CASE REPORT

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Exploring Multiple Endocrinological Issues and Dysautonomia in a Rare Case: Hypoparathyroidism in MIRAGE Syndrome

Sirmen Kızılcan Çetin[1], Elif Özsu[1], Zeynep Şıklar[1], Hasan Fatih Çakmaklı[2], Gizem Şenyazar[1], Zehra Aycan[1], Serdar Ceylaner[3], Merih Berberoğlu[1]

[1]Ankara University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Türkiye
[2]Ankara University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Türkiye
[3]Intergen Genetic Diagnosis and Research Center, Department of Medical Genetics, Ankara, Türkiye

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ABSTRACT

MIRAGE syndrome is a rare multisystemic disorder characterized by the following manifestations: myelodysplasia, susceptibility to infections, growth retardation, adrenal hypoplasia, genital anomalies, and enteropathy. Dysautonomia has also been reported, but rarely. We present a 6.5-year-old girl, who was first admitted with short stature. On follow-up, she exhibited multiple endocrinological issues, including transient hypothyroidism, primary hypoparathyroidism and dysautonomia, along with multisystem involvement. Further investigations revealed recurrent moniliasis, low IgM levels, and transient monosomy 7 in the bone marrow. Whole exome sequencing revealed a heterozygous pathogenic variant of *SAMD9* (c.2159del; p.Asn720ThrfsTer35). Additional complications observed during follow-up included medullary nephrocalcinosis, hypomagnesemia, hypomagnesuria, hypophosphatemia, decreased glomerular filtration rate, and nephrotic proteinuria. The patient also developed hyperglycemia, which was managed with low-dose insulin. This case highlights the diagnostic challenges and the diverse phenotypic presentation that may occur in MIRAGE syndrome.

Keywords: Dysautonomia, hypoparathyroidism, MIRAGE syndrome, monosomy 7, *SAMD9*

What is already known on this topic?

MIRAGE syndrome is a rare, multisystemic disorder It is characterized by myelodysplasia, susceptibility to infections, growth retardation, adrenal hypoplasia, genital anomalies, and enteropathy. The syndrome is associated with pathogenic variants in *SAMD9*.

Corresponding Author: Sirmen Kızılcan Çetin, MD, Ankara University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Türkiye
E-mail: drsrmnkzlcn@gmail.com **ORCID:** orcid.org/0000-0001-7397-3071

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What this study adds?

This case report describes a 3.5-year-old girl with a previously reported *SAMD9* variant (c.2159del; p.Asn720ThrfsTer35). The case report highlights the presence of primary hypoparathyroidism and diabetes mellitus in a patient with MIRAGE syndrome, which expands the spectrum of associated endocrinological issues. Dysautonomia is a relatively rare finding in MIRAGE syndrome and further emphasizes the heterogeneity of clinical presentations in MIRAGE syndrome. Finally, the diagnostic challenges associated with MIRAGE syndrome are illustrated, as its diverse phenotypic presentation can make it difficult to recognize and diagnose the condition rapidly and accurately.

Introduction

MIRAGE syndrome is a rare multisystemic disorder characterized by Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy. MIRAGE is a recently described autosomal dominant disorder caused by gain-of-function (GOF) mutations in the *SAMD9* gene located on chromosome 7q21.2 (1). MIRAGE syndrome is typically diagnosed in early childhood. While the classical features have been well-documented, autonomic dysfunction, such as insensitivity and anhidrosis, has been infrequently reported (2-5). Only 44 affected individuals with MIRAGE syndrome have been documented (6).

Variants in *SAMD9* may cause structural and functional changes in the endosome system. This may result in defective recycling of plasma membrane epidermal growth factor receptors and the accumulation of giant vesicles in adrenocortical cells. These alterations may disrupt normal cellular processes and contribute to developing growth restriction, dysautonomia, and other symptoms observed in MIRAGE syndrome.

Moreover, the loss of chromosome 7 carrying the *SAMD9* mutation may be associated with developing myelodysplastic syndrome (MDS) in some patients (1). Monosomy 7 significantly impacts the survival of individuals with MIRAGE syndrome. Survival in MIRAGE syndrome is generally poor, with a median age of mortality of three years. Around 60% of deaths are caused by infectious diseases. While there have been isolated reports of individuals with MIRAGE syndrome reaching the age of 20 years, the overall survival rates for this condition remain low (6).

Here, we present a case of MIRAGE syndrome with the additional clinical features of primary hypoparathyroidism and dysautonomia, highlighting the diagnostic challenges, clinical manifestations, and multidisciplinary management. To the best of our knowledge, primary hypoparathyroidism and diabetes have not been reported within the endocrine phenotype of MIRAGE syndrome previously.

Case Report

A female infant was born to healthy, non-consanguineous parents at 39 weeks of gestation, with a birth weight of 2790 g. She had unremarkable antenatal ultrasound findings. She exhibited normal neurodevelopmental milestones. However, at 15 days of age, she was diagnosed with compensated congenital hypothyroidism [thyroid stimulating hormone 88.47 mIU/L, fT4 14.52 pmol/L (13.9-26.19), urine iodine 95 mcg/L (100-200), thyroid ultrasound normal with right lobe 11x6x4 mm, left lobe 16x6x5 mm isthmus 1.5 mm; total volume 0.39 mL (-1.3 standard deviation (SD))]. Levothyroxine (LT4) treatment was initiated at 8 mcg/kg/day.

At one year of age, the patient developed thrombocytopenia and neutropenia, which led to a diagnosis of monosomy 7 (45, XX, -7[45]/46, XX[5]) based on bone marrow and peripheral blood tests. However, subsequent bone marrow aspiration at 16 months of age revealed a normal karyotype and normal hemogram, suggesting transient monosomy 7.

At 3.5 years of age, the patient presented to our clinic with short stature and hand stiffness. Physical examination revealed a short stature of 88 cm (-2.8 SD) and a low body mass index (BMI) of 14 kg/m^2 (-1.3 SD). The patient was prepubertal and exhibited dysmorphic facial features, including a short and narrow forehead, synophrys, prominent supraorbital folds, narrow nasal bridge, bulbous nose, full cheeks, high palate, thin lips, and a hypoplastic clitoris. Systemic examinations revealed a 1/6 murmur. Biochemical evaluation showed abnormal levels of calcium (Ca) 6.4 mg/dL (8.5-10.5), phosphorus 7.36 mg/dL (3.8-6.5), parathyroid hormone 8.9 pg/mL with normal magnesium (Mg) 2 mg/dL (1.7-2.1), alkaline phosphatase 217 U/L (142-335), urine Ca/creatinine clearance ratio: 0.24 and 25-hydroxyvitamin D of 53 mcg/L. The patient was diagnosed with primary hypoparathyroidism. Medical history revealed that the daily Ca intake was approximately 850-1000 mg. Recurrent moniliasis and low IgM levels (64.8 mg/dL, reference range: 78-261) were also observed. Di George Syndrome was ruled out through fluorescence *in situ* hybridization (FISH) test. An atrial septal defect was detected and normal hearing was reported. Tests for polyglandular autoimmune syndrome type 1, including adrenocorticotropic hormone (ACTH) levels of 32.1 pg/mL and cortisol levels of 11.12 ng/dL, showed normal results. Furthermore, tests for anti-21-hydroxylase antibody, anti-gliadin antibody (total IgA 0.893 g/L, reference range: 0.39-1.7), anti-thyroid peroxidase antibody, and anti-thyroglobulin antibody were negative. A standard dose ACTH stimulation test was also normal (stimulated cortisol 26.3 mcg/dL). Hypoparathyroidism was successfully managed with calcitriol treatment.

The patient underwent laboratory and imaging evaluations for short stature. Hemogram, biochemical parameters, liver and kidney function, blood glucose, tissue transglutaminase IgA autoantibody, serum total Ig A level, and urine analysis were normal. Insulin-like growth factor 1 (IGF-1) was 280 ng/mL (reference range: 84-447), IGFBP3 was 1700 ng/mL (reference range: 1400-4250), and L-Dopa was 4 ng/mL. The bone survey showed normal dense ivory epiphysis, and pituitary MRI revealed no abnormalities in pituitary size (4.3 mm, reference range: 4±0.7 mm). Although the patient was monitored and evaluated for growth hormone deficiency, growth hormone treatment was avoided due to the patient's history of transient monosomy 7 and the potential risk of developing malignancies.

At the age of four years, treatment with LT4 was discontinued. During the follow-up periods, thyroid function tests were normal. In addition, the patient's cognitive function and neurodevelopmental milestones were assessed during these visits and were within the normal range.

During the follow-up at 4 years and 2 months of age, the patient presented with progressive sensorineural hearing loss and was subsequently diagnosed with hyperglycemia. The fasting blood sugar was 106 mg/dL, while the insulin level was 3 µIU/mL, and the C-peptide was 0.524 ng/mL. The random blood glucose was 332 mg/dL, and HbA1C was 8.3%. Autoantibody tests, including anti-glutamic acid decarboxylase (0.55 U/mL, reference range: 0-1), anti-insulin antibody (4.3%, reference range: 0-5.5%), and anti-islet antibody, were negative. Parents fasting blood glucose (FBG), and HbA1c (maternal FBG 83 mg/dL, HbA1c 5.5%; paternal FBG 92 mg/dL HbA1c 5.4%) were all normal.

Low-dose insulin therapy (0.6 U/kg/day) was initiated for glycemic control. Renal ultrasonography detected medullary calcinosis, but no other renal anomalies were observed. Laboratory investigations for mitochondrial cytopathy, including blood amino acid levels, tandem mass spectrometry analysis of organic acids in urine, serum lactate level (15.38 mg/dL, reference range: 10-14), and serum pyruvate level (0.45 mg/dL, reference range: 0.5-1), did not reveal any pathological findings. Mitochondrial DNA sequencing analysis was normal.

Due to the involvement of multiple systems and severe short stature, microarray analysis was assessed and was reported normal. Considering the patient's history of transient monosomy 7 and significant short stature, MIRAGE syndrome was initially suspected. However, since there was no adrenal insufficiency and the presence of endocrinopathies such as hypoparathyroidism and diabetes mellitus, which are not typically associated with MIRAGE syndrome, whole-exome sequencing (WES) was performed. WES analysis identified a heterozygous variant (c.2159del; p.Asn720ThrfsTer35) in *SAMD9*, classified as likely pathogenic. Consequently, the patient was diagnosed with MIRAGE Syndrome. Segregation analysis revealed that the mother carried the heterozygous mutation in *SAMD9*, while the father had a normal genotype. The patient's gonadal hormone levels were assessed for potential accompanying hypogonadism associated with MIRAGE syndrome. Follicle-stimulating hormone was 4.4 mIU/mL, luteinizing hormone (LH) was 0.4 mIU/mL, estradiol was 5 pg/mL, and anti-Müllerian hormone (AMH) at 8.85 pmol/L (normal range: 1.5-12.6 pmol/L), indicating a prepubertal status. No data from the mini puberty period were available.

During follow-up, the patient experienced several hospital admissions due to intractable vomiting episodes related to dysautonomia. Episodes of hypotension, tachycardia, feeding difficulties, and absence of tears were observed. Body temperature regulation was normal. She recovered with symptomatic supportive treatment in episodic periods. At 4 years and 7 months of age, the patient presented with hypomagnesemia (serum Mg levels of 1.23 mg/dL, reference range: 1.7-2.1 mg/dL) and hypermagnesiuria (FeMg 12%). A decreased glomerular filtration rate (GFR) of 85 mL/min/1.73 m^2 and nephrotic proteinuria (9 mg/m^2/day) were also observed. Mg supplementation was initiated, and the patient was put under close nephrology follow-up.

At 6 years of age, the patient demonstrated developmental milestones such as independent walking and the ability to navigate stairs. However, a comprehensive evaluation revealed a delay in gross motor development and increased support needs compared to peers. Her gross motor development was judged to be -2 SD, indicating a developmental delay. Cognitive development was in the low normal range.

On the last follow-up at the age of 6.5 years, the patient's height was 94 cm (-5 SD), and BMI was 12.5 kg/m^2 (-2.5 SD).

On follow-up, ACTH stimulation test was normal. Adrenal insufficiency has not been confirmed. The most recent ACTH level was 25 pg/mL, while the cortisol level was 17.7 mcg/dL. The patient is on basal insulin therapy at 0.2 U/kg/day with regulated blood glucose and is supplemented with calcitriol and Mg. A multidisciplinary team is closely monitored to ensure comprehensive care and follow-up (Table 1, Figure 1).

Discussion

The protein product of *SAMD9* affects the endosome system, yet its precise mechanisms remain inadequately elucidated. *SAMD9*/*SAMD9L* disrupts protein translation and causes MIRAGE syndrome, involving many systems and is generally associated with a poor prognosis (1,6).

We describe the diagnostic challenges and various clinical manifestations associated with MIRAGE syndrome. Typically,

Table 1. Features, manifestations, and treatment of a patient with MIRAGE syndrome

Features	Manifestation	Age at diagnosis	Treatment
Myelodysplasia	Incident thrombocytopenia and neutropenia during routine laboratory evaluation, led to a diagnosis of monosomy 7 (45, XX, -7[45]/46, XX[5]).	1 year of age	Providing blood transfusion to manage severe cases of anemia and thrombocytopenia
Infection	Not observed yet	-	-
Growth restriction	Weight, height/length, and head circumference <-2.0 SD despite the sufficient caloric intake	3.5 years of age	Adequate caloric intake
Adrenal deficiency	Not observed yet	-	-
Genital anomalies	Hypoplastic clitoris	3.5 years of age	-
Enteropathy	Not observed yet	-	-
Autonomic dysfunction	Episodes of hypotension, intractable vomiting, feeding difficulties, and absence of tears	4 years and 7 months of age	Symptomatic supportive treatment

SD: standard deviation

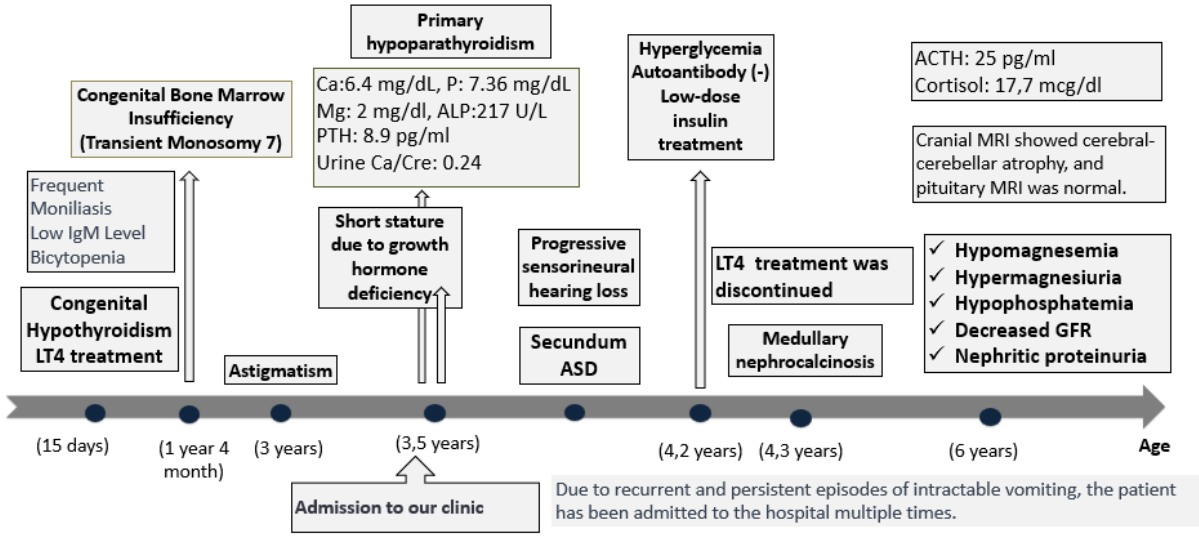

Figure 1. Timeline of the patient's clinical presentation
Ca: calcium, Mg: magnesium, PTH: parathyroid hormone, P: phosphorus, ALP: alkaline phosphatase, Ca/Cre: Ca/creatinine clearance ratio, ACTH: adrenocorticotropic hormone, MRI: magnetic resonance imaging, LT4: levothyroxine, ASD: atrial septal defect, GFR: glomerular filtration rate

MIRAGE syndrome manifests with bicytopenia during infancy (1,3,6,7). Adrenal hypoplasia is a well-known endocrinopathy associated with MIRAGE syndrome. It is frequently detected in investigations to determine the underlying causes of adrenal insufficiency, particularly in individuals with a history of intrauterine growth restriction, postnatal growth retardation, and extra-adrenal involvement. In our case, a standard dose ACTH stimulation test showed sufficient peak cortisol levels, and treatment initiation has not yet been initiated. Upon reviewing the existing literature, adrenal insufficiency was identified in 70% of the 50 reported cases, indicating a relatively low sensitivity for this particular finding (1,6). Although adrenal hypoplasia was absent in our case, the patient displayed rare manifestations within the endocrine system, which is a noteworthy observation.

Due to the rarity of the disease, it is difficult to define the phenotype-genotype relationship. An individual with the same *SAMD9*:c.2159del variant, which was classified as likely pathologic in genetic databases (Franklin by Genoox, ClinVar) is reported. However, we could not find a published case report. To the best of our knowledge, only one case of MIRAGE syndrome has been reported from Türkiye with the variant c.2920G>A (p.E974K) in *SAMD9*. This patient presented with adrenal hypoplasia on the 15th day of life (7). Considering the rarity of the disease and the limited number of diagnosed cases worldwide, the phenotype-genotype relationship may differ on a variant-specific basis, which suggests that adrenal hypoplasia might not have developed yet or may never develop in our case. One patient with c.2318T>C in *SAMD9* has been reported who

developed adrenal hypoplasia at the age of 10 years (8). The effect of the variant in our case may be observed at a later age; hence close monitoring of the patient is ongoing.

This case report contributes to the existing literature by presenting a case of MIRAGE syndrome with additional clinical manifestations, including a previously unreported endocrine representation of primary hypoparathyroidism. The presence of primary hypoparathyroidism might be related to the clinical spectrum of the syndrome.We excluded other conditions that could cause hypoparathyroidism through clinical and laboratory investigations and detailed genetic analyses, including FISH, WES, and microarray analysis. The patient also exhibited subtle findings of clitoral hypoplasia. Since histological examination was not performed due to its invasive nature, ovarian dysgenesis could not be confirmed. However, the AMH level was in the normal range for her age. Close monitoring is also maintained to assess for potential gonadal insufficiency that may occur during puberty.

The *SAMD9* gene product plays a crucial role in regulating cell growth and differentiation, and GOF mutations in this gene have been implicated in the pathogenesis of MIRAGE syndrome (1,6). This mechanism may explain the severe short stature observed in our case. Interestingly, the patient also developed hyperglycemia at around four years of age, requiring low-dose insulin therapy. We initially diagnosed the patient with diabetes while there were still beta cell reserves in the pancreas. We observed decreased C-peptide levels during follow-up, indicating a loss of beta cell reserves, as laboratory tests showed. Despite the depletion of beta cell reserves, it was intriguing to see that blood sugar regulation was achieved under low-dose insulin therapy without any dose increase. Diabetes autoantibodies were also negative. No variants were shown in mitochondrial DNA analysis. This clinical exhibition was different from the classic presentation of type 1 diabetes mellitus and may be linked to the as-yet-undisclosed mechanisms of the syndrome. To the best of our knowledge, diabetes has not been reported in MIRAGE syndrome until now. Although the exact mechanism underlying this glucose dysregulation is not fully understood, it may be related to the underlying genetic abnormalities and the dysregulation of multiple organ systems observed in MIRAGE syndrome. Further research is needed to elucidate the pathophysiological mechanisms linking MIRAGE syndrome and abnormalities in glucose metabolism.

GOF mutations in *SAMD9* generally cause MIRAGE syndrome. The excessive antiproliferative effect by *SAMD9* of-function GOF variants induce various genetic alterations, including loss of chromosome 7 or its long arm (monosomy 7/7q), second-site loss-of-function (LOF) variants in cis or trans configuration, as well as uniparental disomy for the long arm of chromosome 7. However, the involvement of compensatory mechanisms is not clear (9). While inheritance of *SAMD9*-linked MIRAGE from an asymptomatic mother has been reported by Roucher-Boulez et al. (10), these instances were attributed to a reversion mechanism observed in the mother. She carried the GOF variant involved in MIRAGE, alongside another stop mutation in cis, which appeared *in utero* in her but was not transmitted to her child. Variable expressivity and incomplete penetrance in MIRAGE syndrome are consistent with an autosomal dominant inheritance pattern (1,6,11). Segregation analysis revealed that the mother was heterozygous for the c.2159del(p.Asn720ThrfsTer35) variant in *SAMD9*, while the father was normal. Variable age of onset, incomplete penetrance, and expressivity differences are frequently observed in autosomal dominant inherited diseases (11). Therefore, it is common to find cases where children are affected, but parents do not show clinical symptoms. These factors may explain the absence of the disease phenotype in the mother. However, a frameshift variant was detected in our patient, which cause quiet likely a LOF variant. Mehawej et al. (9) reported a case of autosomal recessive MIRAGE-like disease, who had bi-allelic LOF variants in the *SAMD9*. The discovery of a heterozygous LOF in the patient exhibiting a MIRAGE-like phenotype suggested the potential presence of another heterozygous LOF variant inherited from the father, which might have been undetected. This speculation would explain why the mother remained asymptomatic due to the same heterozygous LOF variant. Genetic counseling was provided to the family to elucidate potential inheritance patterns and assist in understanding the risk of recurrence.

MIRAGE syndrome involving *SAMD9* and *SAMD9L* mutations, some of which exhibit transient monosomy 7, has been suggested to be a clonal event followed by somatic correction through uniparental disomy for chromosome 7q (UPD7q) with double wildtype *SAMD9L* (12). Transient monosomy 7 has also been reported in pediatric patients with MDS. Typically, patients with MDS die due to subsequent infections (1,6,7,12,13). *SAMD9* variants may cause syndromic or non-syndromic MDS. Therefore, there may be children who may have isolated enteropathy, isolated immune deficiency, or isolated genital anomalies, as reported by Narumi et al. (1). The presented patient is being closely monitored for the development of MDS.

In recent years, there have been reported cases demonstrating both dysautonomia and proteinuria (5,6,7). Our patient has exhibited proteinuria from the age of 4 years and 7 months. Furthermore, clinical manifestations indicative of autonomic dysfunction have been observed, including frequent episodes of hypotension, feeding difficulties, and absence of tears. Although specific diagnostic tests, such as contractions with the methacholine eye drop test, evaluation of catecholamine metabolite levels, and a histamine intradermal reaction test

have not been conducted, the patient's clinical presentation aligns with symptoms commonly associated with dysautonomia. In addition to the multisystemic manifestations, the patient has experienced recurrent and intractable vomiting episodes, which are indicative of potential dysautonomia symptoms. A case series on hereditary sensory and autonomic neuropathies underscores the presence of autonomic dysfunction (2,3,4,5). Therefore, we suggest that recurrent vomiting episodes should be considered indicative of dysautonomia in MIRAGE syndrome.

Renal involvement in MIRAGE syndrome warrants consideration, as evidenced by the development of medullary nephrocalcinosis, hypomagnesemia, hypomagnesuria, hypophosphatemia, decreased GFR, and nephritic proteinuria, which have been reported in other cases with renal involvement in MIRAGE syndrome (5,6,8).

Hematopoietic stem cell transplantation is the established curative approach. However, syndrome-specific comorbidities may impede treatment success and cause additional challenges, such as possible adverse outcomes and potential complications (14). The CRISPR/Cas9 system holds promise as a future treatment modality for MIRAGE (15). Thus, it becomes imperative to understand the clinical manifestations and molecular mechanisms associated with germline *SAMD9* variants to facilitate the effective management of the disease.

In conclusion, this case report expands the multisystemic nature of MIRAGE syndrome and highlights the diagnostic challenges associated with this rare disorder. The presented case of MIRAGE syndrome is the first description of primary hypoparathyroidism in a patient with MIRAGE. Additional complications such as symptoms of dysautonomia symptoms, glucose dysregulation, and renal and hematological abnormalities highlight the need for multidisciplinary management in individuals with MIRAGE syndrome. Further research is warranted to elucidate the underlying mechanisms linking *SAMD9* variants to the clinical features of MIRAGE syndrome and to develop targeted therapeutic interventions for this rare condition.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sirmen Kızılcan Çetin, Elif Özsu, Zeynep Şıklar, Hasan Fatih Çakmaklı, Gizem Şenyazar, Zehra Aycan, Concept: Sirmen Kızılcan Çetin, Fatih Çakmaklı, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu, Design: Sirmen Kızılcan Çetin, Zeynep Şıklar, Zehra Aycan, Merih Berberoğlu, Data Collection or Processing: Sirmen Kızılcan Çetin, Elif Özsu, Zeynep Şıklar, Gizem Şenyazar, Zehra Aycan, Serdar Ceylaner, Analysis or Interpretation: Sirmen Kızılcan Çetin, Elif Özsu, Zeynep Şıklar, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu, Literature Search: Zeynep Şıklar, Gizem Şenyazar, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu, Writing: Elif Özsu, Zeynep Şıklar, Zehra Aycan, Serdar Ceylaner, Merih Berberoğlu.

Conflict of Interest: One author of this article, Merih Berberoğlu is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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