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Neonatal Form of Nemaline Myopathy with Intramuscular Nerve Immaturity

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Abstract

In an infant with neonatal form of nemaline myopathy, the muscle biopsy showed in addition to the intracytoplamic rods, immature muscle fibres as well as multiaxonal and premyelin fibres in intramuscular nerves. The existence of such fetal muscle and nerve characteristics in an infant with severe muscle weakness and hypotonia suggest the delay or arrest of lower motoneuron maturation.

Introduction

Most of the cases of nemaline myopathy represent mild muscle weakness and non progressive course [1–3]. Neonatal form however is much more severe with respiratory insufficiency and often fatal course [4–9]. Clinical as well as morphological data suggest that the neonatal form starts in fetal life and follows a progressive course [6,8].

Recently we investigated an infant with the severe clinical symptoms at birth. Muscle biopsy displayed morphological features of immaturity both in muscle and intramuscular nerves. None of the previously reported cases to our knowledge presented any evidence of pathological changes in peripheral nerves, whereas in our patient the intramuscular nerves showed morphological features of immaturity.

Case Report

A.G. a baby girl was the first child of old, healthy, unrelated parents. She was delivered by cesarean section at an estimated 38 weeks gestation. The patient's

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parents (mother 41 years old and father 71 years old) were normal on neurological examination. There was no family history of neuromuscular disorder. The pregnancy had been uneventful until the last trimester when the arterial hypertension of mother was noted. The infant weighed 3000 g at birth. The apgar score was 8 at one and five minutes. Generalized hypotonia, lack of moro and of suck reflexes were noted. Because of cyanosis and respiratory insufficiency the baby was referred to the neonate intensive care unit for artificial ventilation. On examination the infant had a characteristic appearence with narrow face, high-arched palate, hypoplastic muscles and Achilles tendon contractures. She was severely hypotonic, areflexic and had little spontaneous activity. Because of poor sucking she was fed through a nasogastric tube. Routine laboratory investigations were normal. EMG was not performed. The rectus femoris muscle was biopsied at age of 3 weeks. The patient's muscle weakness showed no progression or improvement. Her course was complicated by an episodes of pneumonia which were successfully treated with antibiotics. Her weight was poor; at 10 months she weighed only 6300 g. Her motor development was severely retarded. Generalized muscle weakness was noted and she required constant respiratory assistance (Fig. 1). She reacted to the environment with brisk occular movements but her long face minimaly moved because of several facial muscle weakness. The mouth had never closed (Fig. 1). The ankle, knee and biceps jerkes were absent. There was neither myotonic phenomenon nor muscle fasciculation.

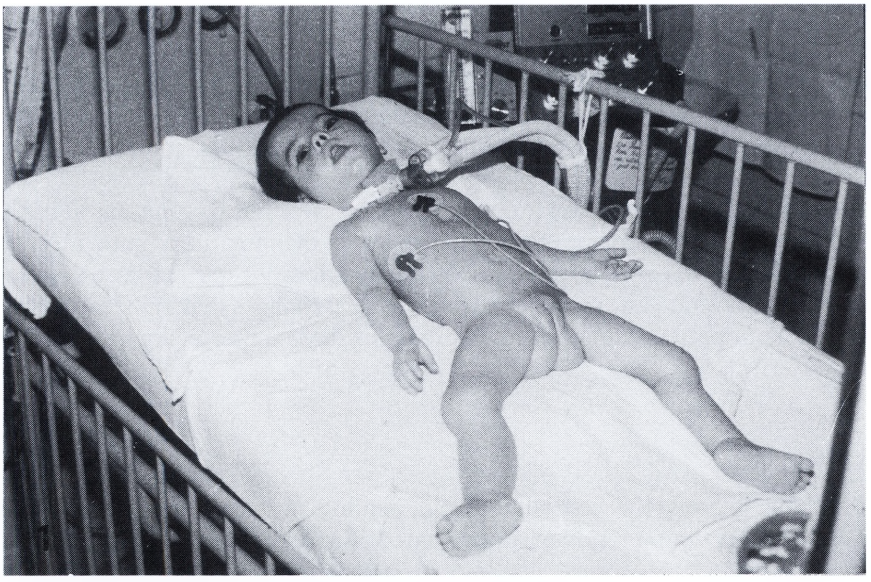

Fig. 1. A proposita, aged 10 months. Note generalized muscular weakness and facial diplegia with a tent-showed mouth.

Material and Methods

The left rectus femoris muscle was biopsied. Serial frozen sections were submitted to routine histochemical stains according to Dubowitz and Brooke [10]. Small pieces were fixed for electron microscopy. Spurr-embedded semithin sections were stained with toluidine blue. Ultrathin sections were examined by JEM 7 electron microscopy.

Results

Cryostat-section stained HE showed variable fibre size and the presence of a number of small, round or polygonal-shaped muscle fibres measuring 3–8 μm in diameter. A larger fibres of 10–12 μm diameter in size were scattered among of others. Many muscle fibres had central nuclei. Fibre splitting, necrosis or degeneration were not observed. There was no interstitial or endomysial fibrosis. In sections stained for Gomoritrichrome numerous dark-red granules were identified in many fibres (Fig. 2).

The rod structures were also easily identified in the electron microscope. They were frequently of rectangular shape and were seen in a small as well as in normal sized muscle fibres (Fig. 3). The rods had a longitudinal periodicity of 10 μm and transverse periodicity of 15–19 μm. Nemaline material also appeared in the form of compact bodies of irregular shape. All these bodies had periodicity characteristic of nemaline rods. Numerous rod containing fibres showed disorganization and loss of myofilaments (Fig. 4). In addition to the intracytoplamic nemaline structures there were a number of muscle cells with fetal muscle characteristics. Numerous muscle cells had round shape, small diameter and central nuclei (Fig. 5). The cluster of two, three cells in different stage of maturation within a common basal lamina were also seen (Fig. 5).

An increased number of satellite cells in close connection with a small muscle fibres was noted. In addition intramuscular nerves showed a great number of unmyelinated fibres (Fig. 6). Some of them were arranged in multiaxonal bundles within a single Schwann cell (Fig. 7). There were also premyelin fibres as well as myelinated fibres whose myelin sheaths were to thin in relation to their axonal diameter.

Discussion

Severe hypotonia, delayed motor development, generalized muscle weakness and respiratory insufficiency are characteristic clinical findings in our infant. This clinical picture is similar to those which have been described in neonates with severe congenital neuromuscular disorders including neonatal myotonic dystrophy [11–13], X-linked myotubular myopathy [14,15], acute form of infantile spinal muscular atrophy [16,17], indicating diagnostic difficulties in the neonatal period. The typical rods that are present in our infant's muscle indicate nemaline myopathy. Since most of the cases with nemaline myopathy represent mild muscle weakness and minimal muscle pathology [1–3] presented case demonstrates severe involvement of the muscle with feature of muscle and intramuscular nerve

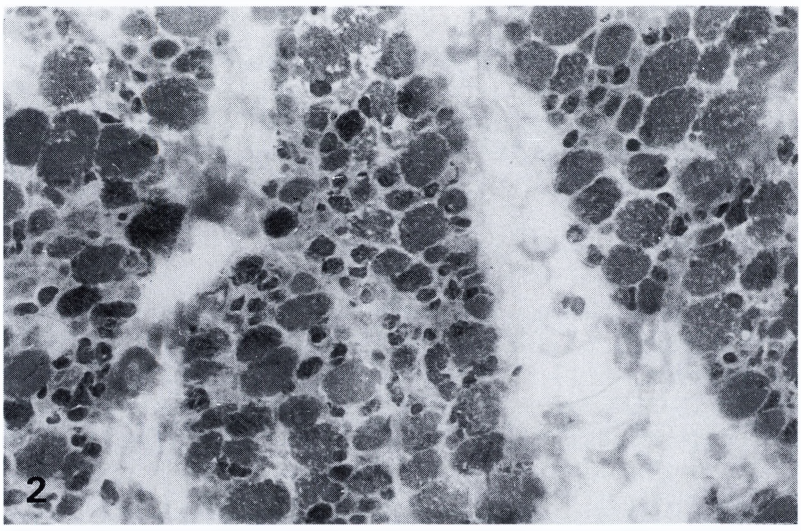

Fig. 2. Quadriceps femoris muscle. Variation in the size of fibres diameter with numerous very small muscle fibres both contain small granules. Trichrom × 448.

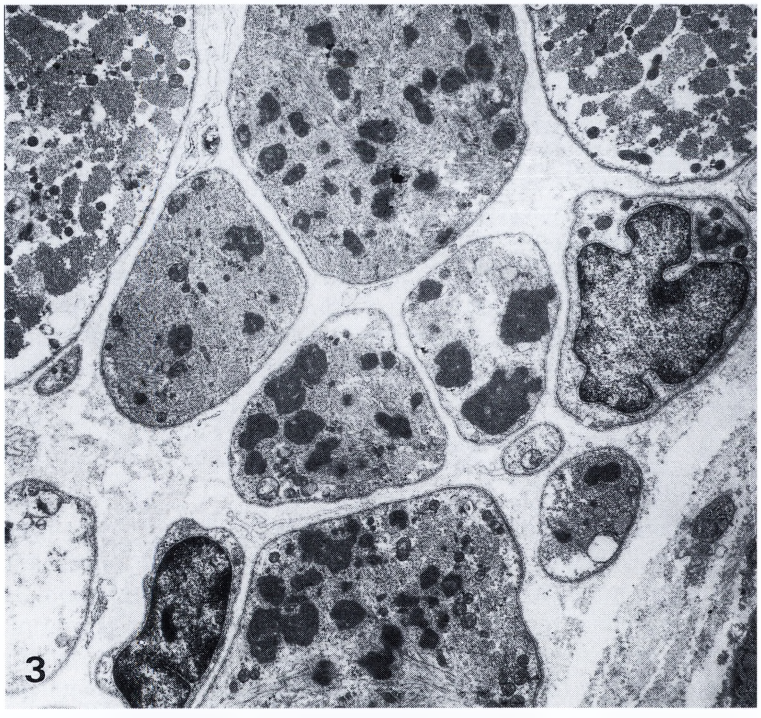

Fig. 3. Small as well as normal in diameter muscle fibres reveal nemaline structures. Mag. × 6800.

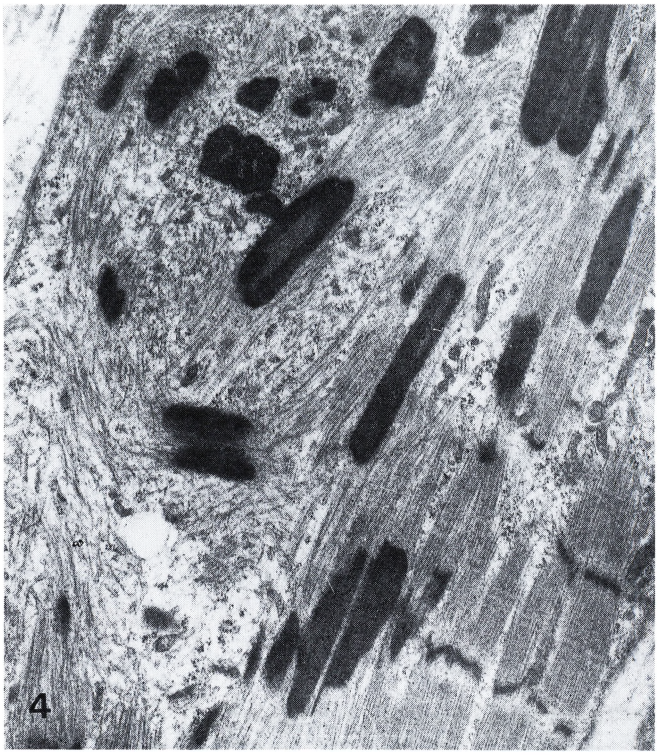

Fig. 4. Disorganization of myofibrils of some muscle fibre containing rod structures. Mag. × 8000.

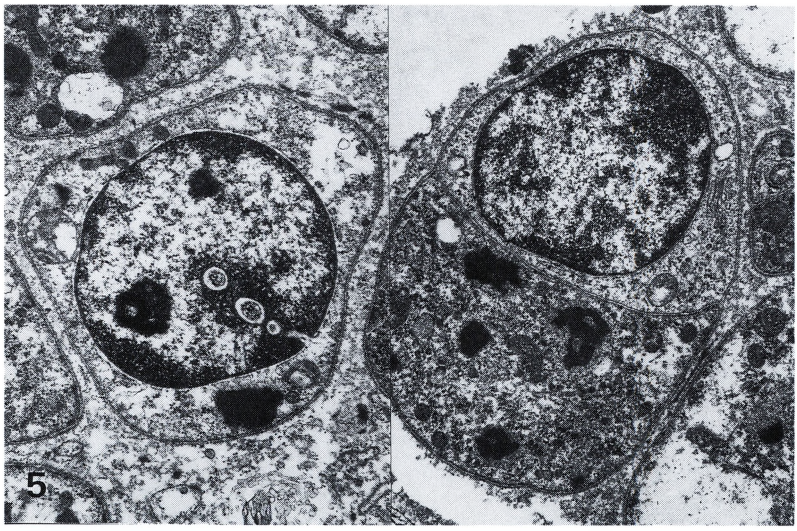

Fig. 5. Fetal appearence of small muscle cells. Mag. × 9000.

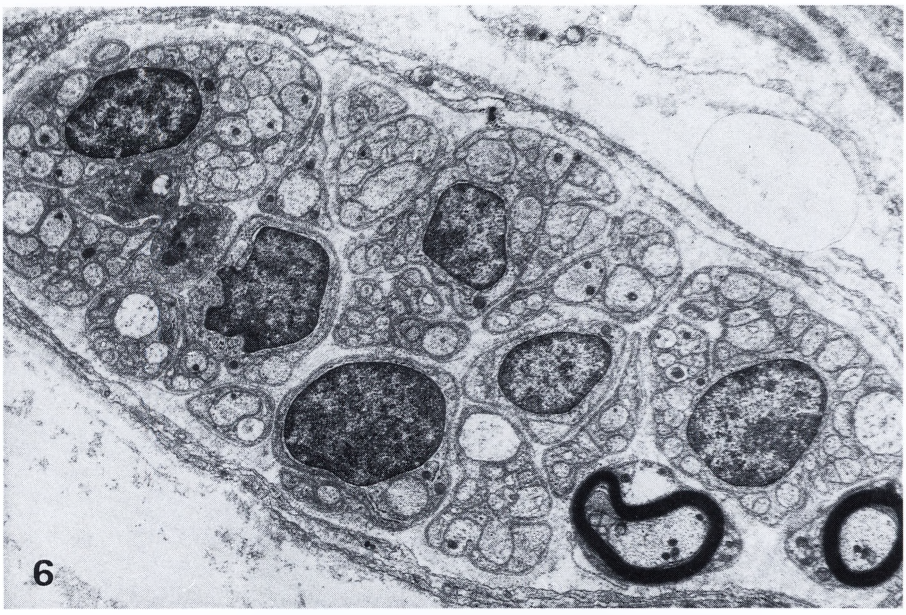

Fig. 6. Intramuscular nerve contain numerous multiaxonal nerve fibres. Mag. × 6800.

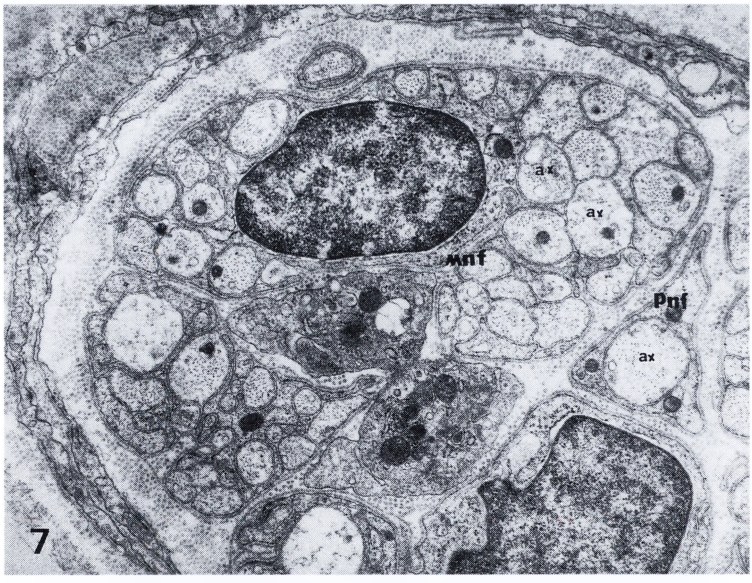

Fig. 7. Multiaxonal nerve fibre (Mnf) and premyelin nerve fibre (Pnf). Mag. × 11 600.

immaturity. The rods presented in the muscle of our infant show a crystaline structure with characteristic periodic pattern. The appearence of nemaline structures on electron microscopy is similar to the original observation by Cohnen et

al.[2] and Shy et al.[1]. In many muscle fibres instead of major rods there were structures which may represent develomentally imcomplete stages of the rods. One distinctive picture of our case is the feature of muscle cell as well as peripheral nerve immaturity. The presence of myotube-like cells, muscle cell in cluster and numerous satellite cells are characteristic feature of human fetal muscle of 16–20 weeks of gestation[18,19] and are not present in normal muscle after birth. In particular, the presence of multiaxonal bundles as well as premyelin fibres in intramuscular nerves without evidence of demyelination are inriguing findings. The characteristic appearence of intramuscular nerves such as axons of small diameter and their arrangement as well as their number[12–26] within one Schwann cell have never been observed in the muscle of healthy newborn, although it is a common feature of fetal nerves[20]. The presence of such immature intramuscular nerves as well as immature muscle fibres in our patient suggest failure in the peripheral motoneuron maturation. Reports of such severe weakness in the neonate with nemaline myopathy are rare. There were described twelve cases with nemaline myopathy, respiratory insufficiency and death within the first year[4–9,21,22]. Tsujihata et al.[8] were the first to evoke immaturity of muscle fibres in neonatal form of nemaline myopathy. A delay in muscle fibres maturation was also described in a 2-year-old child with nemaline myopathy[23]. Fetal muscle characteristics were also found in affected neonate with nemaline myopathy whom muscle biopsy was performed at 3 weeks of age[9], but there was no evidence of intramuscular nerve immaturity.

All these findings as well as the feature of intramuscular nerves immaturity may be a morphological clue of the etiology of severe muscular hyptrophy in infant with neonatal form of nemaline myopathy.

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