Brain & Development 38 (2016) 685–689

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Infantile spinal muscular atrophy with respiratory distress type I presenting without respiratory involvement: Novel mutations and review of the literature

Xinghua Luan [a,1], Xiaojun Huang [b,1], Xiaoli Liu [a], Haiyan Zhou [a], Shengdi Chen [a,*], Li Cao [a,*]

[a] *Department of Neurology and Institute of Neurology, Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai, China*
[b] *Department of Neurology and Institute of Neurology, Ruijin Hospital North Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Received 24 December 2015; received in revised form 31 January 2016; accepted 1 February 2016

Abstract

Spinal muscular atrophy with respiratory distress type 1 (SMARD1), also known as distal spinal muscular atrophy 1 (DSMA1) or distal hereditary motor neuropathies type 6 (dHMN6), is a rare autosomal recessive motor neuron disorder that affects infants and is characterized by diaphragmatic palsy, distal muscular weakness and muscle atrophy. The disease is caused by mutations in the gene encoding immunoglobulinm-binding protein 2 (*IGHMBP2*). We present a female child with novel compound heterozygous mutations in *IGHMBP2* gene c.344C>T (p.115T>M) and c.1737C>A (p.579F>L), displaying distal limbs weakness and atrophy without signs of diaphragmatic palsy or respiratory insufficiency. We review 20 reported SMARD1 cases that have no respiratory involvement or have late onsets. We propose that *IGHMBP2* gene mutations are characterized by significant phenotypic heterogeneity. Diaphragmatic palsy and respiratory distress may be absent and SMARD1 should be considered in infantile with the onset of peripheral neuropathies.

Keywords: Spinal muscular atrophy with respiratory distress type 1 (SMARD1); *IGHMBP2*; Diaphragmatic palsy; Respiratory involvement; Peripheral neuropathy

1. Introduction

Spinal muscular atrophy with respiratory distress (SMARD1) is a rare autosomal recessive motor neuron disorder. It was recognized as a separate clinical entity in 1996 and also classified as distal spinal muscular atrophy 1 (DSMA1) and distal hereditary motor neuropathies type 6 (dHMN6). Since then, about 60 cases have been described [1]. The underlying mutation was identified in the gene which encodes the immunoglobulin-binding protein 2 on chromosome 11q13.3 in 2001. SMARD1 is characterized by progressive length-dependent weakness with diaphragmatic palsy resulting in severe respiratory failure within the first year of life [2]. Apart from classic infantile

* Corresponding author at: Department of Neurology and Institute of Neurology, Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine, No. 197, Rui Jin Er Road, Shanghai 200025, China.
E-mail addresses: chen_sd@medmail.com.cn (S. Chen), caoli2000@yeah.net (L. Cao).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.braindev.2016.02.001
0387-7604/

presentation, there have been a few reports of unusual cases with late onset of diaphragmatic palsy or absence of respiratory involvement [3–6].

Here, we present the clinical, pathological and mutational characteristics of a Chinese female child with SMARD1 carrying two novel compound heterozygous mutations in *IGHMBP2*. She suffered distal limbs weakness and atrophy from 4 months of age without signs of diaphragmatic palsy or respiratory distress up to 54 months.

2. Case report

This girl, who had non-consanguineous parents of Chinese origin, was born at term by normal vaginal delivery after an uneventful pregnancy. No decrease in foetal movement was reported. Family history was negative for neuromuscular disorders. At 4 months of age, bilateral foot drop was noted. She was hospitalized at 6 months. CK values, routine laboratory investigations, tandem mass spectrometry of fatty acids were normal. She underwent electrophysiological test that showed reduced or absent compound muscle action potential (CMAP) and markedly reduced motor nerve conduction velocities (MCVs) of distal lower limbs, while the sensory nerve action potential (SNAP) and sensory nerve conduction velocities (SCVs) were slightly reduced.

The results of electromyogram (EMG) showed fibrillation and positive sharp waves at rest on gastrocnemius and tibialis anterior. Genetic analysis for survival motor neuron (SMN) gene deletion was negative. At 11 months, the lower limbs atrophy was noticed. Spinal cord magnetic resonance imaging and mitofusin 2 (MFN2) gene test were normal. Then she was treated with kinds of rehabilitation training and could walk by herself after a year and a half, wearing the ankle foot orthosis (AFO).

At 25 months, she was referred to our hospital. Upon evaluation, it was found that she had weakness in gastrocnemius (3/5 on a medical research council scale, graded 0–5), tibialis anterior (1/5), and both distal upper limbs mildly involved (−5/5). Furthermore, hypomyotonia, atrophy of the distal lower limb muscles and scoliosis were noted. Achilles tendon reflexes were absent. From the age of three and a half years, she could not walk without support. Until now (four and a half years), neither respiratory distress nor pneumonia was reported. Chest radiography failed to show diaphragmatic paralysis. Sural nerve biopsies showed a reduction of the larger myelinated fibers, especially those with a large diameter and a thick myelin sheath (Fig. 1A). Meanwhile, different stages of axonal degeneration and atrophy were observed (Fig. 1B). Whole exome sequencing (Shanghai Genesky Biotechnologies Inc.) revealed two novel compound heterozygous mutations in the *IGHMBP2* exon3 c.344C>T (p.115T>M) and exon12 c.1737C>A (p.579F>L). Direct PCR sequencing of *IGHMBP2* gene revealed that her father is a heterozygous carrier for the mutation c.1737C>A (p.579F>L)

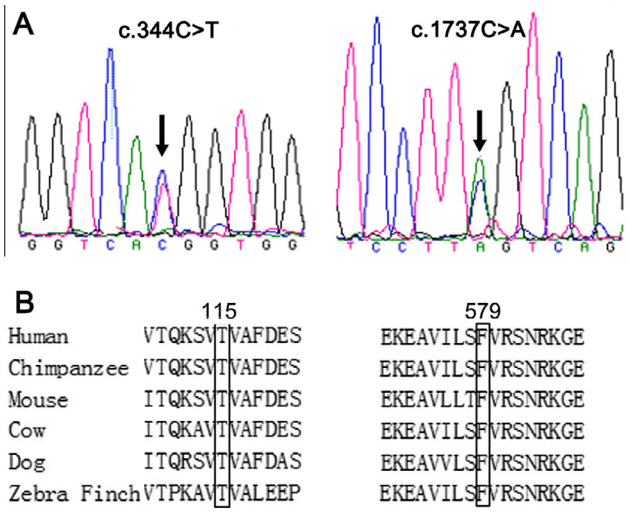

Fig. 2. Exome sequencing result (A). Two novel compound heterozygous mutations in the IGHMBP2 exon3 c.344C>T and exon 12 c.1737C>A were found. p.115T and p.579F are highly conserved between different species (B).

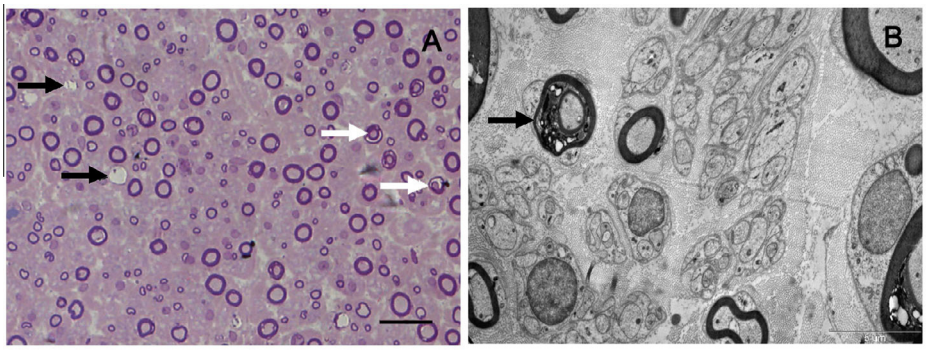

Fig. 1. The semithin section (A) shows reduction of larger myelinated fibers, axonal atrophy (white arrow) and later stage of axonal degeneration appearing vacuole because of the axonal and myelin debris loss (black arrow). Scale bar = 20 μm. Myelin debris and axonal atrophy (B). Scale bar = 5 μm.