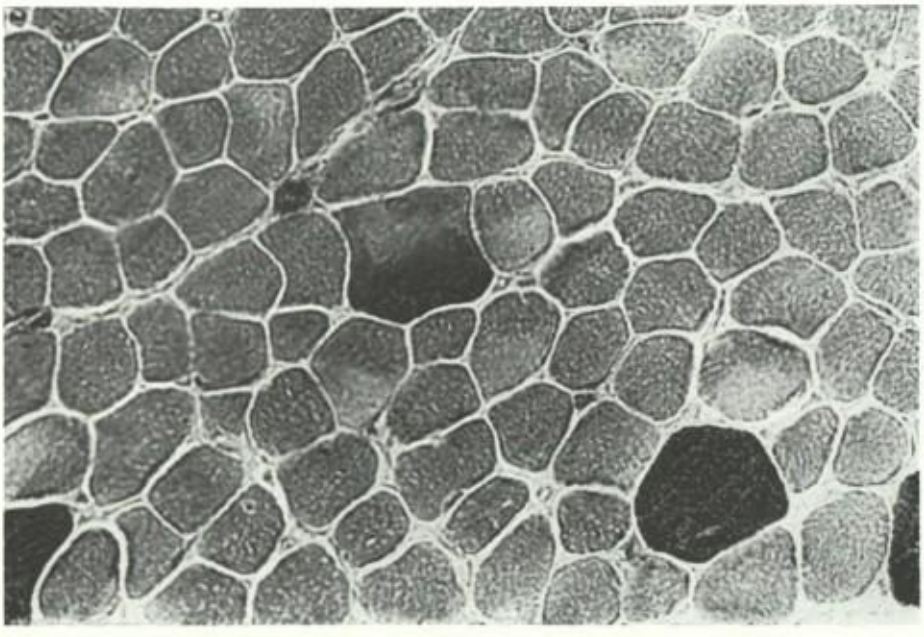

Fig. 2. Only a few scattered type II fibers are present between many type I fibers. The less stained areas are foci with loss of cross striations. Myofibrillar ATPase. ×450

The EMG of the left deltoid and gastrocnemius muscles and of the right biceps brachii, quadriceps femoris and extensor digitorum brevis muscles presented an interference pattern with very short action potentials of low amplitude (200—500 microvolt). The motor conduction velocity of the right peroneal nerve was normal. The examination of the somatosensory evoked response from the right arm and the left leg gave normal results.

Light Microscopic Investigations

1. Histological and Histochemical Studies. Biopsies were taken from the left vastus lateralis and medialis muscles. There was a marked variation of the diameter of the muscles fibers, which never had an angular aspect. In longitudinal sections almost all muscle fibers presented focal lesions with complete absence of cross striations, while the longitudinal myofibrillar arrangement was still present (Fig. 1). Some of these abnormal areas were centrally located in the muscle fiber, while others had a more excentric position. Very often they occupied the complete surface of a transversely sectioned fiber. The shape of the abnormally structured parts of the muscle fiber was very variable. Some foci caused slight ballooning of the muscle fiber. The transition from the normal to the abnormal parts of the muscle fibers was abrupt. There was an increase of internal vesicular nuclei with prominent nuclei in and around the abnormal regions. This was also seen, to a lesser degree, in the normally striated parts of the muscle fibers. Small chains of nuclei were seen sporadically. The parts involved presented a decreased activity of the oxidative enzymes and myofibrillar ATPase. The oxidative enzyme activity was generally somewhat increased at the edges of the abnormal areas. Acid phosphatase activity was slightly increased in the involved parts which also displayed a weak PAS reaction. There was moderate increase of endomysial fat but no proliferation of connective tissue. The intramuscular blood vessels were normal. No cellular infiltrates were present. Fiber types were studied with the myofibrillar ATPase, NADH tetrazolium oxidoreductase and succinic dehydrogenase reactions. Most muscle fibers were type I with ATPase reaction. Only a few scattered type II fibers were observed. Their proportion was approximately 1% (Fig. 2). Many fibers contained a pale central area which corresponded probably to central nuclei. Nearly all fibers were dark with the NADH tetrazolium oxidoreductase and succinic dehydrogenase activity staining, but there were marked variations of staining, which corresponded to the focal lesions.

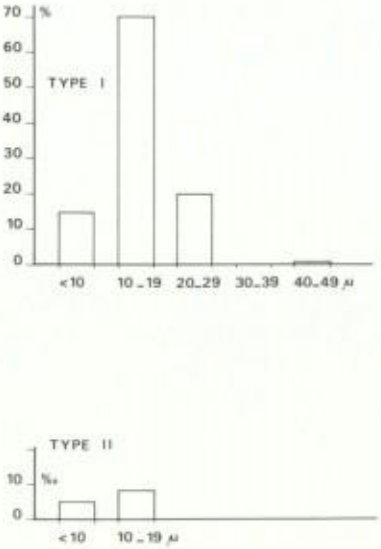

Fig. 3. Histogram of Case 1

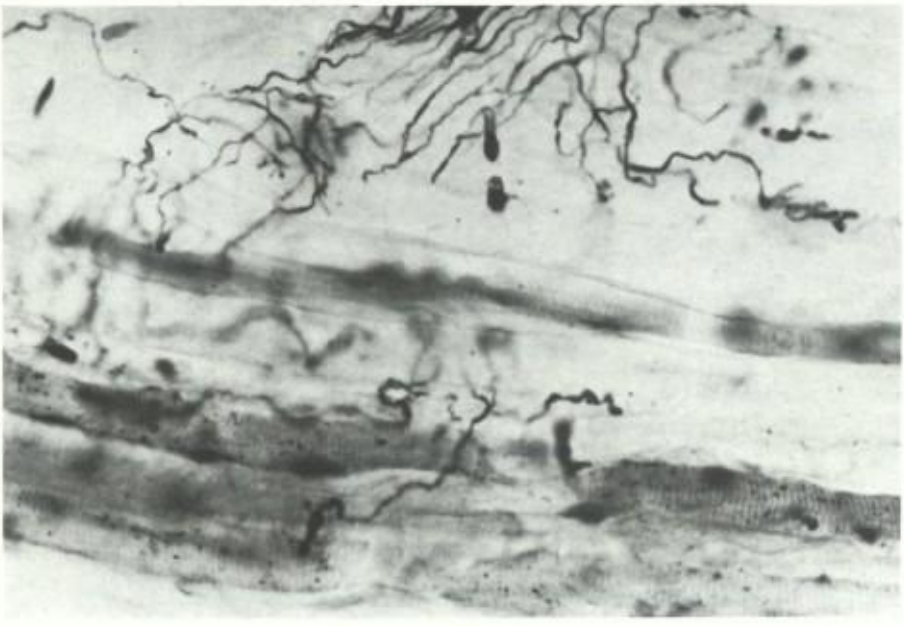

Fig. 4. Small and unramified motor nerve endings. Some endings are reduced to one single expansion. Intravital methylene blue staining. ×600

The abnormal areas were present both in type I and type II fibers. The muscle fibers were abnormally small corresponding to the age of the patient. The normal mean value, at 6 years, should be approximately 30 μ [2]. The mean diameter of the fibers was 15.65 μ ± 6.02 for type I fibers and 10.8 μ ± 5.07 for type II fibers (Fig. 3).

2. Motor Innervation Study. The motor nerve fibers were normal with intravital methylene blue staining. Most motor arborizations were small and poorly ramified, occasionally reduced to one single large axoplasmic expansion (Fig. 4). Collateral ramification of axons was not increased and the terminal innervation ratio, measured on 245 terminal axons, was 1.07.

Electronmicroscopic Investigations

The structure of the muscle fiber was totally disturbed in the focal lesions (Fig. 5). The normal pattern of cross striation was absent. The Z discs were replaced by irregular, longitudinally orientated streaks of electron-dense, fibrillar material. Mitochondria and glycogen were markedly diminished but not completely absent. Collections of triads were very numerous; they usually consisted of 2—3 T tubules and 2—4 sacs of endoplasmic reticulum. All around the lesions there was a narrow transitional zone, characterized by a sparsity of mitochondria as in the lesion proper, and by a conspicous zigzagging of the Z discs. The continuity between the Z discs in the unaffected areas and the electron-dense streaks in the lesions was obvious in this transitional zone. No deviations from the normal structure could be demonstrated outside the lesions.

Three myoneural junctions were observed. The nerve terminals contained numerous synaptic vesicles and normal mitochondria. The secondary synaptic clefts were scanty and abnormally short (Fig. 6), which was confirmed by the study of serial sections.

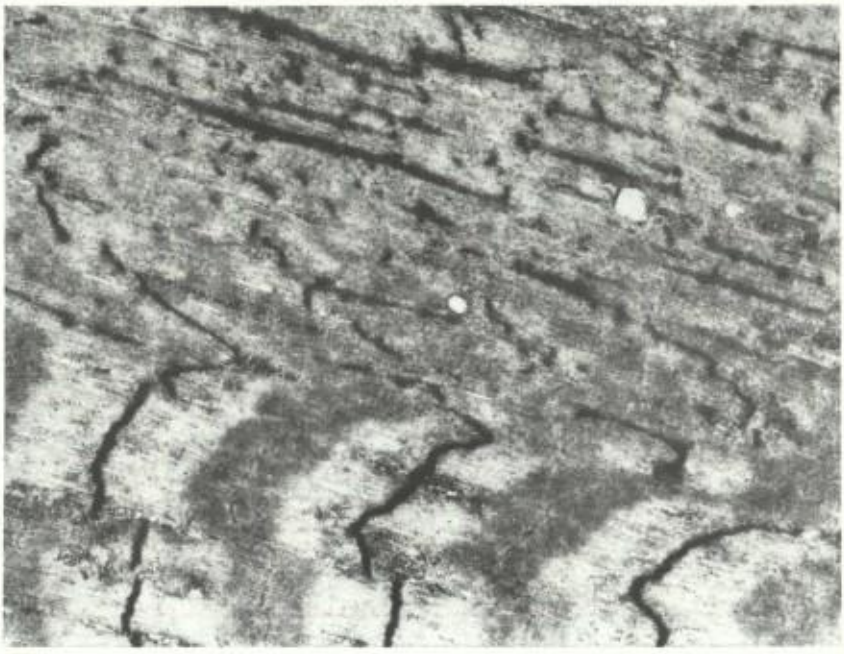

Fig. 5. Transitional zone of a large lesion showing streaks of electron-dense fibrillar material and complete loss of organization in the lesion. Case 1. × 7900

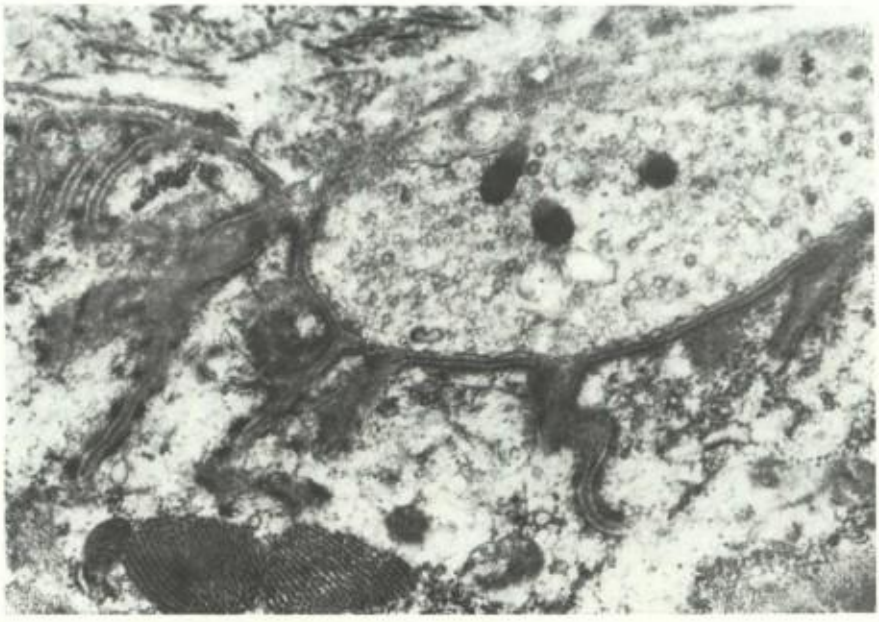

Fig. 6. Myoneural junction. Synaptic folds are scanty and short. Case 1. × 31 000

Case 2, the sister of Case 1, was 22 months old.

The pregnancy had been uneventful with normal fetal movements. The baby was cyanotic at birth, but she recovered soon and breathed normally a few hours later. In the first months of life, she cried weakly and was not able to lift her head. Motor development was only slightly retarded. She stood at 15 months and walked at 21 months. She seemed to be normal intellectually. On examination there was no obvious paresis of the extraocular muscles but there was bilateral involvement of the facial musculature. There was a high arched palate. The flexors of the head were markedly paretic. Although the strength of the extremities seemed to be normal, the patient experienced great difficulty in standing up from the supine and from the sitting position. There were neither fasciculations, nor signs of myotonia. All of the tendon reflexes were absent.

On re-examination one year later there was marked paresis with atrophy of the muscles of the shoulder girdle and an increase of the involvement of the pelvic musculature.

Laboratory Findings

The serum CPK, GOT, GPT, aldolase, lactate, sodium, potassium, calcium and magnesium values were within normal limits. The EMG of the left deltoid and gastrocnemius muscles and of the right biceps brachii, quadriceps femoris and extensor digitorum brevis muscle presented an interference pattern with action potentials of normal shape, duration and amplitude. The motor conduction velocity of the right peroneal nerve was normal.

Light Microscopic Investigations

A biopsy was taken from the left vastus lateralis muscle. There was a slight variation of the diameter of the muscle fibers many of which had focal lesions with the same morphological and histochemical properties as seen in Case 1. The frequency of the lesions varied in different parts of the biopsy. In contrast to Case 1, there were many focal lesions without vesicular nuclei. If vesicular nuclei were present in the lesions their number were less than in Case 1.

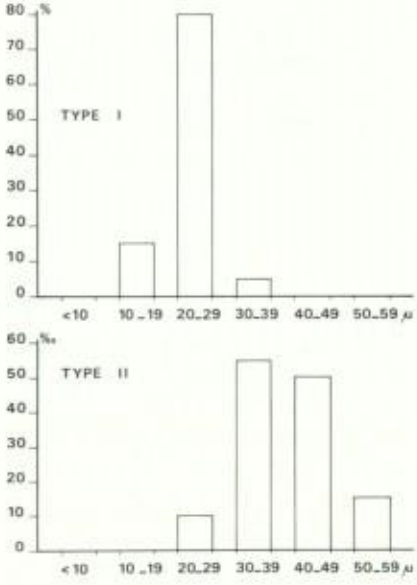

Fig. 7. Histogram of Case 2

In the normally striated parts of the muscle fibers, transverse sections showed 1—2 internal nuclei in approximately 10% of the fibers. There was moderate increase of endomysial fat but no proliferation of connective tissue. The intramuscular blood vessels were normal. No cellular infiltrates were present.

Fiber-type studies, performed in the same way as in Case 1, revealed that there was a marked reduction of type II fibers, the I/II ratio being 200/28. The mean diameter was 23.95 μ ± 4.3 for type I fibers and 41.43 μ ± 8.7 for type II fibers (Fig. 7).

The normal mean value at 22 months being approximately 18 μ [2], these diameters are not too small.

Electronmicroscopic Investigations

The same ultrastructural changes as described in Case 1 were demonstrated in the focal lesions.

Observations in the Parents

Neurological examination of the 31 year old mother and the 40 year old father disclosed no abnormalities. The same blood and urine tests carried out with the patients' specimens were performed and found to be normal. The EMG and the conduction velocities of the motor nerves were normal. Muscle biopsies of the left vastus lateralis muscles were normal.

Discussion

There is a striking resemblance of the clinical, histological, histochemical and electronmicroscopic findings between the present patients and Engel's case [8, 9]. A very probably similar disorder was described by Schotland [14, 15], in a patient with the same clinical symptoms. Abnormal regions with loss of cross striations and many internal nuclei were seen in the muscle biopsy. Although these lesions were interpreted as target fibers, the light microscopic and ultrastructural findings suggest that there is no essential, but only a quantitative, difference between his morphological observations and ours.

An autopsied case of "segmental myopathy" was described by Satoyoshi and Kinoshita [13]. There were also no cross striations seen histologically in the involved segments of the muscle fibers. In the altered parts, there were darkly stained masses. There was an increase of central nuclei. Only the peripheral parts were affected in some fibers. No histochemical or electronmicroscopic observations were given. From the description and the available micrographs, we could not be certain whether these structural changes were similar to those of the present cases.

The focal changes ("myotube-like structures") described by Bethlem et al. [1] were of an entirely different morphological character, although in these areas of the muscle fiber there was also loss of cross striations and increase of vesicular central nuclei, without longitudinal continuity of myofibrillar material. In striking contrast to the present cases, the areas involved showed a high oxidative enzyme activity and a strong PAS reaction. Electronmicroscopic data were not available.

In the cases of familial myopathy with probable lysis of myofibrils in type I fibers described by Cancilla et al. [3] the abnormal parts of the muscle fibers were

light microscopically always located in the subsarcolemmal regions. In these areas, in which there were sarcolemmal nuclei with prominent nucleoli, a high activity of myosin ATPase was seen. Furthermore vacuoles were present in the junctional zones between different appearing parts of the fibers.

Ultrastructural studies revealed a total loss of myofibrils, which were replaced by a finely granular matrix in the affected areas. In all these aspects the cases are different from the present ones.

In the muscle biopsies reported by Radu et al. [12], of two familial cases presenting hypotrophic type I muscle fibers with central nuclei and central myofibrillar lysis preferentially involving type II fibers, the affected parts of the muscle fibers were always located centrally. Some of these areas contained nuclei. The myofibrillar ATPase activity was decreased as well as the activity of the mitochondrial enzymes. Electronmicroscopically the involved regions presented disorganization of the myofibrils and streaming of the Z discs. Although morphologically there is some similarity to the present cases, the location as well as the appearance of the lesions seems different. Moreover in the muscle samples of Radu et al. [12] there were other changes such as type I fiber hypotrophy and central nuclei. In the patients of Cancilla et al. [3] the areas with myofibrillar alteration were confined to the type I fibers. In the patients of Radu et al. [12] they were predominantly present in the type II fibers. In our patients there was neither type I nor type II preference in the occurrence of the foci.

In central core disease, multicore disease [10] and in target fibers there may be a loss of cross striations and/or absence of enzyme activity, while the ultrastructural changes are very similar to those seen in the present cases. But in these conditions the abnormal areas of the muscle fiber never contain nuclei. The same holds true for the Z band streaming and myofibrillar disruptions seen in skeletal muscle of healthy young people described by Meltzer et al. [11].

In our Case 1 the small size and poor ramification of motor arborizations could be related to the small size of the muscle fiber, since the size of the motor endings is proportional to the diameter of the muscle fibers [4]. However, the poverty of synaptic foldings, observed at ultrastructural level, must be taken into account.

This pattern could be related to an immaturity of motor endings. Abnormally small and unramified motor endings were previously described in a hypotonic child [5]. No structural abnormalities of muscle fibers were observed in this case and the changes in nerve endings were assumed to represent a delayed development of motor nerves. Since in our Case 1 there is no excessive collateral branching of the motor nerve fibers, the diminutive motor arborizations cannot be related to denervation [6, 7].

In Case 1, the older patient, the muscle fibers were relatively smaller than in the younger Case 2. No explanation can be given for this fact. It could be due to progressive wasting.

The only other reported cases of focal loss of cross striations [8, 9, 14] were sporadic. Our two patients were familial. This is a suggestion of an autosomal recessive mode of transmission of this disease. It was not possible to identify the heterozygotes.

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