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Case report

Congenital neuromuscular disease with uniform type-1 fibers, presenting early stage dystrophic muscle pathology

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Abstract

We report two male siblings presenting with severe hypotonia, generalized muscle atrophy, multiple joint contractures and respiratory failure. The serum creatine kinase levels were within normal limits, 75 IU/l in the younger boy and 123 IU/l in the older one. Muscle biopsies at the age of 28 days in the younger boy and 48 days in the older one revealed dystrophic pathology with increased interstitial fibrous tissue, scattered basophilic fibers and an increased number of undeveloped type-2C fibers. Although the elder brother died from respiratory failure at 4 months of age, the younger child has been sustained with mechanical ventilation, and has been exhibiting non-progressive muscle symptoms. Upon re-biopsy of the younger sibling at the age of 3 years, neither basophilic regenerating fibers nor degenerating fibers were found. All muscle fibers were found to be extremely atrophic and behaved mostly like type-1 fibers, displaying the features of congenital neuromuscular disease with uniform type-1 fibers. Since early biopsies in congenital myopathies reveal numerous undifferentiated immature muscle fibers, it is difficult to make a definite diagnosis, unless we recognize disease-specific cytoplastic abnormalities of nemaline body formation and abnormalities of core structure.

Keywords: Congenital neuromuscular disease with uniform type-1 fiber; Muscular dystrophy; Immature type-2C fibers; Re-biopsy

1. Introduction

Although congenital non-progressive myopathies and congenital muscular dystrophies (CMD) are distinct diseases classified according to clinical course and muscle pathology, differential diagnosis is sometimes difficult in the early stages.

In this report, we present two siblings who exhibited non-progressive hypotonia since birth. In the younger sibling, muscle histology differed between early infancy and early childhood. The biopsies in early infancy showed a dystrophic pathology, whereas re-biopsy in early childhood revealed abnormal fiber distribution of uniform type-1 fibers. We report these cases because, although there have been past reports of congenital myopathies with pathologic transformation [1,2], the CMD phenomenon appears to be quite rare.

2. Patients

The brothers (Fig. 1), 2 years apart in age, were hospitalized in Oita University Hospital during their respective neonatal periods. Their father was healthy, but their mother suffered from symptomatic localization-related epilepsy and took phenytoin during both pregnancies. The parents did not show myopathic face, bald head, cataract and percussion myotonia, and their serum creatine kinase (CK) levels were both within the normal range. No relatives were known to have or have had neuromuscular diseases. The mother reported little fetal movement, but the serum levels of folic acid and alpha-fetoprotein were not examined. Both siblings were delivered at term by cesarean section due to of fetal distress. The elder brother weighed 2810 g and the younger brother weighed 3372 g at birth. They were

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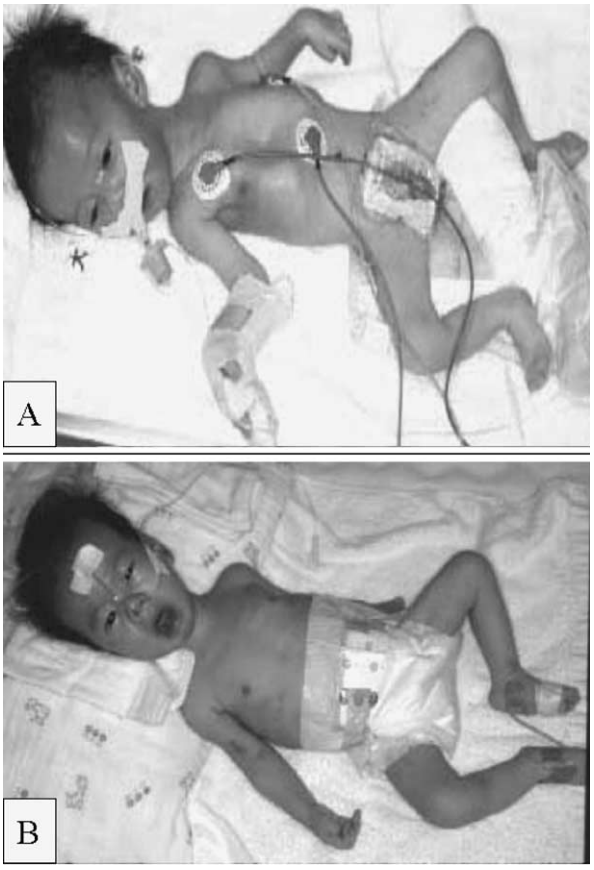

Fig. 1. Patient photographs: (A) elder brother; (B) younger brother. Both exhibited severe hypotonia, feeble crying, and difficulties with feeding and respiration from birth. Physical examination revealed frog posture, generalized muscle atrophy, masked face, open mouth and multiple joint contractures. These photographs are presented for academic use only with their parents' informed consent.

severely hypotonic, exhibited feeble crying, and had feeding and respiratory difficulties. Both required tube feeding and assisted ventilation in early infancy. Physical examination revealed frog posture, generalized muscle atrophy, masked face, open mouth, and multiple joint contractures (hand, finger and knee joints). Deep tendon reflexes were reduced.

The elder child could never acquire head control and died from respiratory failure at 4 months of age. The younger is now 5 years old. He has developed slowly and steadily, and his muscle weakness is stable and non-progressive. Now he can smile and move his hands and legs voluntarily in accordance with music and instructions.

3. Laboratory data

No gross chromosomal abnormalities were observed; both children were 46XY. Routine blood and urine chemistry were within normal ranges. During the neonatal period, the CK level of the elder child was 123 IU/l, while that of the younger was 75 IU/l. Folic acid levels were also within the normal range in both children. Electromyograms revealed evidence of myopathic alternation and low amplitude pattern, less than 500 μV. Both motor and sensory nerve conduction velocities were within the normal range, 30–40 ms. Head MRIs revealed normal myelination without white-matter lucency.

4. Muscle biopsies and histological findings

We studied the muscle biopsies taken form the left quadriceps femoris on days 48 and 28 after the birth of the elder [3] and younger child (Fig. 2A and B), respectively. Both showed dystrophic changes. There was marked variation in fiber size, with fibers ranging between 10 and 40 μm in diameter. Also seen were basophilic regenerating fibers, but with no apparent necrotic fibers. There were an increased number of type-2C fibers: the 2C fibers comprised 45% of the total muscle fibers in the elder and 12% in

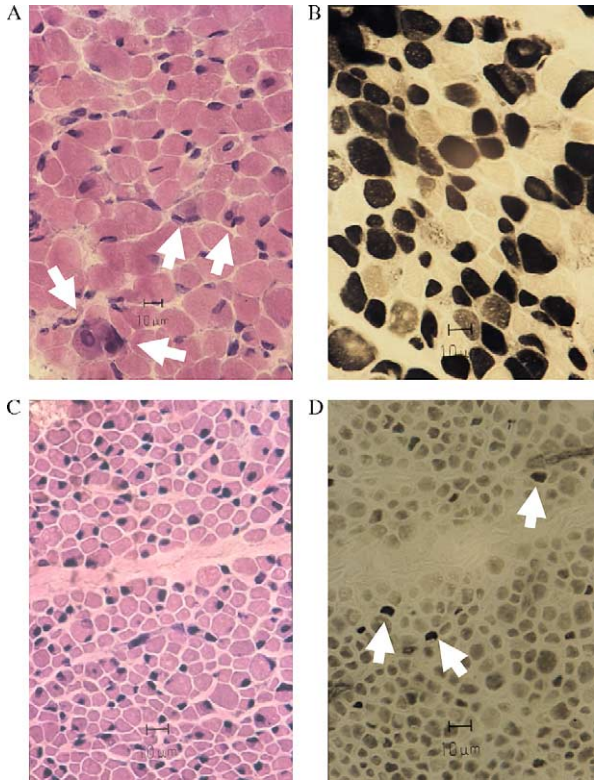

Fig. 2. Muscle histology of the younger brother. (A) and (B): 1 month old; (C) and (D): 3 years old. (A) and (C): HE; (B) and (D): routine ATPase (pH 9.4). A scale of 10 μm is drawn in all figures. One month old: (A) there was marked variation in fiber size, with fibers ranging between 10 and 40 μm in diameter. Also seen were basophilic regenerating fibers (arrow), but apparently no necrotic fibers. (B) There was an increased number of type-2C fibers (gray-colored staining), which comprised 12% of the total fibers. Three years old: (C) there were neither basophilic regenerating fibers nor degenerating fibers. All muscle fibers were atrophic, mostly measuring 10 μm in diameter. (D) Except for a few scattered type-2 fibers (arrow), most behaved like type-1 fibers.