Distal Spinal Muscular Atrophy: An Overlooked Etiology of Weaning Failure in Children with Respiratory Insufficiency

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Abstract

Keywords

- respiratory insufficiency
- spinal muscular atrophy
- diaphragmatic paralysis

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare autosomal recessive neuromuscular disorder that involves the anterior horn motor neurons. It is a disease with a poor prognosis presenting with progressive distal motor weakness and respiratory insufficiency from diaphragmatic paralysis followed by distal muscle weakness before 6 months of age. With the intent to spread the awareness of this rare and life-threatening disease, we report a 2.5-month-old female infant with a subsequent diagnosis of SMARD1, who was admitted in our pediatric intensive care unit with chief complaint of progressive respiratory distress and poor feeding.

Case History

A 2.5-month-old female infant was referred to Bahrami Children's Hospital in October, 2016, due to poor feeding and respiratory distress.

On admission to the hospital, she was immediately intubated for severe cyanosis and gasping and then immediately transferred to the pediatric intensive care unit (PICU). Birth history revealed that she was delivered at a gestational age of 36 weeks by cesarean section for breech position. Her birth weight was 1,600 g and her head circumference was 30 cm. Her mother was a 32-year-old lady who was completely healthy. She was born in good condition, without history of a neonatal period admission. Two weeks earlier, she was admitted to the PICU for 3 days for a short apneic episode and poor feeding that did not continue during her admission. She was discharged in good condition with a presumed diagnosis of gastroesophageal reflux disease. Her parents

were first cousins. She had two siblings, an 8.5-year-old brother and a 5.5-year-old sister without any apparent disorder. She also had a 3-month-old brother with similar clinical symptoms who died 20 months ago. Unfortunately, diagnostic evaluation did not demonstrate any significant etiology for his death.

Primary physical examination in the PICU was as follows: her weight was 4.2 kg, head circumference was 34.5 cm, temperature was 37.2°C, and O₂ saturation was 97% while she was ventilated, heart rate was 140 beats per minute, and respiratory rate was 40 breaths per minute. Respiratory examination revealed fine diffuse crackles in right lung and mild decreased breath sounds in left lung. She was conscious with intact cranial nerve function. Extremities did not show any major deformity with normal deep tendon reflexes and normal tone. Remaining physical examination appeared to be normal.

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Primary laboratory data including cell blood count, C-reactive protein, and serum biochemistry were normal. Urinary toxicology screen was negative. Her cerebral spinal fluid (CSF) was normal and a bacterial blood culture was negative. Chest radiography showed right upper lobe atelectasis.

Her admission diagnosis was septicemia; so, appropriate antibiotic therapy was administered. During her hospital course, she experienced severe respiratory acidosis while trying to gradually wean her from ventilator support. Several attempts were made at weaning her from ventilator which were all unsuccessful. Tracheostomy was performed on the 35th day of her admission. To clarify the etiology of weaning failure in the patient, we performed fluoroscopy that showed bilateral diaphragmatic paralysis. Other diagnostic investigations such as brain ultrasonography, echocardiography, chest computed tomography (CT) scan, and metabolic screening were normal.

In the meantime, she developed distal involvement of both upper and lower extremities. Bilateral equinovarus deformity and Achilles contractures was evident in her feet while wrist drop in her hands developed later (→Fig. 1). Urinary retention was also another symptom during her primary admission clinical presentation. Tongue fasciculations were not evident. Electromyography (EMG) was normal, and due to lack of appropriate equipment, nerve conduction velocity (NCV) was not performed.

After 63 days of ICU admission, she experienced severe nosocomial infection that did not respond to appropriate antibiotic treatment and unfortunately died. Postmortem skin biopsy was performed and prepared for genetic analysis. DNA was extracted from skin biopsy cells. Direct DNA sequencing was done for all 15 exons as well as approxi-

mately 20 bases of flanking noncoding sequences of *IGHMBP2* gene. Finally, homozygote mutation in *IGHMBP2* gene, defined as c.257-1 G > T variation as seen in other cases of spinal muscular atrophy with respiratory distress type 1 (SMARD1), was revealed.¹

Discussion

Spinal muscular atrophy is a neuromuscular disorder with several diverse mutations of the survival motor neuron gene (SMN1). It is characterized clinically into four types; three types present in infancy or childhood. Of these three types, type 1 is the most common and severe known as Werdnig-Hoffmann disease.^{2,3} Patients with SMA type 1 are floppy, with symmetrical paralysis, proximal muscle weakness, and areflexia. This occurs prior to the respiratory insufficiency.⁴ SMARD1 is a different type of SMA in that occurrence of respiratory failure due to diaphragmatic paralysis precedes distal extremity weakness. The exact incidence of SMARD1 is not clear but it seems more than 60 patients have been described worldwide. The most important clinical finding in patients with SMARD1 is appearance of respiratory failure and ventilator dependency between 6 weeks and 6 months of age.⁴⁻⁸ Other clinical findings are intrauterine growth retardation, weak cry, prematurity, and decreased fetal movements.

Distal limb involvement, progressive hypotonia and hyporeflexia, finger contractures, and lower limb deformities are some other phenotypes that can be considered as SMARD1 clinical symptoms. These findings usually appear after respiratory insufficiency, as in our patient.^{4,8,9} Autonomic features are also well described in SMARD1. Urinary retention or incontinence, cardiac arrhythmias, constipation, and excessive sweating are some autonomic nervous system

Fig. 1 Equinovarus deformity and wrist drop in lower and upper extremity of the patient.

features described in this disorder.^{1,10–12} In our patient, urinary retention appeared late in the course of the disease.

Additionally, although generally believed that the respiratory insufficiency in patients with SMARD1 is due to diaphragmatic paralysis, there has been a report of a patient with diaphragmatic palsy and no signs of severe respiratory involvement.¹ Recent studies have shown the heterogeneity of clinical phenotypes in patients with similar *IGHMP2* gene mutation.^{13,14} The possibility of existence of variety of clinical findings in patients with SMARD1 necessitates further prospective studies with long-term follow-up. Due to severe respiratory involvement and subsequent wasting, patients with SMARD1 rarely survive after infancy. There are a few reports revealing SMARD1 patients with survival into the second decade of age.^{9,15,16}

IGHMBP2 is a unique gene that encodes the immunoglobulin mu-binding protein 2 on chromosome 11q13 and consists of 15 exons. *IGHMP2* acts as a 5'-3' RNA/DNA helicase and with loss of its function will lead to the prevention of DNA replication and hence protein production. This problem especially affects α -motor neurons of the brain stem and anterior horn of the spinal cord.^{11,17} Recent studies have shown some new de novo mutations in the X-linked *LAS1L* gene with a similar phenotype to SMARD1. It seems that both genes have a significant role in ribosomal maturation and biogenesis, which may be the possible pathogenic mechanism of the disorder.¹⁸ Due to the wide spectrum of heterogeneity of the mutation in the *IGHMBP2* gene, prenatal genetic counseling is much more complex. The clinical criteria of SMARD1 are still the most reliable tool in the establishment of diagnosis.¹⁹

Understanding the basic mechanism and pathophysiology of the disease is key in finding a possible treatment option for this disorder. Unfortunately, no effective treatment is currently available for SMARD1. Conservative treatment during admission periods is the mainstay of treatment. Nutritional support, physical, and occupational therapy are essential. Gene therapy and stem cell therapy represent promising sources of treatment for neurodegenerative disorders such as SMARD1. Gene therapy is focused on using adeno-associated virus vectors in the treatment of SMARD1 specifically. Other strategies, such as exon skipping with antisense oligonucleotides (AON), are unreliable because of the potential threat that they pose. Since the mutation in the *IGHMBP2* gene is in the fundamental helicase domain, so skipping the exon can harm the functional capacity of the gene.⁵ Insulin-like growth factor 1 (IGF1) and other neurotrophic factors also hold promise as a potential therapeutic option. Future studies are needed to define novel treatment strategies.^{20–22}

In conclusion, spinal muscular atrophy with respiratory distress type 1 is an unusual type of SMA with respiratory failure and an ominous prognosis. It is of the utmost importance for pediatric intensivists to keep this life-threatening diagnosis in mind in infants dying with undetermined respiratory illness, weaning failure, or sudden death. Accurate genetic counseling and prenatal diagnostic investigation can be performed for families with positive family history.

Conflict of Interest

None.

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