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Infantile-onset Spinal Muscular Atrophy with Respiratory Distress-1 diagnosed in twenty-year old man

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Abstract

Spinal muscular atrophy with respiratory distress (SMARD1) presents within the first thirteen months of age with low birth weight, progressive length dependent motor neuropathy, and respiratory failure from diaphragmatic paralysis. SMARD1 is caused by mutations in *IGHMBP2*, encoding the immunoglobulin μ -binding protein 2. Because of the severity of the disorder, many infantile-onset SMARD1 patients do not live past the first decade of life. This report documents the clinical course of a twenty-year old man diagnosed with SMARD1.

Keywords

SMARD1; IGHMBP2; neuromuscular degeneration mouse; motor neuron disease

INTRODUCTION

Spinal muscular atrophy with respiratory distress (SMARD1; MIM#604320) is a rare infantile neuromuscular disorder that presents with diaphragmatic paralysis and a length-dependent polyneuropathy [1, 2]. Also known as autosomal-recessive distal spinal muscular atrophy 1 or distal hereditary motor neuronopathy type 6, this disorder is caused by mutations in the *IGHMBP2* gene, which resides on chromosome 11q13.3 and encodes the immunoglobulin μ -binding protein 2 [3]. A member of the DEXDc DEAD-like superfamily of DNA/RNA helicases, *IGHMBP2* is thought to function in transcriptional activation and/or associates with pre-messenger RNA (mRNA) splicing complexes [4].

Initially described as an unusual variant of spinal muscular atrophy (SMA; MIM#600354), SMARD1 has now been recognized to have its own unique phenotype. Features include decreased fetal movements, oligohydramnios, low birth weight, distal muscular atrophy,

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foot/finger deformities, and diaphragmatic dysfunction resulting in the need for ventilation prior to 13 months of age [2, 5]. The numerous individuals reported with SMARD1 [2, 3, 5–14] presented in a fairly homogenous fashion. A similar phenotype is found in the neuromuscular degeneration (*nmd*) mouse, a spontaneously-generated model with mutations in *Ighmbp2*. These mice present with a motor neuron disease that is fatal by 3–4 months of age [15]. Interestingly, neuron-specific rescue of *Ighmbp2* expression revealed that *nmd* mice also exhibit a skeletal myopathy and dilated cardiomyopathy [4, 9, 16]. The cardiomyopathy has not been seen in humans to date. Most reported SMARD1 patients have been under the age of ten and so the disease course and prognosis for adolescence and young adulthood have not been documented. We present a recently diagnosed 20 year-old male with infantile-onset SMARD1 requiring ventilation since four months of age.

2. Case Report

A 20 year-old male of non-consanguineous parentage presented to the NIH Undiagnosed Diseases Program with a history of infantile-onset distal weakness, right hemi-diaphragmatic paralysis, and ventilator dependence. In childhood, he developed a length-dependent progressive sensory-motor neuropathy associated with loss of sensation, muscular denervation and atrophy. He has remained ventilator dependent since age 4 months and had no functional motor control except for facial expression, shoulder shrug, and internal/external rotation of his shoulders.

He was the product of the first pregnancy for his 35 year-old mother; gestation was notable for oligohydramnios and decreased fetal movements. Labor was spontaneous and without complications. Birth weight and length were less than the fifth percentile; while head circumference was at the thirtieth percentile. The child went home with his mother, but at 14 days he had an apneic episode that required hospitalization with continued home apnea monitoring after discharge. Feeds were difficult and continued apneic episodes resulted in another hospitalization at four months of age requiring intubation and ventilation. At that time, he was noted to have right hemi-diaphragmatic eventration and spent four months in the neonatal intensive care unit with continued deterioration of muscular function. During this time he had nerve conduction studies and electromyography documented “diffuse neuropathic changes.” A muscle biopsy showed “no diagnostic alteration.” Shortly after intubation, the patient underwent tracheostomy and gastrostomy-tube placement.

Normal studies, performed in childhood, included a karyotype, creatinine kinase, *SMN* gene analysis, alpha-glucosidase assay, mitochondrial DNA (mtDNA) for mutations including deletions and duplications, and measurement electron transport chain activity. The patient had mild-to-moderately elevated serum copper studies with normal ceruloplasmin. There was no evidence of Kayser-Fleischer rings on ophthalmological exam and copper levels have responded to zinc therapy. Serum carnitine was elevated on numerous occasions, but has resolved; muscle carnitine was normal. Whether any of these abnormalities represent physiologic elevations or were artifacts of nutritional supplementation is undetermined.

The medical course was been complicated. Pubarche was at 10–11 years of age. The patient had transient hyperthyroidism, which resolved without treatment. His parents have noted episodes of excessive sweating and hypertension of unknown etiology. Episodic tachycardia and/or bradycardia occurred during sleep. Echocardiograms and electrocardiograms, performed annually, were normal (with the exception of episodic tachy/bradycardia). The patient recently developed cholelithiasis associated with mildly elevated AST and ALT levels. Skeletal evaluation noted severe thoracic scoliosis. The patient was hospitalized twice since becoming ventilator-dependent. The first hospitalization occurred at 14-years of age and was due to persistent hypertension, neurogenic bladder, and reflux nephropathy

resulted in his persistent need for catheterization. The second hospitalization was at 19 years for streptococcal pneumonia associated with acute respiratory distress syndrome. This hospitalization lasted for one month and required chest tube placement for recurrent pneumothoraces.

Neurologically, the patient continued to have progressive distal-to-proximal weakness associated with fasciculation's; his deficits plateaued at his present motor abilities at 3–4 years of age. During this time, his parents noted he did not seem to react to pain or temperature changes. At eight years of age, repeat nerve conduction studies and electromyography showed “no response for motor or sensory conduction velocities, which represents a severe diffuse axonal sensory-motor neuropathic process.” He has never had a sural nerve biopsy. His cognitive ability has been difficult to assess due to his motor limitations and his only means of communication is with sounds representing yes or no answers. Battelle Developmental Inventory (2nd edition) revealed a moderate-severe level of cognitive dysfunction; however, his parents and caregivers have always felt his capabilities are more advanced than testing has shown. He has never had any regression or loss of cognitive ability. His parents had deferred further neuroimaging to address these cognitive issues and so whether this is an intrinsic part of SMARD1 or the result of a early anoxic injury is not able to be determined.

Examination revealed an awake and alert male with a pleasant, smiling disposition. He answered questions somewhat unreliably by making sounds for yes or no answers. He could follow one-step commands with some reliability, but could not follow two-step commands. He had mild facial diplegia. There were some tongue fasciculation's; otherwise, his cranial nerves were normal. He had decreased muscle bulk diffusely, most obvious in his hands and feet. Tone was flaccid throughout. Ankle and elbow contractures were present. He had trace movement with shoulder shrug and internal/external rotation of the shoulders. He had no neck control. Sensation was absent below the neck and he was areflexic throughout.

There are no other members of the family with SMARD1 or neurological disease. His 12 year-old brother has a history of a bicuspid aortic valve with moderate aortic insufficiency and mild learning difficulties. Genetic evaluation at twenty years revealed two SMARD1 mutations (c.1082 T>C, p.L361P; c.1144 G>A, p.E382K) that have been characterized in other patients [8]. His father and mother had appropriate heterozygosity at this locus.

3. Discussion

SMARD1 is an autosomal-recessive neuromuscular disorder due to mutations in *IGHMBP2*. This protein is thought to be involved in transcriptional activation and pre-mRNA processing [9, 15]. In most cases, alteration of *IGHMBP2* function results in infantile-onset of distal weakness and respiratory failure requiring ventilatory support, although some cases of juvenile-onset SMARD1 have been reported [10]. To date, most cases of infantile-onset SMARD1 have resulted in lethality in the first decade of life due to respiratory failure or complications associated with persistent ventilatory support. We report the recent diagnosis of a 20 year-old man with infantile-onset SMARD1. As this patient is the oldest reported patient with confirmed *IGHMBP2* mutations, it would be of some value to chronicle his disease course.

This patient's disease presentation was typical of many infantile-onset SMARD1 patients, with distal weakness and respiratory failure associated with diaphragmatic eventration at four months of age. Also typical was his development of disease-related complications including scoliosis, joint contractures, autonomic dysfunction (neurogenic bladder, episodic diaphoresis, hypertension, brady/tachycardia), motor neuronopathy, muscle atrophy and

weakness. Less common features of his course included his generalized lack of somatic sensation and absent sensory nerve responses on nerve conduction studies. The predominant feature noted in previous reports is a motor neuronopathy; however, similar sensory findings have been previously reported [8, 12]. Cognitive testing was limited but revealed intellectual disability, which is not a consistent feature of SMARD1. Unique features of this case are his numerous elevations of serum carnitine and copper. Whether these findings were the result of an intrinsic process of the disorder or the result of dietary oversupplementation is unclear.

The most unique feature of this SMARD1 patient has been his longevity. Available information indicates specific mutations do not correlate with the severity of the clinical features [8, 14]. His longevity has largely been due to the exemplary care provided by level of care his parents and caregivers. Many ventilated patients would require numerous hospitalizations for pneumonia and other respiratory complications over a twenty-year period, but he has only been hospitalized once for this. His unique age for someone with this disorder has provided an opportunity for further insight into this disorder. He has not had any other significantly novel disease manifestations as he has progressed into his third decade. Puberty was not early or delayed. Cognition, although below average, has not deteriorated. Importantly, he has not developed any cardiac myopathy, dilated or otherwise, as seen with the *nmd* mice [4, 9, 16]. Continued monitoring of this unique patient's condition will provide more insight for the prognosis and care of other SMARD1 patients.

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