Short report

Hypotrophy of type I fibres with central nuclei: recovery 4 years after diagnosis

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SUMMARY A case of myopathy is reported in a child, first biopsied at 1½ years of age and whose muscle showed hypotrophy of type I fibres with central nuclei. The case was followed up with another biopsy from the contralateral muscle at 6 years of age. The second sample showed only predominance of type I fibres.

We describe the clinical and morphological changes in a boy presenting a congenital myopathy with hypotrophy of type I fibres with central nuclei.¹ He was biopsied twice with an interval of 4.5 years. During this time clinical symptoms and histological findings improved almost to total recovery.

Case report

A 16-month-old boy, was born at term. The mother stated she had experienced weak fetal movements since the fifth month of pregnancy. He was a floppy infant from birth, with poor suck and cry and diminished breathing movements. Motor development was slow. He was able to sit up at nine months and stand up at 14 months. His mental development was normal. He is the first child of non-consanguineous normal parents and there were no similar cases in the family. Physical examination showed marked generalised hypotonia. Muscles of the neck, pelvic and shoulder girdles, as well as the proximal muscles of the limbs were markedly weak and slightly wasted. Deep tendon reflexes were present although diminished. No fasciculations were seen. Laboratory examinations including creatine kinase, disclosed normal values. Electromyographic studies of deltoid, biceps brachialis, quadriceps, tibialis

anterior and triceps suralis muscles revealed small amplitude potentials of short duration. The pattern was compatible with a myogenic lesion. A biopsy of the right quadriceps muscle was performed at 16 months of age.

The child was studied again at the age of six years. The parents reported a progressive improvement in his muscular strength. He carried on a normal life. The hypotonia had disappeared and there was only slight weakness of the neck and pelvic and shoulder girdle muscles, without wasting. Deep tendon reflexes were normal. Laboratory studies including creatine kinase, were normal. EMG examination of the same muscles studied at 16 months was also normal. A second biopsy from the left quadriceps muscle was obtained at this age.

Methods

Muscle biopsies were performed under local anaesthesia. Specimens were prepared for paraffin (HE, Masson's trichrome and PTAH), frozen sections for routine histochemical reactions and fixed in paraformaldehyde-glutaraldehyde at 2% for 3 h at 4° C and embedded in epoxy-resin for electron microscopy. Fibre diameters were measured on transverse sections stained with ATP-ase at pH 9.4 at a magnification of ×400. Counts of central nuclei were performed on transverse frozen sections stained with HE. The presence of a clear peripheral halo or central masses positive with oxidative enzymes were noted in both biopsies. Subtypes of type II fibres were counted on transverse sections stained with ATP-ase at pH 4.6 and 4.3.

Results

First biopsy (sixteen months of age). Light micro-

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scopy showed Type II fibres were generally large, ranging from 10 to 50 μm in diameter. Type I fibres were small, its diameters ranging from 5 to 30 μm and appeared as small groups surrounding the larger type II fibres. Type I fibres were predominant. Type II fibres were not differentiated into subtypes and they all stained as type II-C fibres. The small type I fibres showed collections of oxidative material in their centre, with a clear peripheral halo with DPNH and SDH reactions. 10% of type I fibres had central nuclei (fig A, B). The ultrastructural study showed abundant small fibres with centrally placed mitochondria and glycogen. Myofibrils were localised in the periphery. In some of them, the nucleus was centrally placed.

Second biopsy (six years of age). Light microscopy showed only a few isolated small fibres scattered between normal sized fibres. Some of them had cen-

Table *Comparative histological findings of both biopsies*

Type of fibres	I		II	
Age (years)	1/4	6	1/4	6
Central nuclei	10%	4%	0	0
Oxidative enzymes:				
—Central collections	72%	0.5%	0	0
—Peripheral halo	72%	0.5%	0	0
Fibre percentage	77	74	23	26
Mean diameter (μm)	12 ± 4	25 ± 4	31 ± 7	30 ± 4
Variability coefficient	333	148	225	133
Subtypes of II Fibres:				
—II-A			0	91
—II-B			0	7
—II-C			100	2

tral condensation of oxidative material. A thin peripheral halo devoid of oxidative material was seen in less than 0.5% of type I fibres. Differentiation of type II fibres into subtypes was normal. Occasional central nuclei were present. The pre-

Fig (A, B) First biopsy (sixteen months). Light microscopy findings. Numerous hypotrophic fibres with central nuclei and central collections of oxidative enzymes. (A: HE $\times 400$. B: DPNH-TR $\times 200$). (C, D): Second biopsy (six years). Light microscopy findings.

Normalization of histological picture. (A: DPNH-TR $\times 100$. B: ATPase pH 9.4 $\times 100$). (E) Histograms of muscular fibres diameters of both biopsies (expressed in percentage). Left: First biopsy. Right: Second biopsy.

dominance of type I fibres persisted (fig C, D). The ultrastructural study disclosed no abnormalities in fibres nor intramuscular nerves; bundles. Comparative semiquantitative findings are shown in the table. Comparative histograms of both biopsies in the fig (e).

Discussion

The first biopsy specimen showed predominance and hypotrophy of type I fibres, central nuclei and numerous cytochemical alterations of type I fibres (oxidative enzyme activity and no ATP-ase activity in the central region of the fibre with no oxidative enzyme activity in the periphery). There was moderate hypertrophy and lack of differentiation into subtypes of the type II fibres. Ultrastructurally, nuclei and organelles were located in the centre of the fibre and the myofibrils at the periphery giving the fibre a myotubular appearance.

The first description of a similar case was made by Spiro *et al.*,² who reported a patient with a congenital myopath whose muscle biopsy showed fibres resembling fetal myotubules. They called it "myotubular myopathy" and postulated that the

pathogenic mechanism was an arrest in the development of muscle. Sher *et al.*³ observed a similar pathologic picture in a mother and two daughters. Many fibres had central nuclei and high oxidative enzyme activity with low ATP-ase activity in the centre of the fibre. Due to the central localisation of the nuclei they called it "centronuclear myopathy". After this, cases with similar characteristics have been described,⁴⁻²² several of them with small type I fibres.⁴⁻⁹ This group was called by Engel *et al.* "type I fibre hypotrophy with central nuclei".¹⁰ They postulated an alteration during the fetal period of the alpha motoneuron which innervated type I fibres as the pathogenic mechanism. Histologically they all showed central nuclei and the majority showed predominance of type I fibres. In all the cases studied there were cytochemical alterations similar to those observed in the first biopsy of our case. Ultrastructurally, these fibres had myotube-like appearance, with occasional abnormalities of the perinuclear myofibrils.^{3 15 19 22}

The cytochemical and structural alterations of these fibres recall those seen in the embryonal stages of muscle maturation.²³⁻²⁵ We think, therefore, that these processes must be considered pathogenetically

as alterations in the maturation of the muscle fibre and more specifically, as a maturative retardation due to unrecognised causes.

The idea of a dysmaturative pathogenesis in these cases, led us to think that these conditions may improve with age. In our case, we performed a second biopsy 4 years and 8 months after the first one, which showed almost total normalisation of the histological picture. This finding therefore shows that at least some of these myopathies are dysmaturative and are not static disorders, but processes that evolve towards normality. It is possible that other pictures of hypotrophy of type I fibres without central nuclei²⁶ and of congenital disproportion of fibre types,²⁷ might also be expression of a maturative retardation of muscle fibres. They may represent only differences in the severity of the disease. In a previous work²⁸ we have analysed 16 cases of myopathies fitting in the categories above mentioned: myotubular/centronuclear myopathy, type I fibre hypotrophy with or without central nuclei and congenital disproportion of fibre types. We consider them as dysmaturative myopathies and regard an alteration in the normal maturation of muscle as the common pathogenic mechanism underlying all of them. We based this assumption on the finding of immature fibres and the overlap of the histological features considered characteristic of each one of these entities. In addition, the unitary concept of all these processes is supported by the occurrence of these different entities within the same family. For example, the occurrence of a myotubular myopathy in a girl aged 11 months and a myopathy with hypotrophy of type I fibres without central nuclei in her mother.²⁹

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