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Case Report

Peripheral nerve pathology at fixed stage in spinal muscular atrophy with respiratory distress type 1

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Abstract

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is characterized by severe respiratory failure due to diaphragmatic paralysis and distal muscular weakness in early infancy. After an initial decline in respiratory state and motor function until 1–2 years of age, residual capabilities reach a plateau.

We report the peripheral neuropathological findings of a patient with SMARD1 at 1 year and 1 month of age, when his muscle strength and respiratory symptoms had deteriorated and then stabilized for several months. Peripheral nerve biopsy revealed severely progressed axonal degeneration. This finding suggests the rapid progression of peripheral axonal neuropathy in SMARD1 that leads to its characteristic clinical course of respiratory failure and paralysis in the early infantile period.

Keywords: Spinal muscular atrophy with respiratory distress type 1 (SMARD1); Immunoglobulin helicase μ-binding protein 2 (IGHMBP2); Axonal degeneration; Neuropathological findings

1. Introduction

Spinal muscular atrophy with respiratory distress type 1 (SMARD1, OMIM #604320) is a rare autosomal recessive neuromuscular disease characterized by early-onset severe respiratory distress due to diaphragmatic palsy and distal muscular weakness. Presenting symptoms are intrauterine growth retardation (IUGR), prematurity, foot deformities, hypotonia, areflexia, autonomic nervous system dysfunction, and severe respiratory failure requiring permanent mechanical ventilation [1]. Rapid worsening of the respiratory state and motor function are usually seen in infancy, and residual capabilities plateau after 1–2 years [2]. The clinical symptoms of SMARD1 are different from SMA in that SMA shows proximal muscular weakness and gradual intercostal muscular atrophy in contrast SMARD1 shows lower limb dominant distal muscle weakness and sudden respiratory failure due to diaphragmatic palsy.

SMARD1 is caused by IGHMBP2 gene mutation [3], but its molecular mechanism in the pathology is unclear. The peripheral neuropathology of SMARD1 presents as axonal degeneration [4], which is limited to the disease onset period of 2–6 months. We report the peripheral

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neuropathological findings of severely progressed axonal degeneration in a SMARD1 patient at 1 year and 1 month of age, when his muscle strength and respiratory symptoms had already deteriorated and then stabilized for several months.

2. Case report

A male patient presented with iIUGR after 36 gestational weeks. He was born at 39 gestational weeks with a birth weight of 2156 g and head circumference of 32.5 cm. He had hypotonia, weak cry, and talipes equinovarus since birth. He had normal pursuit at 1 month and facial expression change at 4 months, but could not hold his head up at 4 months. His oral feeding and weight gain were favorable. He was admitted to our hospital with acute respiratory failure due to respiratory infection, and mechanical ventilation was initiated at 4 months. Despite respiratory distress, chest retractions were absent. Physical examination showed generalized hypotonia, areflexia of the lower extremities, talipes equinovarus, and mild talipes cavus. Deep tendon reflexes of the upper extremities were weakly seen but disappeared at 6 months. He could hold his upper limbs and move his lower limbs slightly in the extension position. Subcutaneous fat of the palm, forearm, thigh, and calves became prominent. Excessive sweating and tachycardia were seen after 6 months. Although non-invasive positive pressure ventilation was attempted after extubation, maintenance was difficult. He underwent tracheostomy at 8 months, and home mechanical ventilation was continued.

Nerve conduction studies at 5 months showed decreased compound muscle action potential and motor conduction velocities in the upper extremities (median nerve; CMAP 1.22 mV, MCV 26.2 m/s (mean ± SD; CMAP 4.8 ± 1.1 mV, MCV 37.0 ± 4.4 m/s [5]), ulnar nerve; CMAP 1.75 mV, MCV 25.1 m/s (mean ± SD; CMAP 6.6 ± 1.7 mV, MCV 40.5 ± 4.2 m/s [5])). No electrophysiological response was elicited in the lower extremities. Sensory conduction velocities (SCV) were not detected in both upper and lower extremities. After 7 months, electrophysiological response was not detected in the upper and lower extremities. Electromyography revealed a neurogenic pattern in the lower extremities. Brain magnetic resonance imaging (MRI) at 4 months of age showed a decrease in white matter volume (Fig. 1) which were similar to those reported previously [6]. Spinal MRI showed normal construction.

Sural nerve biopsy was performed at 1 year and 1 month. The density and diameter of myelinated fibers were decreased and interstitial collagen tissue was increased (Fig. 2). Axons were deformed and atrophied (Fig. 3A). Unmyelinated fibers were preserved, although some myelinated fibers turned to very thin myelin components. Some unmyelinated fibers were surrounded by

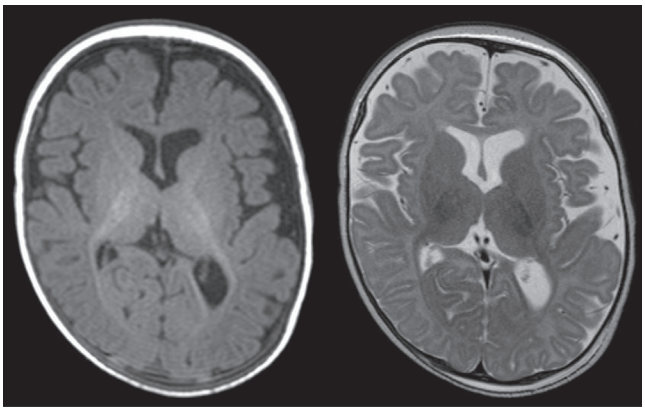

Fig. 1. Brain magnetic resonance imaging at 4 months of age (left: T1 weighted image, right: T2 weighted image). White matter volume is moderately decreased.

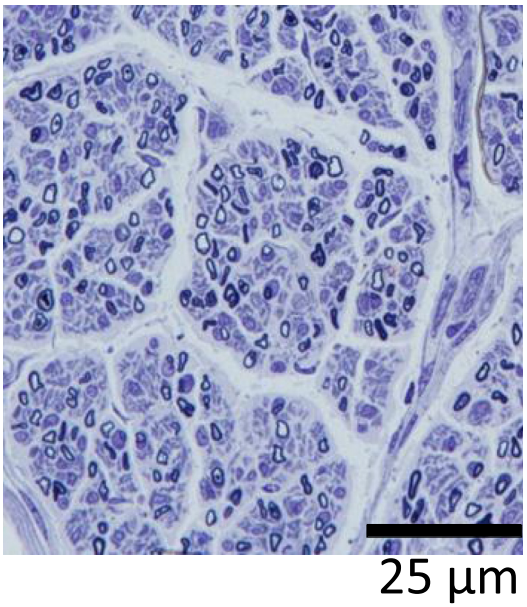

Fig. 2. Light micrographs of the sural nerve biopsy. Epon-embedded semi-thin section stained with toluidine blue. Density and diameter of myelinated fibers are decreased. Scale bar: 25 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

layered Schwann cell cytoplasm, forming pseudo-onion bulb structures (Fig. 3B). A gastrocnemius muscle biopsy showed neurogenic muscular fiber atrophy with fiber-type grouping.

Genetic screening for hereditary peripheral neuropathy in the patient and his parents was conducted. A compound heterozygous mutation of the IGHMBP2 gene (c826C > T, p.Gln276* and c.1702C > T, p.Gln568*; both of these were novel nonsense variants) was identified.

After 8 months, his respiratory condition and muscular strength were stable on home care. He had various facial expressions and responded to his name at 1 year and 4 months (Fig. 4).

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