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Case Report

Patient with spinal muscular atrophy with respiratory distress type 1 presenting initially with hypertonia

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Abstract

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare autosomal recessive neuromuscular disorder caused by mutations in the *IGHMBP2* gene and characterized by life-threatening respiratory distress due to irreversible diaphragmatic paralysis between 6 weeks and 6 months of age. In this study, we describe a two-month-old boy who presented with hypertonia at first and developed to hypotonia progressively, which was in contrast to the manifestations reported previously. Bone tissue compromise was also observed as one of the unique symptoms. Muscle biopsy indicated mild myogenic changes. He was misdiagnosed until genetic screening to be confirmed as SMARD1. SMARD1 is a clinical heterogeneous disease and this case broadens our perception of its phenotypes.

Keywords: Spinal muscular atrophy with respiratory distress type 1 (SMARD1); *IGHMBP2*; Diaphragmatic paralysis; Hypertonia; Bone tissue compromise

1. Introduction

SMARD1 is a rare autosomal recessive neuromuscular disease characterized by degeneration of anterior horn α-motoneurons and manifested as irreversible diaphragmatic paralysis, respiratory failure as well as progressive symmetrical muscular weakness, predominantly in the distal lower limbs, and muscle atrophy between 6 weeks and 6 months of age [1,2]. It is caused by mutations in the *IGHMBP2* gene located on chromosome 11q13.3 and encodes the immunoglobulin μ-binding protein 2 (IGHMBP2) [3]. IGHMBP2 is ubiquitously expressed [4] and has a cell-type-specific phenotype with motoneurons and myocytes being predominantly affected, although the exact pathomechanism remains unknown [5].

Here we report the first case of SMARD1 with a compound heterozygous mutation of *IGHMBP2* gene in a Chinese boy, who presented with hypertonia as the initial manifestation. Later he developed bone tissue compromise, which symptom was not seen previously.

2. Case report

This boy, the first child of healthy unrelated parents, was born at the gestational age of 37^{+4} weeks by

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Cesarean section because of oligohydramnios. His family history was unremarkable and no decrease in fetal movement was reported. The Apgar score was 10 at the time and his birth weight was 1770 g, below the 3rd percentile.

At two months of age, he was admitted to the hospital with a 10-day history of a weak cry and stiffness of four limbs. On admission, his weight was 3700 g, less than the 3rd percentile of his age. Physical examination showed that he was malnutritioned, afebrile with normal vital signs, alert but with poor reaction. Pectus excavatum was observed as well as marked hypertonia of four limbs and few spontaneous movements, more evident in the legs. He can move both of his upper arms and shoulders but not the hands. His thighs can be lifted a little bit away from the bed while feet cannot. Fatty pads on the proximal phalanges and the calves together with contractures of the elbows and ankles can be noticed (Fig. 1A–B). Deep tendon reflexes were absent and he seemed to be insensitive to pain stimulation on the legs. However, the cranial nerves were not involved except for mild tongue fasciculation.

On the 6th day after admission, this boy developed tachypnea and acute cyanosis without any obvious causes. Tracheal intubation and artificial ventilation was soon necessary.

For investigation, the blood tests and metabolic screening of urine were normal. A chest X-ray revealed the eventration of the right hemi-diaphragm (Fig. 2A), indicating diaphragmatic paralysis. Despite this, thinning of the cortical bone and loosening of the trabecular bone on the upper limbs can also be noticed (Fig. 2A). Muscle biopsy was undertaken. Hematoxylin and eosin (H&E) staining identified a wide variation in fiber sizes and a large quantity of scattered atrophy muscle fibers, as well as hypercontracted fibers (Fig. 3A), in conjunction with changes showed in other stainings, indicating mild myogenic changes.

Over the next month, his muscle tone decreased progressively. However, he developed signs of weakness and wasting of muscles diffusely, particularly in the lower limbs with frog-like posture. Subsequently, few antigravity movements can be seen while he even cannot lift his arms or move his legs. Episodes of excessive sweating and urinary retention were also exhibited during his clinical course.

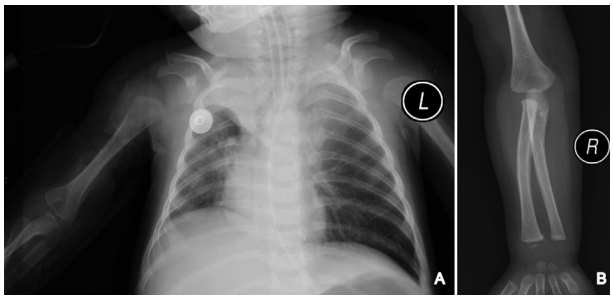

Fig. 2. (A) Chest radiograph of our patient showing eventration of the right hemi-diaphragm, indicating diaphragmatic paralysis. X ray of the right upper limb showing thinning of the cortical bone and loosening of the trabecular bone. (B) The normal X ray of the right upper limb of the boy at the same age (2 months old).

At the age of four months, genetic screening related to the neuromuscular diseases was done. A compound heterozygous mutation in the *IGHMBP2* gene was identified (Allele 1: a novel frame shift mutation, c.48delG, p.Leu17Trpfs*21; Allele 2: a novel missense mutation, c.1730T > G, p.Leu577Arg). Therefore, the diagnosis of SMARD1 was confirmed.

At one year old, the X-ray of lower limbs reported decreasing of the muscle bulk and hyperplasia of the interstitial tissue, associated with the osteoporosis of the tibia with thinning of the cortical bone and loosening of the trabecular bone (Fig. 1C), just the same as upper limbs. The biochemical values including parathyroid hormone, osteocalcin, alkaline phosphatase level were normal, while the only altered variables were slightly deficiency of Vitamin D and slightly elevated of serum phosphate.

As time went by, multiple attempts were tried to wean him off the ventilator, but remained unsuccessful. At his age of 1.2, the boy died of complications of sepsis and post mortem examination was declined.

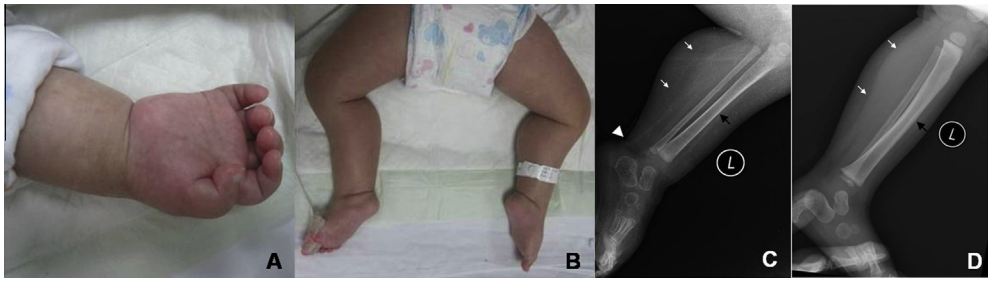

Fig. 1. (A) Fatty pads on the proximal phalanges with finger flexors contractures. (B) Frog-like posture with contractures of the ankles and fatty pads of the calf muscles. (C) X ray of the left lower limb showing thinning of the cortical bone and loosening of the trabecular bone (black arrow), atrophy of the calf muscle, interstitial hyperplasia to form the fatty pad (white arrow), and the contracture of the ankle (arrowhead). (D) The normal X-ray of the left lower limb of the boy at the same age (1 year old).