10.4274/jcrpe.galenos.2024.2023-12-4

Case Report

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

What is already known about this topic?

- MIRAGE syndrome is a rare multisystemic disorder It is characterized by various manifestations, including myelodysplasia, susceptibility to infections, growth retardation, adrenal hypoplasia, genital anomalies, and enteropathy.
- The syndrome is associated with pathogenic variants in the *SAMD9*.This case report involves a 3.5-year-old girl with a specific *SAMD9* variant (c.2159del; p.Asn720ThrfsTer35).

What this study adds to the literature?

- 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 underscores the heterogeneity of clinical presentations within this disorder.
- This case report emphasizes the diagnostic challenges associated with MIRAGE syndrome, as its diverse phenotypic presentation can make it difficult to recognize and diagnose the condition accurately.

Abstract
MIRAGE syndrome is a rare multisystemic disorder characterized by various manifestations, such as myelodysplasia, susceptibility to infections, growth retardation, adrenal hypoplasia, genital anomalies, and enteropathy. In the literature, there have been rare cases of dysautonomia. We present a 6.5-year-old girl, who was first admitted to our department 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, hypermagnesiuria, 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 observed in MIRAGE syndrome.
Keywords: Dysautonomia, hypoparathyroidism, MIRAGE syndrome, monosomy 7, *SAMD9*

Sirmen Kizilcan Cetin, MD, Department of Pediatric Endocrinology, School Of Medicine, Ankara University, Ankara, Turkey
+903125956635
drsrmnkzlcn@gmail.com
12.12.2023
19.03.2024

Published: 26.03.2024

Introduction
MIRAGE syndrome is a rare multisystemic disorder characterized by **M**yelodysplasia, **I**nfection, **R**estriction of Growth, **A**drenal Hypoplasia, **G**enital Phenotypes, and **E**nteropathy syndrome. It is a recently described autosomal dominant disorder caused by gain-of-function mutations in the *SAMD9* located on chromosome 7q21.2 (1). This syndrome is typically diagnosed in early childhood. While the classical features of the syndrome have been well-documented, autonomic dysfunction, such as insensitivity and anhidrosis, has been infrequently reported (2-5). A total of 44 affected individuals with MIRAGE syndrome have been documented(6).
Variants in the *SAMD9* can cause structural and functional changes in the endosome system. It leads to 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. Additionally, the loss of chromosome 7 carrying the *SAMD9* mutation may be associated with developing myelodysplastic syndrome 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 mortality age of three years. Most deaths, around 60%, are caused by infectious diseases. While there have been isolated reports of individuals with MIRAGE syndrome reaching the age of 20, the overall survival rates for this condition remain low(6).
Here, we present a unique case of MIRAGE syndrome with the additional clinical features of primary hypoparathyroidism and dysautonomia, highlighting the diagnostic challenges, clinical manifestations, and multidisciplinary management. To our knowledge, primary hypoparathyroidism and diabetes have not been reported within the endocrine phenotype of MIRAGE syndrome.

Case Presentation
A current case was born to healthy, non-consanguineous parents at 39 weeks of gestation, with a birth weight of 2790 g. The patient had unremarkable antenatal ultrasound findings. She exhibited normal neurodevelopmental milestones. However, at 15 days of age, she was diagnosed with congenital hypothyroidism [TSH: 88.47 mIU/l, sT4: 14.52 pmol/l (13.9-26.19), urine iodine: 95 mcg/L (100-200), thyroid ultrasound normal with right lobe 11x6x4mm, left lobe 16x6x5mm isthmus 1.5 mm; total volume 0,39 ml (-1.3 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 BMI of 14 kg/m2 (-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 (P) 7.36 mg/dL (3.8-6.5), parathormone (PTH) 8.9 pg/ml with normal magnesium (Mg) 2 mg/dL (1.7-2.1), alkaline phosphatase (ALP) 217 U/L (142-335), urine Ca/Cre: 0.24 and 25-Hydroxyvitamin D:53 mcg/L. The patient was diagnosed with primary hypoparathyroidism. Medical history revealed that the daily calcium 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 FISH testing, and an atrial septal defect (ASD) and normal hearing were detected. Tests for polyglandular autoimmune syndrome type 1, including 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 (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 autoantibody Ig A, serum total Ig A level, and urine analysis were normal.. IGF-1 was 280 ng/mL (reference range: 84-447), IGFBP3was 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 4 years, treatment with LT4 was discontinued. During the follow-up periods, thyroid function tests were normal. Additionally, the patient's cognitive function and neurodevelopmental milestones were assessed during these visits and 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 (respectivley mother: FBG: 83 mg/dl, HbA1c %5.5, father: 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 showed 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 the *SAMD9*, classified as likely pathogenic. Consequently, the patient was diagnosed with MIRAGE Syndrome. Segregation analysis revealed that the mother carried the heterozygous mutation in the *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 (FSH) 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 at mini puberty 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 magnesium 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 m² and nephrotic proteinuria (9 mg/m²/day) were also observed. Magnesium supplementation was initiated, and the patient was 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. The patient's gross motor development was -2 SD, indicating a developmental delay. Cognitive development was in the low normal.

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/m2 (-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 calcitriol, magnesium supplementation. A multidisciplinary team is closely monitored to ensure comprehensive care and follow-up (Table 2, Figure 1).

Discussion

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

We describe the diagnostic challenges and various clinical manifestations associated with MIRAGE syndrome. Typically, 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. We observed an entry for an individual with the same *SAMD9*:c.2159del variant which was classified as likely pathologic in genetic databases (Franklin by Genoox, ClinVar). However, we could not find a case report in the literature. To our knowledge, only a case from Turkey has been reported with a variant c.2920G>A (p.E974K) in the *SAMD9*, presenting 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 in our case. A patient with c.2318T>C in the *SAMD9* has been reported to develop adrenal hypoplasia at the age of 10 (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 unique 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 exhibits 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* plays a crucial role in regulating cell growth and differentiation, and gain-of-function mutations in this gene have been implicated in the pathogenesis of MIRAGE syndrome(1, 6). This mechanism has explained the severe short stature observed in our case.

Interestingly, the patient also developed hyperglycemia at a later stage, 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 the patient's 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 diabetes and may likely be linked to the as-yet-undisclosed mechanisms of the syndrome. To 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.

Gain-of function mutations in the *SAMD9* generally cause MIRAGE syndrome. The excessive antiproliferative effect by SAMD9 gain-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 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 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 the *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 can explain the absence of the disease phenotype in the mother. However, a frameshift variant was detected in our patient, which cause quiet likely a loss of function (LOF) variant. Mehawej C et al. (9) reported a case with an 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 loss-of-function variant inherited from the father, which might have been undetected. This speculation supports that 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 myelodysplastic syndrome (MDS). Typically, patients with MDS die due to subsequent infections(1, 6, 7, 12, 13). *SAMD9* variants can cause syndromic or nonsyndromic myelodysplastic syndrome (MDS). This condition suggests the presence of children who may have isolated

enteropathy, isolated immune deficiency, or isolated genital anomalies, as reported by Narumi et al(1). The patient is closely monitored for the development of MDS, too.

In recent years, there have been reported cases demonstrating both dysautonomia and proteinuria (5-7). Our patient has exhibited proteinuria since 4 years and 7 months of age. 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 (2-5). Therefore, the recurrent vomiting episodes should be considered indicative of dysautonomia in MIRAGE syndrome.

Renal involvement in MIRAGE syndrome warrants attention, as evidenced by the development of medullary nephrocalcinosis, hypomagnesemia, hypermagnesiuria, hypophosphatemia, decreased glomerular filtration rate, 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 can 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 our understanding of the multisystemic nature of MIRAGE syndrome and highlights the diagnostic challenges associated with this rare disorder. The identification of a novel endocrine manifestation of primary hypoparathyroidism might be related to MIRAGE syndrome.Additional complications such as dysautonomia symptoms, glucose dysregulation, and renal and hematological abnormalities emphasize 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.

Statements

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This case report was not supported by any sponsor or funder.

Author Contributions

Medical Practices:SKC, ZA, ZS, EO,HC GS , Concept:SKC, ZA, SC,HC, SC, MB, Design: SKC,ZA, ZS, MB, Data collection: SKC, ZA,ZS SC, EO,GS , Analysis: : SKC, ZS, EO, SC,ZA, MB, Literature Search: SC, ZA, ZS, MB, GS , Writing: SC, ZA, ZS, EO, MB

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Narumi S, Amano N, Ishii T, Katsumata N, Muroya K, Adachi M, et al. SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet. 2016;48(7):792-7.
2. Kawashima-Sonoyama Y, Okuno K, Dohmoto T, Tanase-Nakao K, Narumi S, Namba N. The case of a patient with MIRAGE syndrome with familial dysautonomia-like symptoms. Hum Genome Var. 2021;8(1):27.
3. Jeffries L, Shima H, Ji W, Panisello-Manterola D, McGrath J, Bird LM, et al. A novel SAMD9 mutation causing MIRAGE syndrome: An expansion and review of phenotype, dysmorphology, and natural history. Am J Med Genet A. 2018;176(2):415-20.
4. Shima H, Koehler K, Nomura Y, Sugimoto K, Satoh A, Ogata T, et al. Two patients with MIRAGE syndrome lacking haematological features: role of somatic second-site reversion SAMD9 mutations. J Med Genet. 2018;55(2):81-5.
5. Ishiwa S, Kamei K, Tanase-Nakao K, Shibata S, Matsunami K, Takeuchi I, et al. A girl with MIRAGE syndrome who developed steroid-resistant nephrotic syndrome: a case report. BMC Nephrol. 2020;21(1):340.
6. Tanase-Nakao K, Olson TS, Narumi S. MIRAGE Syndrome. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
7. Mengen E, Uçaktürk SA. A rare etiology of 46, XY disorder of sex development and adrenal insufficiency: A case of MIRAGE syndrome caused by mutations in the SAMD9 gene. Journal of Clinical Research in Pediatric Endocrinology. 2019;12(2):206-11.
8. Perisa MP, Rose MJ, Varga E, Kamboj MK, Spencer JD, Bajwa RPS. A novel SAMD9 variant identified in patient with MIRAGE syndrome: Further defining syndromic phenotype and review of previous cases. Pediatr Blood Cancer. 2019;66(7):e27726.
9. Mehawej C, Ibrahim M, Khalife L, Chouery E, El Hachem S, Sayad A, et al. A homozygous frameshift variant expands the clinical spectrum of SAMD9 gene defects. Clinical Genetics. 2022.
10. Roucher-Boulez F, Mallet D, Chatron N, Dijoud F, Gorduza DB, Bretones P, et al. Reversion SAMD9 mutations modifying phenotypic expression of MIRAGE syndrome and allowing inheritance in a usually de novo disorder. Frontiers in endocrinology. 2019;10:625.
11. Cooper DN, Krawczak M, Polychronakos C, Tyler-Smith C, Kehrer-Sawatzki H. Where genotype is not predictive of phenotype: towards an understanding of the molecular basis of reduced penetrance in human inherited disease. Human genetics. 2013;132:1077-130.
12. Pastor VB, Sahoo SS, Boklan J, Schwabe GC, Saribeyoglu E, Strahm B, et al. Constitutional SAMD9L mutations cause familial myelodysplastic syndrome and transient monosomy 7. Haematologica. 2018;103(3):427-37.
13. Rahim MQ, Rahrig A, Overholt K, Conboy E, Czader M, Saraf AJ. A familial SAMD9 variant present in pediatric myelodysplastic syndrome. Cold Spring Harb Mol Case Stud. 2023;9(2).
14. Sarthy J, Zhang L, Babushok D, Shenoy A, Fan JM, Wertheim G, et al. Poor outcome with hematopoietic stem cell transplantation for bone marrow failure and MDS with severe MIRAGE syndrome phenotype. Blood Adv. 2018;2(2):120-5.
15. Pera J, Castaño J, Casamitjana J, Giorgetti A, Romero-Moya D. Generation of heterozygous SAMD9 CRISPR/Cas9-edited iPSC line (ESi086-A-3), carrying p.I1567M mutation. Stem Cell Res. 2022;64:102906.

Figure 1. Timeline of the patient's clinical presentation

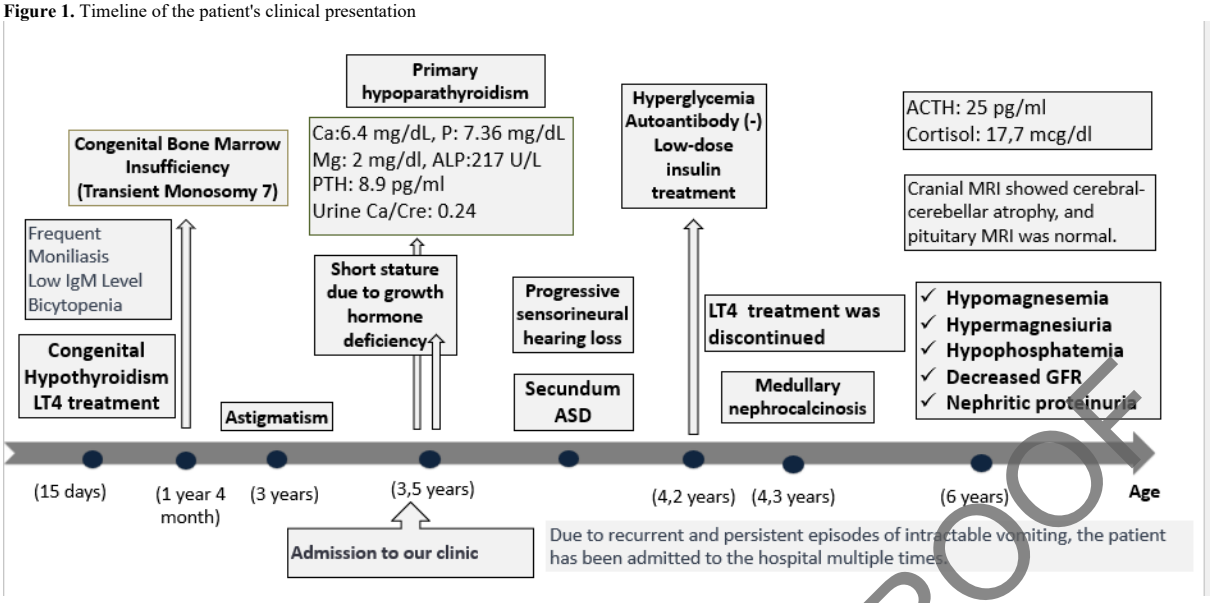

Table 1.

Age (year)	TSH(μIU/mL) (0.38-5.33)	sT4 (pmol/L) (7-15.96)	Levothyroxine (mcg/kg/day)
3	2.49	11.68	2.5
3.22	1.77	11.86	2.5
3.53	1.71	10.33	2.5
3.55	2.08	11.68	2.5
3.74	1.72	11.58	2.5
3.86	2.12	13.53	2.5
3.88	0.72	13.42	2.5
4.11	2.45	11.86	2.5
4.2	1.57	12.92	2.5
4.3	5.09	14.3	ceased
4.32	5.45	13.8	-
4.48	5.55	12.6	-
4.51	5.32	12.5	-
4.68	5.51	13.6	-
4.8	5.26	9.61	-
5.1	5.87	14.5	-
5.6	4.4	12.8	-
6.1	3.64	12.3	-
6.5	4.01	12.9	-