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Case Report

Spinal muscular atrophy with respiratory distress type 1 (SMARD1): a rare cause of hypotonia, diaphragmatic weakness, and respiratory failure in infants

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ABSTRACT

Background. Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a very rare autosomal recessive disorder caused by mutations in the immunoglobulin μ-binding protein-2 (IGHMBP2) gene on chromosome 11q13.2-q13.4. The initial symptoms of patients with SMARD1 are respiratory distress and distal muscle weakness manifesting in the infantile period due to progressive degeneration of α-motor neurons. Preterm birth, intrauterine growth retardation, feet deformities, sensory and autonomic neuropathy are other main features.

Case. Herein, we report the characteristics of a 6-year-old Turkish girl with a diagnosis of SMARD1 confirmed by homozygous c.1738G>A (p.Val580Ile) missense *IGHMBP2* variant. She had unusual features such as vocal cord paralysis, nystagmus, and lack of congenital foot deformities besides typical findings including hypotonia, respiratory distress, and diaphragmatic weakness in the early infantile period. Epileptic seizures, cognitive impairment, and brain magnetic resonance imaging (MRI) abnormalities were other, unexpected, features which developed during the course of the disorder possibly due to several hypoxic episodes.

Conclusions. SMARD1 should be kept in mind in hypotonic infants with diaphragmatic weakness and respiratory failure during the early infantile period, even in the presence of unexpected findings including vocal cord paralysis, nystagmus, epileptic seizures, and brain MRI abnormalities.

Key words: spinal muscular atrophy with respiratory distress type 1, hypotonia, diaphragmatic weakness, vocal cord paralysis.

Spinal muscular atrophy with respiratory distress type 1 (SMARD1, OMIM #604320) is a very rare autosomal recessive disorder caused by mutations in the immunoglobulin μ-binding protein 2 (IGHMBP2, OMIM #600502) gene on chromosome 11q13.2-q13.4.[1] Only slightly more than 100 SMARD1 patients have been reported in the literature thus far. Although SMARD1 and spinal muscular atrophy (SMA) share some similar pathological characteristics, such as anterior horn motor neuron degeneration, they occur as a result of mutations in distinct genes and have diverse clinical phenotypes. The initial symptoms of patients with SMARD1 are respiratory distress and distal muscle weakness, manifesting during the infantile period due to progressive degeneration of α-motor neurons.[2] Progressive respiratory distress is thought to be related with unilateral or bilateral diaphragmatic weakness.[3] Although lower limbs and distal muscle involvement are more prominent, muscle weakness becomes generalized during the course of the disease. Preterm birth, intrauterine growth retardation, feet deformities, sensory

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and autonomic neuropathy are other main features of SMARD1.[4,5] In 2003, Pitt et al.[4] developed a set of clinical, histopathological and electrophysiological criteria for SMARD1 diagnosis (Table I). A few years later, a cluster analysis showed that the onset of respiratory distress between the ages of 6 weeks and 6 months, in combination with preterm birth or diaphragmatic weakness, had a 98% sensitivity and 92% specificity for predicting *IGHMBP2* mutation in 47 out of 141 patients presenting with respiratory distress and a spinal muscular atrophy phenotype.[5]

IGHMBP2 consists of 993 amino acids and has ATP-dependent 5→3 helicase activity. It is composed of three domains: DNA/RNA helicase, a R3H and a zinc-finger. Inactivation of the helicase domain is likely to be the cause of clinical symptoms and the majority of the pathological variants are found in this domain. R3H domain is thought to play a regulatory role on helicase activity. Although the precise function of IGHMBP2 is still uncertain, it has been demonstrated that it has a role in transcription, pre-mRNA processing, and translation.[6,7]

Herein, we report the characteristics of a 6-year-old Turkish girl with homozygous c.1738G>A (p.Val580Ile) missense *IGHMBP2* variant.

Case Report

The subject was the only child of healthy nonconsanguineous Turkish parents. She was born by a caesarian section weighing 2,180 g at 39 weeks of gestation due to fetal distress. There was no abnormality at antenatal follow up visits. Among her relatives, there were individuals who died during the infantile period (Fig. 1). She was admitted to the neonatal intensive care unit on the first day of life due to respiratory distress during postnatal adaptation. Following clinical improvement with non-invasive respiratory support, she was discharged from the hospital in a week.

At about 6 weeks of age, the parents noticed less than usual spontaneous movement in her legs. Physical and neurological examination revealed laryngomalacia, prominent generalized hypotonia, lack of head control and deep tendon reflexes at the age of 3 months. There were no fasciculations on the tongue. Complete blood count, serum biochemistry tests, creatine phosphokinase level, thyroid function tests, ferritin, vitamin B12, folate, uric acid, and metabolic tests (lactate, pyruvate, ammonia, homocysteine, biotinidase activity, long chain fatty acids, serum free carnitine / acyl carnitine profile, serum and urine amino acids, and urine organic acid) were all within normal limits.

Table I. Diagnostic criteria of spinal muscular atrophy with respiratory distress type 1 (SMARD1) from *Pitt et al.*[4]

Clinical criteria
- Low birthweight below the 3rd centile
- Onset of symptoms within the first 3 months
- Diaphragmatic weakness either unilaterally or bilaterally
- Ventilator dependence within less than one month of onset with an inability to wean
- Absence of other dysmorphology or other conditions

Histopathological criteria
- Reduction of myelinated fiber size in sural nerve biopsies
- Minimal evidence of ongoing myelinated fiber degeneration in biopsies taken up to 3 ± 4 months
- No evidence of regeneration or of demyelination that might account for the change in fiber size.

Electromyography criteria
- Evidence of acute or chronic distal denervation
- Evidence of severe slowing [<70% of lower limit of normality in one or more nerves (motor or sensory)]

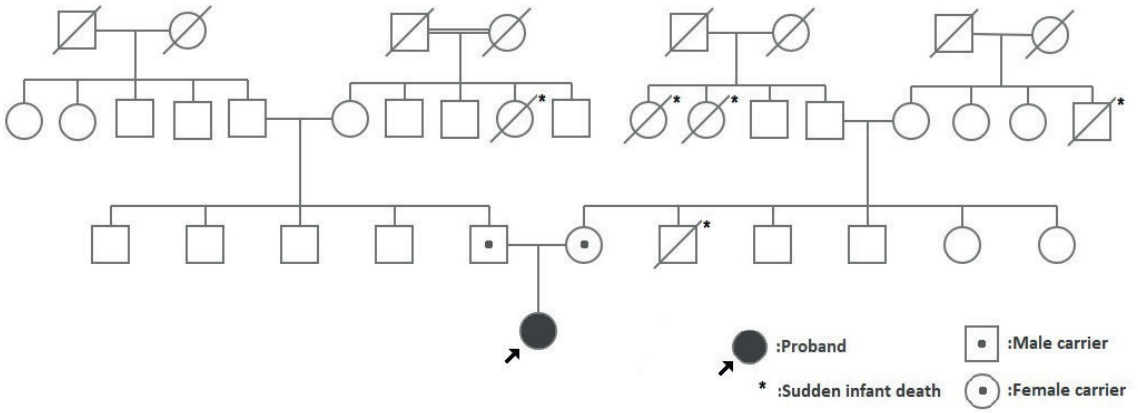

Fig. 1. Family pedigree of the SMARD1 case. The asterix (*) indicates sudden infant death.

Multiplex ligation probe amplification (MLPA) methodology and sequence analysis of the SMN gene revealed non-diagnostic heterozygous deletion in exon 8. At 4 months of age, she was admitted to the emergency department with respiratory distress and intubated during follow-up. Elevation of the right hemidiaphragm was noted on a chest X-ray (Fig. 2), and paradoxical movement on ultrasonography. Laryngoscopic examination of the vocal cord revealed bilateral mild impairment in abductor motion. The duration of intubation was longer than six months and repeated extubation attempts failed. Hemidiaphragm elevation has ameliorated only at moderate to high peak inspiratory pressures on the ventilator, and it was obvious following extubations. Tracheostomy and percutaneous endoscopic gastrostomy (PEG) were performed at the age of 14 months and 20 months, respectively. She had to be admitted to hospital several times with respiratory symptoms. At 17 months of age, she experienced clonic and myoclonic seizures during hospitalization for pneumonia in the intensive care unit. Interictal electroencephalography (EEG) revealed left temporal, frontotemporal and generalised sharp waves with normal background activity. Complete seizure cessation was achieved with levetiracetam treatment. Dilatation of lateral ventricles and decreased frontal white-matter volume were detected on brain magnetic resonance imaging (MRI) at 18 months of age. Nerve conduction studies demonstrated undetectable motor action potentials of peroneal, posterior tibial, median and ulnar nerves. Muscle biopsy of gastrocnemius muscle indicated neurogenic changes with atrophic myofibers. She had episodes of sweating, constipation, hypertension, sinus bradycardia, and tachycardia attributed to autonomic dysfunction. There was no abnormality in echocardiography. A custom target capture – based on next generation sequencing (NGS) panel (Celemics, Inc., Seoul, Korea) containing 579 genes associated with hereditary diseases indicated a homozygous c.1738G>A (p.Val580Ile) variant in *IGHMBP2* gene which was likely pathogenic according to ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/9114/), confirming the

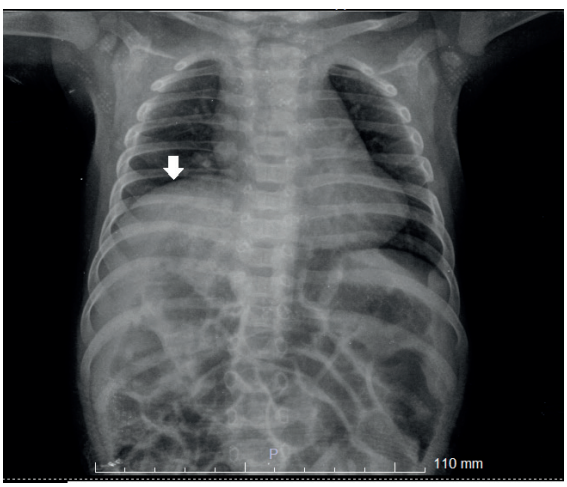

Fig. 2. Right hemidiaphragm elevation (white arrow) on chest X-ray at 5 months old.

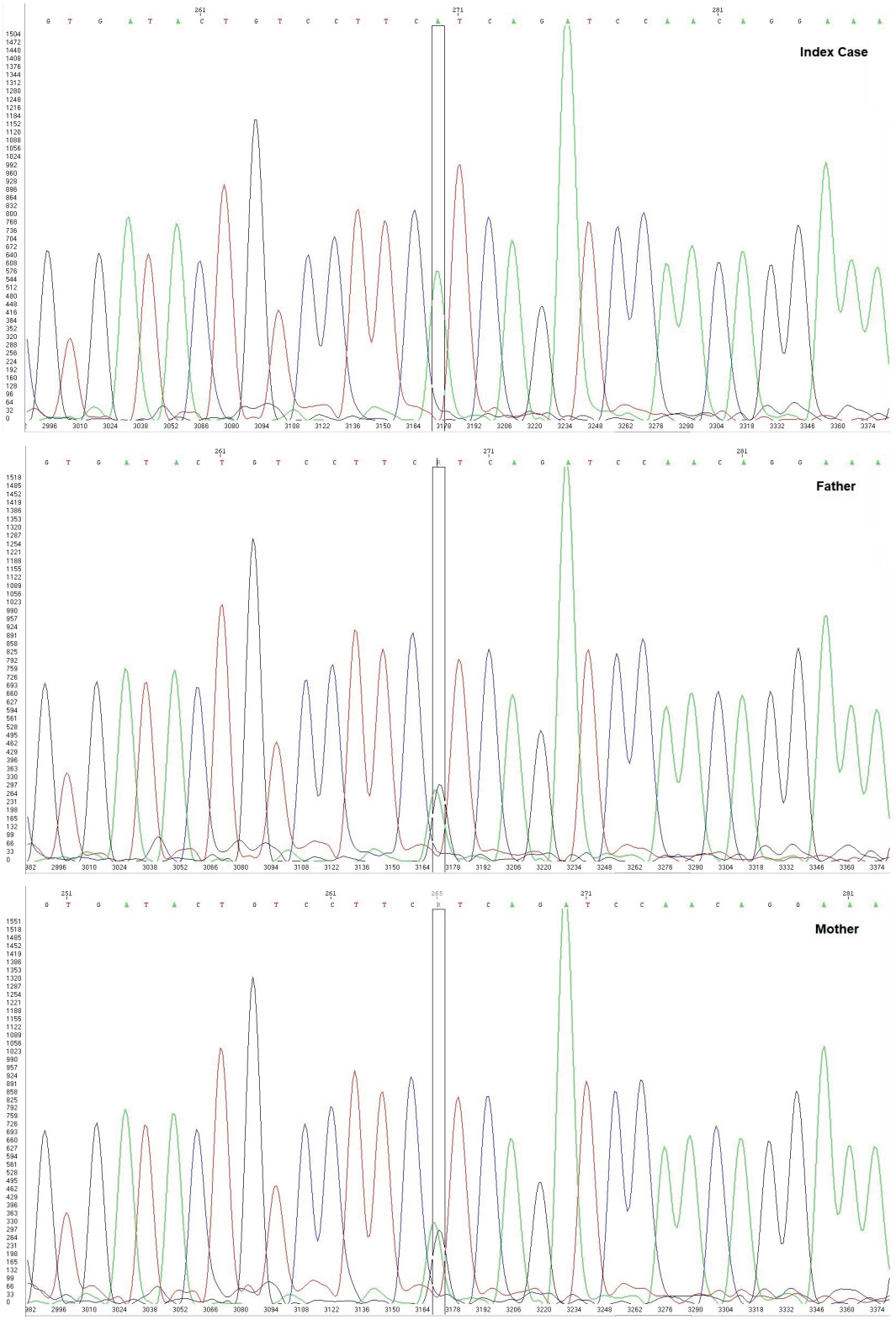

Fig. 3. Sanger sequencing electropherogram of IGHMP2 gene of the patient and family. Homozygous c.1738G>A (p.Val580Ile) variant in *IGHMBP2* gene of the patient, and maternal and paternal heterozygosity were confirmed by Sanger sequencing.

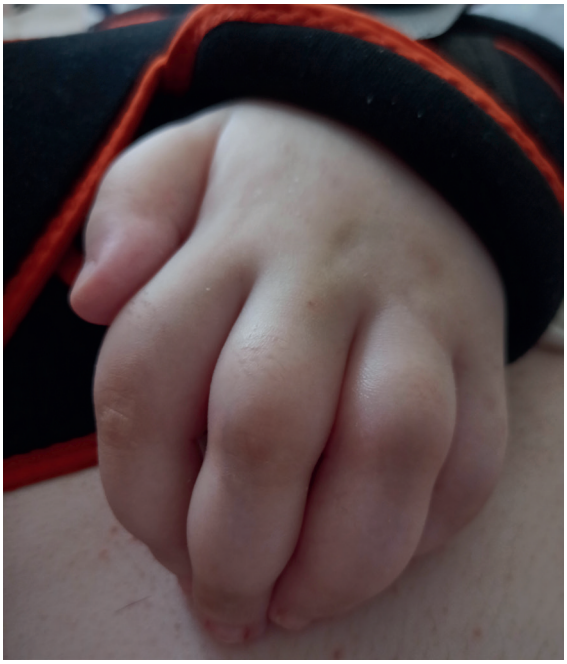

Fig. 4. Fatty pads on the paralyzed fingers of the patient with SMARD1.

diagnosis of SMARD1 at the age of 3.5 years. Sanger sequence analysis of parents revealed that both father and mother are heterozygous carriers of c.1738G>A (p.Val580Ile) variant (Fig. 3).

At the most recent examination, she had severe mentally retardation, unable to move both proximal and distal parts of her extremities against gravity, dependent on mechanical ventilation and gastrostomy tube feeding at the age of 6 years. Fatty pads at the fingers (Fig. 4), moderate contractures in the wrist, elbow, knee, and ankle were apparent. Facial weakness, absence of deep tendon reflexes, lack of eye tracking ability and bilateral horizontal nystagmus were the other features.

Informed consent was received from the family of the patient for publication.

Discussion

SMARD1 is a very rare autosomal recessive neuromuscular disorder with high mortality. Low birth weight, early onset respiratory distress (requiring permanent artificial ventilation), diaphragmatic paralysis, and progressive wasting of the distal muscles are the main delineated features of reported patients, (Table II) although variations exist in clinical phenotypes. In this case report, we presented a 6-year-old Turkish girl with a homozygous c.1738G>A (p.Val580Ile) variant in *IGHMBP2* gene causing SMARD1. This rare variant has been previously reported in a few SMARD1 patients with compound heterozygosity and to the best of our knowledge in only one other Turkish girl with homozygosity.[1,8] Experimental studies have demonstrated that this variant impairs enzymatic activity in vitro conditions.[9]

The subject was born as a full term baby weighing 2,180 g, small for gestational age, indicating intrauterine growth retardation and she had respiratory distress shortly after delivery. SMARD1 patients have been characterized by intrauterine growth retardation, premature birth and decreased fetal movements, but respiratory distress is rare in the early neonatal period.[2,5] Onset of respiratory failure appears a key clinical diagnostic factor for SMARD1 patients with *IGHMBP2* mutation. While the single criterion scoring highest in favor of an *IGHMBP2* mutation with 87% sensitivity and 92% specificity was the ''manifestation of respiratory failure between 6 weeks and 6 months'', ''congenital manifestation of respiratory failure'' was found to be the single criterion shown scoring highest against the diagnosis of SMARD1 with a 66% sensitivity and 98% specificity in a cluster analysis.[5] Consistently, respiratory failure developed at about 4 months of age in our case, although transient respiratory distress was observed in the early neonatal period, where elevation of the diaphragm was not a chest radiograph finding. Among the expected findings of SMARD1, weakness manifested by congenital foot deformities was not found in our patient.[3,5]

Life threatening progressive respiratory distress in infancy, due to diaphragmatic paralysis which requires mechanical ventilation, is the most prominent presenting symptom

Table II. Characteristics of spinal muscular atrophy with respiratory distress type 1 (SMARD1) patients in previously published studies with detailed analysis of clinical, electrophysiological and histopathological findings.

Characteristics	Studies		
	Grohmann K. et al., 2003	Viguier et.al., 2019	Rudnik-Schöneborn S. et al., 2004 (Previously reported patient with homozygous c.1738G>A IGHMBP2 variant*)
No of patients (male:female)	29 (15:14)	22 (15:7)	1 female
Consanguinity	7 of 29 families (24%)	38% of the families	+
IUGR	¾ of the patients	11 of 22 patients (50%)	-
Distal and/or foot deformities	19 of 22 patients (86%)	14 of 21 patients (67%)	Multiple distal contractures
Poor feeding	15 of 26 patients (58%)	All 22 patients (100%) had tube feeding	+ (tube feeding was initiated at 11 weeks of age)
Onset of respiratory distress	Median: 3 months (range: 0.1 -12)	Median: 2 months	2 months
Respiratory support	All 29 patients (100%) had respiratory failure at a median age of 3.5 months	15 of 22 patients required artificial ventilation at a median age of 10 months	Tracheostomy at 4 months of age
Inspiratory stridor	7 of 14 patients (50%)	Not mentioned	+ (soon after birth)
Diaphragm elevation	23 of 25 patients (92%)	20 of 20 patients (100%)	+ (right hemidiaphragm)
Muscular hypotonia	22 of 27 patients (86%)	20 of 22 patients (91%) (median: 2 months)	+
Cognitive functions	Not mentioned	Normal cognition in 14 of 17 patients (82%)	Appropriate for age (able to communicate with an electronic communication system)
Seizures	Not mentioned	5 of 20 patients (25%)	+
Cardiac arrhythmias	5 of 7 patients (71%)	7 of 22 patients (32%)	Not mentioned
Electromyography	22 of 25 patients (88%) had neurogenic changes	17 of 17 patients (100%) had motor and 14 of 17 patients (82%) had sensory neuropathy	Normal motor and sensory conduction velocities at 5 months, but no action potentials in 7 months
Muscle biopsy	Neurogenic muscle atrophy with fiber hypertrophy (21 of 22 patients)	Neurogenic muscle atrophy with a heterogeneous decrease in skeletal muscle fiber caliber and endoneural fibrosis	Neurogenic muscle atrophy
Sural nerve biopsy	Axonal degeneration (10 of 15 patients).	Hypomyelination or demyelination	Axonal atrophy, occasional hypermyelination in electron microscopy

* Patient #3 in reference 15. IUGR: intrauterine growth retardation.

in SMARD1.[1,2,9] In a retrospective study of twenty-nine SMARD1 patients, all patients had respiratory distress between 1–13 months of life with a median age of 3.5 months.[2] Muscle weakness usually becomes obvious shortly after the onset of respiratory symptoms.[9] However, the initial parental concern of our patient was the less than usual spontaneous movement of the legs, which was regarded as distal muscle weakness by two months of age before the respiratory symptoms started. Respiratory distress was the chief complaint at 4 months of life and she was intubated at the age of 5 months. She had inspiratory stridor and a weak cry at 3 months of age, both of which are usually the first indicators of respiratory distress in SMARD1.[2] Inspiratory stridor due to laryngomalacia and impaired abduction of the vocal cords were remarkable and gave rise to the thought of vagus or its branch recurrent laryngeal nerve paralysis. Vocal cord paralysis is an unexpected finding for SMARD1, although it can be significant for other certain types of SMA-like motor neuron disorders.[10,11] Laryngomalacia and tracheomalacia without vocal cord paralysis were also reported in two infants with SMARD1, presenting with stridor.[12,13] Interestingly, they had the mutation c.1737C>A (p.Phe579Leu) which is located in exon 12 of *IGHMBP2* gene, the same affected exon as in our patient.

Diaphragm elevation leading to respiratory failure is the hallmark of SMARD1, in comparison with SMA, which is characterised by the involvement of the intercostal muscles causing a bell-shaped thorax deformity, whilst the diaphragm is relatively spared. It is more commonly seen in the right side, presumably secondary to the mass effect of the liver, but bilateral involvement is possible.[14] Interestingly, diaphragmatic elevation may not be apparent in chest X-rays at the onset of respiratory symptoms and occur with a delay.[14] A chest X-ray of our patient revealed eventration of the right hemidiaphragm which was confirmed by paradoxical movement on ultrasonography at the onset of respiratory symptoms. Thin and membranous appearance of diaphragm was observed during surgery of the previously published patient with the same homozygous variant who underwent plication.[4] Plication of the diaphragm has not been shown to be beneficial to the clinical courses of reported SMARD1 patients and therefore is not a recommended intervention.[12,13,15] The main cause of death in the infantile period is respiratory failure. Most of the patients need invasive or non-invasive respiratory support and once mechanical ventilation is initiated, it is highly unlikely that the patient will be able to be weaned off ventilation.[15] However, a case was reported in which a girl had regained independent breathing for twelve hours per day by 4 years of age after a dramatic loss of independent breathing in the first year of life, despite persisting diaphragmatic paralysis.[9] A multicentric retrospective study has shown that tracheostomy had a positive impact on life expectancy of children with SMARD1, and only 1 of 22 patients survived without artificial ventilation beyond 2 years of age.[14] Therefore, families should be encouraged in favor of this procedure.

After the initial distal muscle weakness, predominantly in lower limbs, progressive generalized hypotonia, and absent deep tendon reflexes are inevitable features in SMARD1 patients. The natural course of the disease leads to complete paralysis of both limbs and trunk, which were noted on the follow-up examinations of our patient.[9,16] Marked distal weakness and atrophy caused adipose tissue replacement as fatty pads on the fingers, another characteristic finding of SMARD1 patients. This was a late manifestation in our patient, appearing after 2 years of age.[3,9,16]

Facial muscle weakness and tongue fasciculations can be observed due to the involvement of facial and hypoglossal nerves during the course of the disease.[2] Eckart et al.[9] have observed approximately one third of patients had facial weakness over an observational period of eight years. On the other hand, the oculomotor nerve is mostly spared and eye

movement disorders have not been previously reported in SMARD1 patients. A complete lack of eye tracking ability and bilateral horizontal pendular nystagmus of our patient was noted at 18 months of age although she had appropriate eye coordination and ability to follow brightly colored objects at 3 months of age prior to the onset of respiratory distress. Besides recurrent severe pneumonia episodes and autonomic dysfunction, she developed chronic filamentary keratitis with prominent epithelial erosion and mucopurulent discharge involving both eyes. Repeated slit lamp examinations of eyes revealed mucoepithelial strands attached to the corneal surface and epithelial defects after a long-term intubation period at 1-year old. Facial weakness and sedatives, to avoid patient-ventilator asynchrony, caused lagophthalmos and aqueous tear deficiency, which were thought to be main risk factors for filamentary keratitis. Fundoscopic examination and visual evoked potential responses were normal. In addition, hypoxic episodes may have contributed to eye movement disorders and visual impairment. Thereby, nystagmus and visual tracking disorder of our patient do not seem to be etiologically related to the disease itself, but most likely occurred as a secondary complication.

Epileptic seizure was another manifestation in our patient, uncommon in SMARD1 and generally thought to be related to secondary phenomena such as hypoxic episodes.[3,17] Electroencephalography revealed left temporal, frontotemporal and generalized sharp waves. The seizures were well controlled by levetiracetam treatment. No abnormalities were detected in brain ultrasonography during the infantile period. Brain MRI revealed mild dilatation of lateral ventricles and decreased frontal white-matter volume at 18 months of age, after the onset of epileptic seizures. Imaging abnormalities of the central nervous system are not expected in SMARD1. In a multicentric study, brain MRIs were normal in 71.4% of SMARD1 patients and most of the rest had non-specific imaging features.[13] However, an atypical SMARD1 patient was previously reported with microcephaly, cerebral atrophy and thin corpus callosum.[18] Cognitive skills and social interactions of SMARD1 patients were usually found appropriate for age in the literature.[15,19] Viguier et al.[14] in 2018, reported normal cognition in 14 of 17 children with SMARD1, and 7 of 9 survivors beyond 2 years of age were also able to talk and had normal facial expressions. Moreover, Eckart et al.[9] noted that most SMARD1 patients were well integrated into their home environment and two thirds of them were able to attend kindergarten or school, although severe disabilities in a long term follow-up were observed in 11 SMARD1 patients. In contrast, our patient had obvious impairment in cognitive functions although she wasn't assessed with objective psychometric tests. Both MRI findings and cognitive impairment may be attributed to the hypoxic episodes but not the natural course of the disease.

Dysfunction of the autonomic nervous system in SMARD1 is not rare and symptoms of autonomic neuropathy should not be overlooked or misinterpreted. Sudden changes in vital signs due to dysautonomia may lead to deterioration in the clinical condition of critically ill patients. Cardiac arrhythmia, variability of blood pressure, excessive sweating, urinary retention and constipation may be observed in the course the of the disease.[9,14] The prevalence of constipation, excessive sweating and cardiac arrhythmia were found in 53%, 58%, and 71% of 29 patients SMARD1 patients respectively.[2] Moreover, in a longitudinal study with a mean observational period of 7.8 years, all of 11 SMARD1 patients developed signs of autonomic neuropathy during the course of the disease, the latest was beyond 9 years of age.[9] Our patient had multiple periods of constipation, sweating, blood pressure fluctuations and arrhythmia which were prominent features consistent with autonomic neuropathy.

Reduction of the compound muscle action potential and abnormal nerve conduction velocities are commonly seen in patients with SMARD1. Electromyography (EMG) studies of SMARD1 patients revealed motor neuropathy, frequently accompanied by sensory neuropathy, and muscle biopsies indicated distally pronounced neurogenic muscular atrophy.[14] Nerve conduction studies of our patient failed to reveal any electrophysiological response in peroneal, posterior tibial, median and ulnar nerves, and muscle biopsy revealed neurogenic changes with atrophic myofibers at 1-year old. Although SMARD1 is also currently named as distal spinal muscular atrophy 1 (DSMA1, MIM#604320) and distal hereditary motor neuropathy type VI (dHMN6), both of which are confusing because these terms do not take into account sensory neuropathy and demyelination. This confusion of terminology may have occurred as a result of a broad spectrum of manifestations and electrophysiological results of defined SMARD1 patients initally.[20] Grohmann et al.[2] described clinical features of 29 SMARD1 patients who had neurogenic changes in EMG studies (22 of 25 patients), decrease in motor nerve conduction velocity (16 of 20 patients), and absent motor response after maximum stimulation (11 of 12 patients). Needle EMG results indicated chronic and active denervation in more than two thirds of patients.[14] Axonal degeneration was observed in sural nerve biopsies (10 of 15 patients) and histopathological examinations of muscle biopsy specimens revealed neurogenic changes with fiber hypertrophy and atrophy (21 of 22 patients).[2] Abnormal EMG results of the diaphragm compatible with denervation have previously been mentioned in patients with SMARD1.[4]

Homozygous c.1738G>A (p.Val580Ile) missense *IGHMBP2* variant in our patient was previously reported in only one other Turkish girl.[1,15] These two patients with the same homozygous variant, had similar clinical characteristics in the infantile period, although the onset of respiratory distress was earlier in the previously reported patient. Inspiratory stridor, facial weakness, absent deep tendon reflexes, distally marked weakness and progressive muscular hypotonia were common features. They were completely paralysed at 2 years of age but a slight improvement in the motor functions of the previous patient, mentioned above, was noted. Although she was not able to speak, her cognitive and social skills were appropriate for her age in contrast to our patient.[15]

SMARD1 is a severe motor neuron disease and the prognosis is usually poor.[9,14] The majority of patients die due to respiratory problems unless ventilatory support is initiated and few will survive into adulthood.[9,19] Viguier et al.[14] have shown that patients with diaphragmatic paralysis or areflexia before 3 months of age had significantly lower survival rates. In a multicentric retrospective study, tracheostomized patients had evidently higher survival rates and all survivors beyond 32 months of life were tracheostomized, and weaning from ventilation was unlikely once initiated.[14,15] Although most of the patients develop respiratory distress in the first few months of life and become non-ambulant and ventilator dependent during the infantile period, a plateau phase or even slight improvement of clinical symptoms may occur in survivors beyond 2 years of age.[9] Milder clinical courses with a late onset respiratory distress and distal muscle weakness have also been reported.[3,9,21] In 2015 Hamilton et al.[19] reported one of the oldest SMARD1 patients, a 21-year-old tracheostomized woman who had presented with respiratory distress at 16 months of age and remained stable for several years with only nocturnal mechanical ventilation. She was working full time in an office using her self-propelled electric wheelchair after completing her education. Previous studies showed high residual levels of IGHMBP2 enzymatic activity in fibroblasts and lymphoblastoid cells of the patients which correlated with a late onset form of the disease and/or better prognosis.[5,7,9,21] On the other hand, there is no evidence for a

genotype-phenotype correlation of the disease.[14] Treatment is primarily supportive with no known cure. Studies are ongoing for new treatment modalities and therapies.[10,22] Genetic counseling is crucial for the families with history of a child with SMARD1 and preimplantation genetic diagnosis should be considered to prevent this rare and lethal disease. Recent clinical advances in the treatment of another similar neuromuscular disease, SMA, give hope to development of new possible therapeutic approaches for this disease as well.

In conclusion; physicians should be alert for the possible diagnosis of SMARD1 in hypotonic infants presenting with respiratory distress and/or distal muscle weakness, and assess diaphragmatic weakness, congenital foot deformities, pre- and peri-natal medical history, siblings of sudden infant death syndrome, even in the presence of unexpected findings such as vocal cord paralysis, nystagmus, epileptic seizures, cognitive impairment, and brain MRI abnormalities. Concomitant motor and sensory neuropathy revealed by electrophysiological studies and dysautonomia are also noteworthy characteristics of the disease. Despite rapid progressive life threatening clinical symptoms in the first years of life, the clinical course of some survivors may remain stable without deterioration over many years and they may have normal social interactions with other people. Appropriate management, with supportive care, during the progressive phase of the disease and prevention of devastating complications may have a positive impact on quality of life and survival in these patients with an incurable disease.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SP, ÜY; data collection: YG; analysis and interpretation of results: SS, ÖK. SP; draft manuscript preparation: SP, AÜ. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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