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A case report of SEPN1-related myopathy: Expanding the spectrum of clinical, genetic and radiological features

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Abstract

SEPN1-related myopathies (SEPN1-RM) encompass a rare subset of neuromuscular disorders stemming from mutations in the SELENON gene. Here, we present a case of a 15-year-old Saudi child harboring an autosomal recessive homozygous c.2T>A. (chr1:25800232 T>A) (NM_020451.3), exhibiting a distinct clinical profile of hypotonia, motor delay, muscle weakness, scoliosis, and sleep apnea. Advanced genetic testing revealed additional heterozygous variants in the CNGA1 and BTD genes. Our report underscores the complexity of SEPN1-RM, highlighting the challenges in correlating genotypes with phenotypes and emphasizing the early onset of respiratory insufficiency in affected individuals. This case contributes novel insights to the clinical and genetic landscape of SEPN1-RM, emphasizing the need for continued research to enhance diagnostic and therapeutic strategies for improved patient care and outcomes.

Keywords: SELENON, SEPN1, Selenoprotein N, congenital myopathy, respiratory insufficiency.

INTRODUCTION

SEPN1-related myopathies (SEPN1-RM) represent a subset of rare neuromuscular and multi-minicore disorders resulting from an inherited defect in Selenoprotein N, encoded by the SELENON gene (SEPN1, OMIM#602771) situated on chromosome 1p36. This defect stems from a pathogenic variant in the gene[1], leading to a gradual axial muscle weakness, early-onset spine rigidity, scoliosis, and respiratory insufficiency.[2,3] SEPN1 is ubiquitously expressed in endoplasmic reticulum glycoproteins[4], playing a crucial role in myogenesis, calcium signaling and homeostasis regulation, as well as cellular defense against oxidative stress (see Figure 1).[5] Nonetheless, the pathophysiology of SEPN1-RM remains inadequately understood. SEPN1-RM is estimated to constitute 11.65% of congenital muscular dystrophy cases[6] and 16% of congenital myopathies.[7] At least 17 mutations have been pinpointed in the SELENON gene.[8] Furthermore, it is distinguished by unique minicores observable on muscle biopsy.[9] Clinical reports have identified patients exhibiting symptoms from early infancy, characterized by severe neck and trunk muscle weakness leading to respiratory failure and, ultimately, death.[10] As individuals age, a spectrum of abnormalities may emerge, including limb muscle weakness and fatigue that, in severe instances, can result in ambulatory difficulties[11], necessitating increased assistance with daily activities as they progress in age.[12] In the pediatric population, sequential loss of early developmental milestones has been predictive[13], yet despite the multisystem involvement, the pathophysiology of this condition remains obscure. This case study offers additional insights into the progression and management of SEPN1-RM, shedding light on distinct clinical features that have not been widely reported.

CASE REPORT

The proband, a 15-year-old Saudi child, presents with hypotonia, motor delay, muscle weakness, scoliosis, and sleep apnea. Her antenatal history was uneventful, born via spontaneous vaginal delivery with up-to-date vaccination records. Symptoms first manifested at one year of age, raising suspicion of congenital myopathy. Although she achieved independent walking at

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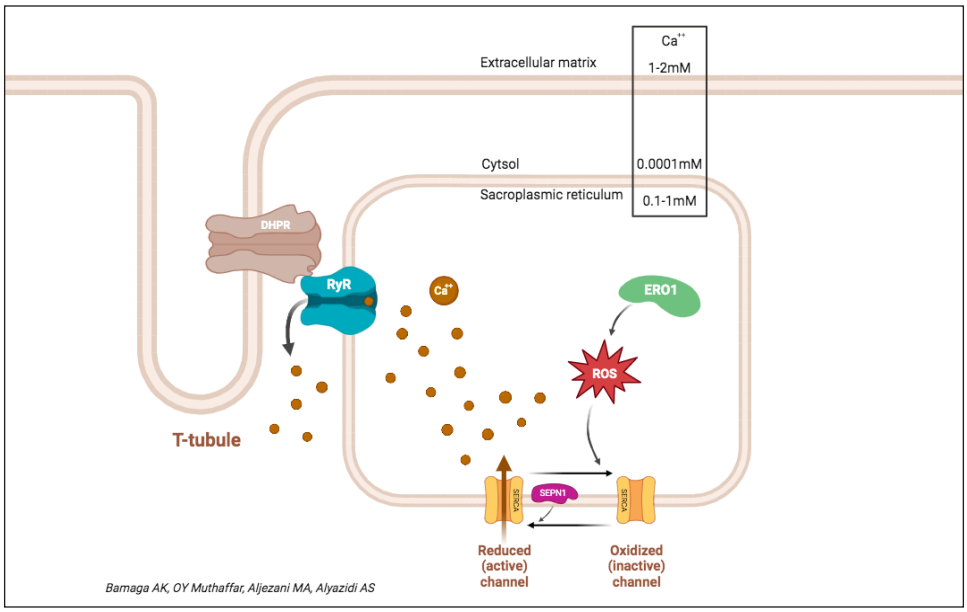

Figure 1. A diagram illustrating the interaction of SEPN1 and SERCA to facilitate calcium ions re-uptake by the sarcoplasmic reticulum after a muscle cell contraction. It results in the muscle phenotype of SEPN1-RM. Both SEPN1 and RyR proteins engage in ER calcium facilitation. RyR channel is activated by the dihydropyridine receptor (DHPR) on the T tubule.

1.5 years, she experiences easy fatigue, struggles with stairs and rising from the floor, exhibits weak fine motor skills, and presents with hypernasal speech. Cognitive abilities are age-appropriate.

On physical examination, neck flexion was graded at 4/5 with bilateral scapular winging. Muscle power was notably stronger on the right side. Upper limb strengths were as follows: deltoid 4/4, biceps 4+/4+, triceps 4-/4-. Lower limb strengths were: hip flexion 1/2, knee extension 4/4, knee flexion 3/3, dorsiflexion 4/4, plantar flexion 4/4. Muscle tone was low with hypoactive deep tendon reflexes in the upper limbs and absent in the lower limbs. Sensory examination yielded normal results. Gait exhibited lordosis with a positive Gower sign. Past medical history included surgically corrected scoliosis and sleep apnea.

Creatinine kinase level was within normal limit at 173 units/L. Nerve conduction studies showed normal motor and sensory responses in bilateral median, ulnar, peroneal and tibial nerves. Electromyography (EMG) study however showed evidence of small and narrow motor units potential (myopathic) in paraspinal muscles, iliopsoas and semimembranosus. Normal EMG findings were seen in distal leg muscles, deltoid and extensor digitorum communis.

Genetic testing disclosed an autosomal recessive homozygous c.2T>A (chr1:25800232 T>A) variant in the SELENON/SEPN1 gene. Whole genome sequencing additionally revealed a heterozygous, likely pathogenic variant in the CNGA1 gene (chr4:47936734 TCAT, c.1746_1747del p.[Glu583Valfs*32]:exon:11), and a heterozygous, pathogenic variant in the BTD gene (chr3:15645186 GC, c.1270G>C p.[Asp424His]), both following autosomal recessive inheritance patterns. The parents, who are first cousins, have no history of neuromuscular diseases.

DISCUSSION

Our report highlights a unique case where advanced genetic testing unveiled a SEPN1 mutation (Table 1). SEPN1-RM constitutes a subtype of congenital muscular dystrophy encompassing conditions like rigid spine muscular dystrophy, severe classic multi-minicore myopathy, desmin-related myopathy with Mallory body inclusions, and congenital fiber-type disproportion myopathy.[11,14] These disorders arise from mutations in the SEPN1 gene, presenting a diverse array of clinical phenotypes (Table 2). Despite this diversity, a definitive genotype-phenotype correlation remains elusive, complicating the implementation of clinical trials.[11,15]

The variability in clinical presentations has given rise to uncertainties concerning the

Table 1: Genetic and demographic characteristics of reported patients

Patient No.	Authors	Age	Gender	Reported country	Parental consanguinity	Genetic variant
1 (present case)	Bamaga *et al*. 2025	15y	F	Saudi Arabia	+	SEPN1:heterozygous (c.2T>A. (chr1:25800232 T>A)(NM_020451.3)
2	Mohamadian *et al*. 2020[22]	9y	M	Iran	+	SEPN1: c.1446delC (p.Asn483Thrfs*11
3	Ziyaee *et al*. 2019[23]	14y	M	Iran	+	SEPN1:homozygous (chr1:25812784, exon:10, c. 1379 C > T, p.Ser460Phe)
4	Saini *et al*. 2018[24]	10y	M	India	-	SEPN1:homozygous (c.826_827insCCT:exon:6, p. Ala276_Cys277insSer
5	Viprey *et al*. 2017[25]	13y	M	France	+	SEPN1:homozygous ([-19+73 del])
6	Viprey *et al*. 2017[25]	17y	F	France	NM	SEPN1:heterozygote ([-19+73 del] and [Met1Val;ATG > GTG])
7	Dai *et al*. 2017[26]	17y	M	China	-	SEPN1:heterozygote (c.1384T>C; p.Sec462Arg and SEPN1:heterozygote (c.1525C>T; p.Gln509Ter)
8	Lal *et al*. 2016[27]	8y	M	Turkey	+	SEPN1
9	Lal *et al*. 2016[27]	26y	M	Turkey	+	SEPN1:homozygous (p.G239R[c.715G>A, NM_206926.1, p.G239R])
10	Lal *et al*. 2016[27]	17y	M	Turkey	+	SEPN1:homozygous (p.G239R[c.715G>A, NM_206926.1, p.G239R])
11	Ardissone *et al*. 2016[28]	14y	M	Italy	-	SEPN1:homozygous (c.1176delA)(NM_020451)
12	Ardissone *et al*. 2016[28]	16y	M	Italy	-	SEPN1:homozygous (c.1176delA)(NM_020451)
13	Ardissone *et al*. 2016[28]	3.5y	M	Morocco	+	SEPN1:homozygous (c.828_829insTCC) (NM_020451)
14	Kostera-Pruszczyk *et al*. 2006[29]	8y	M	Poland	-	SEPN1
16	Okamoto *et al*. 2006[30]	41y	M	Japan	+	SEPN1:homozygous:exon1
17	Okamoto *et al*. 2006[30]	31y	F	Japan	-	SEPN1:homozygous:exon1
15	Kaindl 2006[31]	21y	M	Germany	-	SEPN1:heterozygote: c.863_delTG:exon:6 and c.1469G>T;W490L:exon:11
18	D'Amico *et al*. 2005[32]	9y	F	Italy	+	SEPN1:homozygous: c.817GOA
19	Venance *et al*. 2005[33]	45y	M	Canada	NM	SEPN1

Abbreviation. Y: years; M: male; F: female; NM: not mentioned; (+) indicates positive consanguinity; (-) indicates negative consanguinity.

Table 2: Clinical background of reported patients

Patient No.	Authors	Age of onset	Hypo-tonia	Develop-mental delay	Respiratory function	Motor function	Radiological findings
1 (present case)	Bamaga *et al*. 2025	1y	+	+	Hypernasal speech	Delayed motor functions	ND
2	Mohamadian *et al*. 2020[22]	Birth	+	+	Respiratory insufficiency	Delayed motor functions	NM
3	Ziyaee *et al*. 2019[23]	4y	-	-	Respiratory insufficiency	Progressive falls	NM
4	Saini *et al*. 2018[24]	7y	-	+	Progressive insufficiency	Diminished muscle stretch reflexes	NM
5	Viprey *et al.* 2017[25]	7y	+	NM	Respiratory insufficiency	NM	NM
6	Viprey *et al.* 2017[25]	1y	+	NM	Respiratory insufficiency	Frequent falls	NM
7	Dai *et al.* 2017[26]	Birth	-	+	Respiratory insufficiency	Hardly able to run with frequent falls	NM
8	Lal *et al.* 2016[27]	3.5y	+	+	Ventilatory failure	Difficulties to sit up from supine position	NM
9	Lal *et al.* 2016[27]	Early child-hood	+	+	SOB	Waddling gait	NM
10	Lal *et al.* 2016[27]	3.5y	+	+	Ventilatory failure	Waddling gait, unable to run fast and has difficulties to sit up	NM
11	Ardissone *et al*. 2016[28]	Early infancy	+	-	Respiratory insufficiency	Unsteady gait	Triventricular hydrocephalous with signs of intracranial hypertension, re-quiring surgical third ventriculostomy.
12	Ardissone *et al*. 2016[28]	Early infancy	+	-	Respiratory insufficiency	Muscle weakness	NM
13	Ardissone *et al.* 2016[28]	NM	+	+	Normal	Generalized hypotrophy	Normal brain MRI and diffuse fatty infiltration and hypotrophy of thigh muscles on lower limb MRI
14	Kostera-Pruszczyk *et al.* 2006[29]	Early infancy	NM	+	NM	Difficulties in clim-bing stairs, rising from the floor and frequent falls	Normal
15	Okamoto *et al.* 2006[30]	7y	-	+	Severe restrictive respiratory failure	Abnormal gait and he was never able to run or jump	NM
16	Okamoto *et al.* 2006[30]	12y	-	-	Severe respi-ratory failure	Waddling gait and Gower's sign	NM
17	Kaindl 2006[31]	11y	+	-	Restrictive respiratory disease	Difficulties with his antigravity power	15

18	D'Amico *et al*. 2005[32]	1y	-	-	Respiratory insufficiency	Persistent weak head control	NM
19	Venance *et al*. 2005[33]	NM	NM	NM	NM	Revealed a marrow-replacing process involving the clivus and odontoid process and an enhancing 9-mm dural-based mass resulting in compression of the medulla oblongata with T2 signal abnormality extending from the brainstem to C6 to C7 level. A Chiari I malformation was present	NM

Abbreviation. Y: years; M: months; NM: not mentioned; ND: no done; (+) indicates the presence of the feature; (-) indicates the absence of the feature.

association between specific genetic mutations and their pathological manifestations.[15] Nevertheless, pathways regulated by SEPN1 stand as potential targets for drug intervention, with some ex-vivo studies demonstrating promising outcomes.[16] Nevertheless, the development of successful in-vivo models has been hindered by the absence of comprehensive quantitative data on the disease spectrum.

Typically, SEPN1-RM manifests in infancy with symptoms such as spinal rigidity and respiratory insufficiency.[17] A study that comprehensively detailed data from a patient cohort suggested an early onset of hypotonia, poor neck/head control, spinal rigidity, progressive scoliosis, and the necessity for early respiratory support among these patients.[18] Additionally, we observed that a majority of SEPN1 mutation carriers exhibited early respiratory problems, with some displaying symptoms from birth. This implies that certain manifestations may arise earlier than conventionally reported. Motor delays, alongside axial weakness and rigidity, are often overlooked initially but become more pronounced as patients near puberty.[2] Other studies described the frequency of additional complications and features like swallowing difficulties and ptosis.[18] Moreover, conflicting data on the ability to walk have been reported, with a percentage of 17%[18] contrasted with prior literature citing 5%.[19-21] Furthermore, preceding studies have underscored the development of scoliosis and respiratory failure in SEPN1-RM patients. In our case, these symptoms were consistent with existing literature, where respiratory failure was observed in 93% of patients by an average age of 10 years.[2] Despite these observations, no definitive genotype-phenotype correlation was discerned, except for a suggested link between biallelic null mutations and heightened disease severity.[2,15] Developmental delays are commonly noted; however, our case demonstrated normal cognitive function, potentially due to the lack of SEPN1 gene involvement in cognitive brain regions.

Comprehending the full scope of SEPN1 mutations and their clinical implications remains a challenge, with certain data, such as prevalence and specific clinical aspects, remaining unknown. Continuous and expanded research is imperative to address these gaps. Our case report contributes to this endeavor by documenting a novel SEPN1 case in Saudi Arabia, thereby expanding the clinical and genetic comprehension of SEPN1-RM and offering valuable genetic counseling for affected families.

In conclusion, our case report elucidates a spectrum of clinical findings associated with SEPN1 mutations. Respiratory insufficiency emerged as a prevalent and early-presenting symptom in affected children. Additionally, motor impairments were frequently observed, although radiological signs lacked specificity, complicating diagnosis. Despite exhaustive investigation, no clear correlation between symptom severity and specific genetic variants was established. This absence of correlation suggests that other factors may influence the clinical presentation, highlighting the intricacy of SEPN1-RM. These findings underscore the importance of ongoing research to deepen our understanding of these complexities. Advancing our knowledge in this

realm could lead to enhanced diagnostic tools and therapeutic strategies, ultimately improving patient care and outcomes.

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DISCLOSURES

Ethics: This study was waived from obtaining ethical approval by the Unit of Biomedical Research Ethics at the Faculty of Medicine at King Abdulaziz University. Written informed consent was obtained to publish the details of the reported cases from the patient's legal parents.

Data availability: The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request.

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