Clinical, Radiologic, and Genetic Spectrum of Schimke Immuno-Osseous Dysplasia

Mehtap Akbalık Kara, Beltinge Demircioğlu Kılıç, Mithat Büyükçelik, Ayşe Balat

Department of Pediatric Nephrology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye

Schimke immuno–osseous dysplasia (SIOD) was first described by Schimke in 1971.[1] It is a rare, autosomal recessive multisystem disorder characterized by facial dysmorphism, spondylo–epiphyseal dysplasia (SED), T-cell immunodeficiency, and nephrotic syndrome (NS).[1] Although the exact prevalence is unknown, it is estimated to range from 1:1,000,000 to 1:3,000,000 live births.

The multiprotein complex, which includes a member of the well-conserved sucrose non-fermenting type 2 (SNF2) protein family, is involved in chromatin remodeling required for gene regulation, replication, recombination, and DNA repair. SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A-like 1 (SMARCAL1) encodes an enzyme homologous to SNF2 chromatin-remodeling proteins. Pathogenic variants in SMARCAL1 that lead to the SIOD phenotype affect protein expression, stability, subcellular localization, chromatin binding, and enzymatic activity.

Elizondo et al.[2,3] reported that SMARCAL1 mRNA and protein, which contain a conserved C-terminal SNF2 domain, are expressed in all affected tissues, including bone, kidney, thymus, thyroid, teeth, bone marrow, hair, eye, and blood vessels, in patients with SIOD.

We report six pediatric cases of SIOD from a single center, characterized by growth retardation, immunodeficiency, renal failure, and vascular complications. The study was approved by the Ethics Committee of Gaziantep University (approval number: 409/2021, date: 27.01.2021), and informed consent was obtained from the patients' families for the publication of images and clinical information.

All patients were born to consanguineous parents and demonstrated intrauterine growth retardation and preterm birth. The demographic, clinical, and radiological findings are summarized in Table 1.

Patient 1 was a 6-year-old girl who presented with steroid-resistant NS. Genetic testing revealed a homozygous NM_014140.3 (SMARCAL1): c.2459G > A (p.Arg820His) variant. She developed cerebral infarction and Coombs-positive hemolytic anemia. Following steroid therapy, a favorable hematologic response was observed. Despite supportive care and anticoagulation, she died from bacteremia and acute respiratory distress at 11 years of age.

Patient 2, a cousin of Patient 1, was diagnosed with NS and hypertension at 6 years. She was treated with cyclosporine A (CsA) for NS. She exhibited typical SIOD features, including a triangular face, low nasal bridge, bulbous nasal tip, pigmented macules, short neck, and trunk with lumbar lordosis (Figure 1a). Genetic analysis identified the same homozygous NM_014140.3 (SMARCAL1): c.2459G > A (p.Arg820His) variant. After CsA cessation, generalized edema recurred; CsA was temporarily resumed and later discontinued. Peritoneal dialysis (PD) was initiated due to end-stage renal disease (ESRD). She developed neurological symptoms with cerebral white matter lesions and died from bacteremia at age 11.

Patient 3 was an 8-year-old boy who presented with NS. Kidney biopsy revealed focal segmental glomerulosclerosis (FSGS). He exhibited growth retardation, hypogammaglobulinemia, and harbored a homozygous NM_014140.3 (SMARCAL1): c.2459G > A (p.Arg820His) variant (Figure 1b). PD was initiated at age 9. He later experienced a generalized tonic-clonic seizure; brain MRI and electroencephalography were unremarkable. Anti-epileptic therapy and low-molecular-weight heparin were administered. The patient remains under follow-up.

Patient 4, an 8-year-old Syrian refugee girl (Figure 1c), carried a novel homozygous NM_014140.3 (SMARCAL1): c.1177C > T (p.Arg393*) variant, classified as likely pathogenic. Two siblings had died of similar symptoms in Syria. She developed cerebral infarction, status epilepticus, progressive neurocognitive impairment, and bone marrow failure, and died from sepsis at 12 years of age.

Patient 5 was a 7-year-old girl who presented with ESRD and dysmorphic features (Figure 1d). She harbored the homozygous

Corresponding author: Mehtap Akbalık Kara, Department of Pediatric Nephrology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye

e-mail: mehtapakbalik@hotmail.com

Received: October 07, 2025 **Accepted:** December 02, 2025 **Available Online Date:** xxxxxx • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-10-27

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: M.A.K. 0000-0003-0790-323X; B.D.K. 0000-0001-9408-2139; M.B. 0000-0002-6815-196X; A.B. 0000-0002-8904-1348.

Cite this article as: Akbalık Kara M, Demircioğlu Kılıç B, Büyükçelik M, Balat A. Clinical, Radiologic, and Genetic Spectrum of Schimke Immuno-Osseous Dysplasia: A Six-Patient Single-Center Case Series. Balkan Med J.;

TABLE 1. Demographical, Clinical and Radiological Findings of Children with Schimke Immuno-Osseous Dysplasia.

	Number of affected patients/number of all patients
Demographical and physical findings	
Gender	
Female	4/6
Male	2/6
Parental consanguinity	6/6
Age at presentation	
6 years	2/6
7 years	2/6
8 years	2/6
IUGR	6/6
Delayed postnatal growth	6/6
Physical features	
Triangular face	5/6
Low nasal bridge	5/6
Bulbous nasal tip	5/6
Microdontia	3/6
High pitched voice	3/6
Unusual hair	2/6
Pigmented macules	6/6
Short neck and trunk	6/6
Lumbar lordosis	6/6
Big hands	6/6
Protruding abdomen	6/6
Corneal opacities	2/6
Final status	
Follow-up	1/6
Exitus	5/6
Radiological findings	
Ovoid flat vertebrae	4/6
Hypoplastic pelvis	4/6
Abnormal femoral heads	6/6
System based follow-up findings	
Renal findings	
Proteinuria	6/6
ESRD	4/6
Hematological and auto-immune findings	
Lymphopenia	6/6
Thrombocytopenia	1/6
Anemia	6/6
Neutropenia	1/6
Coombs-positive hemolytic anemia	1/6
Bone marrow failure	1/6
Immunological findings	
Hypogammaglobulinemia	2/6
Recurrent infections	2/6
Neurological findings	
Cerebral ischemia	3/6
Arteriosclerosis	2/6

IUGR, intrauterin growth retardation; ESRD, end-stage renal disease.

NM_014140.3 (SMARCAL1): c.2459G > A (p.Arg820His) variant. Despite PD and antihypertensive therapy, she died at 10 years of age.

Patient 6 was a 7-year-old boy who initially presented with growth retardation and was subsequently diagnosed with FSGS. Genetic testing revealed a homozygous NM_014140.3 (SMARCAL1): c.2450G > A (p.Arg817His) variant. He progressed to stage IV chronic kidney disease and died from ischemic stroke at 9 years of age.

All patients in this cohort demonstrated characteristic SIOD features, including dysmorphic facies, short stature (height SDS: Patient 1, −6.08; Patient 2, −7.03; Patient 3, −3.77; Patient 4, −7.09; Patient 5, −5.09; Patient 6, −4.89), SED (Supplementary Figures 1a, b), immunodeficiency—predominantly CD3/CD4 lymphopenia—and progressive renal dysfunction. Neurovascular complications, particularly ischemic strokes, were common and contributed significantly to mortality. The majority of patients did not respond to immunosuppressive therapy, and outcomes remained poor despite supportive treatment. A comparative table summarizing our SIOD cohort alongside previously reported SMARCAL1-related phenotypes is provided in Supplementary Table 2. Pedigrees of all patients are shown in (Supplementary Figures 2-7).

SIOD is a rare autosomal recessive multisystem disorder characterized by growth failure, T-cell immunodeficiency, recurrent infections, spondyloepiphyseal dysplasia, hypothyroidism, cerebral ischemia, distinctive facial features, NS, and progressive kidney dysfunction.[1] Mutations in the *SMARCAL1* gene, which encodes a protein homologous to the SNF2 family of chromatin-remodeling enzymes, are responsible for SIOD.[4]

Disease severity is influenced by the type of SMARCAL1 mutation. Nonsense, frameshift, and splicing mutations are generally associated with severe clinical manifestations, whereas most missense mutations result in milder phenotypes.[5] Definitive diagnosis can be achieved through molecular testing, including single-gene analysis, multigene panels, or broader genomic approaches such as exome sequencing, genome sequencing, or mitochondrial sequencing.[6]

In this study, SMARCAL1 variant analysis was performed using a targeted next-generation sequencing approach on the Illumina MiSeq platform. Parental segregation analysis was not conducted due to unavailability of parental samples. Genetic screening and prenatal diagnosis are feasible if familial mutations are known.[6] All patients in this cohort were born to consanguineous parents, and Patients 1 and 2 were cousins. Prenatal genetic testing was not performed due to the absence of previously identified familial mutations.

All individuals, except one, carried previously reported SMARCAL1 variants. In-silico pathogenicity analyses supported these findings. For the recurrent missense variants c.2459G > A (p.Arg820His) and c.2450G > A (p.Arg817His), SIFT predicted "damaging" (scores 0.00 and 0.01, respectively), PolyPhen-2 predicted "probably damaging" (0.99 for both), and CADD scores were high (PHRED 27–29 and 25–27). MutationTaster classified both variants as "disease causing." The novel nonsense variant c.1177C > T (p.Arg393*) demonstrated a very high CADD score PHRED ≈ 35) and was predicted as "disease causing" by MutationTaster, consistent with a loss-of-function effect.

A key contribution of this study is the identification of a novel homozygous variant, c.1177C > T (p.Arg393*), in SMARCAL1. According to ACMG/AMP criteria, this variant is classified as "likely pathogenic" (PVS1, PM2, PP3). Other variants identified, including c.2459G > A (p.Arg820His) and c.2450G > A (p.Arg817His), are known pathogenic variants consistent with the SIOD phenotype. The novel variant introduces a premature stop codon, predicted to result in a truncated or non-functional protein. This loss-of-function mechanism aligns with the severe clinical manifestations observed, including early-onset cerebral infarction, bone marrow failure, and rapid progression to renal failure. Compared with missense variants such as p.Arg820His or p.Arg817His, the nonsense variant appears to confer a more severe phenotype, supporting the concept that truncating mutations lead to complete loss of SMARCAL1 activity. The association of this novel variant with multisystem involvement expands the known phenotypic spectrum of SIOD and underscores the importance of early genetic testing for timely clinical management.[7,8]

Short stature was observed in nearly all patients due to SED.[9] SED has been reported in approximately 94.5% of SIOD cases.[9] Radiographic features include ovoid and mildly flattened vertebral bodies, small and deformed capital femoral epiphyses, and shallow, dysplastic acetabular fossae.[8] Additional findings reported in the literature include osteopenia (75%), lumbar lordosis (85.7%), platyspondyly (75%), ovoid vertebral bodies (50%), thoracic kyphosis (50%), and short, broad iliac bones (100%).[9]

In our cohort, all patients exhibited small, deformed femoral heads. Pelvic X-rays of Patients 2 and 4 demonstrated hypoplastic pelvises with shallow acetabular fossae, dysplastic femoral heads, and flattened vertebral bodies (Supplementary Figures 1a, b).

Neurological complications occur in approximately 50% of SIOD patients and include migraines, transient neurological attacks (TNAs), and ischemic strokes. The underlying mechanisms remain unclear.[10] TNAs are often non-ischemic focal events; some patients are heat-sensitive and experience central nervous system symptoms in warm environments.[11] Transient ischemic episodes have been associated with hypertension, hyperlipidemia, renal dysfunction, and arterial wall abnormalities.[12] Cerebral ischemia was first described by Spranger et al.[1] and later confirmed by Ehrich et al.[13]

In our series, Patients 1, 4, and 6 experienced cerebral ischemia and were treated with low-molecular-weight heparin. Arteriosclerosis was observed in Patients 1 and 4. Patient 6 did not undergo magnetic resonance angiography (MRA) due to clinical instability. Patient 2 had suspected TNAs, although MRA findings were unavailable; prophylactic heparin therapy was initiated. Despite the high prevalence of cerebrovascular events in SIOD, no standardized treatment protocol exists. Samanta and Ramakrishnaiah.[14] recommend early neuroimaging, aggressive management of systemic risk factors, prophylactic antithrombotic therapy, and, in cases of severe vascular stenosis, surgical revascularization.Renal ultrasound findings were normal in all patients except Patient 6, who had a right-sided ectopic pelvic kidney with evidence of scarring; bladder function was preserved. Bertulli et al.[15] recently described two SIOD patients with atypical renal anomalies—one with a right ectopic kidney and cerebral defects, and another with a multicystic dysplastic kidney and cardiac anomalies—expanding the spectrum of congenital anomalies of the kidney and urinary tract.

Nearly all SIOD patients develop nephropathy, typically presenting with proteinuria or NS, most frequently due to FSGS. Other reported glomerulopathies include minimal change disease, membranous nephropathy, and nephronophthisis.[16] In our cohort, three of four

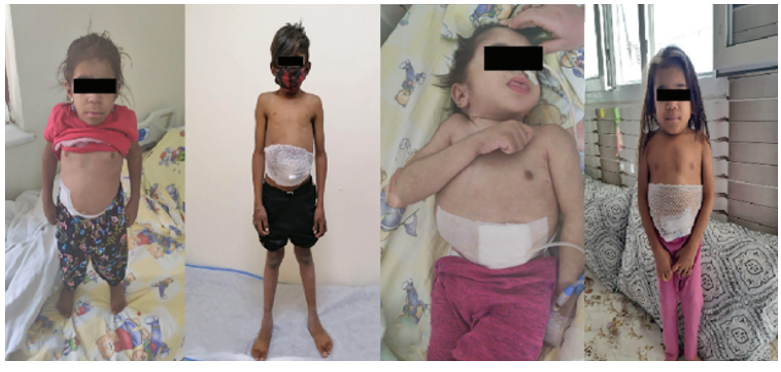

FIG. 1. (a) Patient 2. (b) Patient 3. (c) Patient 4. (d) Patient 5.

biopsied patients had FSGS, and one had C1q nephropathy. This genetic form of NS is generally steroid-resistant, although temporary reductions in proteinuria using ACE inhibitors and CsA have been documented.[16] Our patients demonstrated poor responses to steroids and immunosuppressants. CsA was discontinued after SIOD diagnosis in Patient 2, briefly restarted due to hypoalbuminemia, and later stopped as renal function deteriorated. Patients 1 and 6 died before reaching ESRD; Patient 6 had progressed to stage IV chronic kidney disease. Kidney transplantation in SIOD remains challenging; however, favorable outcomes have been reported in select cases.[17]

Cellular immunodeficiency in SIOD is characterized by recurrent lymphopenia and impaired mitogen-induced lymphocyte stimulation. Studies have reported reductions in CD4+ T cells and, occasionally, moderate hypogammaglobulinemia secondary to protein loss.[18] Immunological assessment in our patients revealed lymphopenia, decreased T-cell counts, and compromised cellular immunity. Patients 3 and 5 also exhibited hypogammaglobulinemia, likely attributable to persistent proteinuria.

Zieg et al.[19] reported that T-cell immunodeficiency in SIOD may predispose patients to autoimmune manifestations. In their survey of 41 SIOD patients with SMARCAL1 variants, eight exhibited autoimmune conditions, including thrombocytopenia, hemolytic anemia, and pericarditis with anti-cardiolipin antibodies. One patient had rituximab-resistant Evans syndrome.[19] In our series, two patients developed autoimmune complications. Patient 1 was diagnosed with Coombs-positive hemolytic anemia and initially responded to steroid therapy. The other patient developed bone marrow failure characterized by pancytopenia and died from sepsis before a hematopoietic stem cell transplant could be arranged, although successful transplants have been reported in similar cases.[20]

All parents in our cohort were consanguineous. Although parental segregation analysis was not performed, genetic counseling is strongly recommended for all families, emphasizing recurrence risk and the availability of prenatal or preimplantation genetic diagnosis.

In conclusion, SIOD is a rare multisystem disorder that is often misdiagnosed or recognized late. Our cases highlight the importance of considering SIOD in children presenting with unexplained growth failure and skeletal dysplasia. Screening for proteinuria may aid in early diagnosis. Multidisciplinary care and close monitoring for renal and vascular complications are essential, and timely planning for renal transplantation is critical for optimal management, although overall prognosis remains poor.

Acknowledgements: We would like to thank our peritoneal dialysis nurse Melek Aksay, Mustafa Göksular and Eylem Özkınalı for their hard work on our patients with peritoneal dialysis.

Ethics Committee Approval: The study was approved by the Ethics Committee of Gaziantep University (approval number: 409/2021, date: 27.01.2021).

Informed Consent: Informed consent was obtained from the patients' families for the publication of images and clinical information.

Authorship Contributions: Concept– M.A.K; Design– M.A.K, B.D.K.; Supervision– B.D.K., A.B. M.B.; Materials– M.A.K; Data Collection and/or Processing– M.A.K; Analysis and/or Interpretation– M.A.K.; Literature Review– M.A.K, M.B., A.B.; Writing– M.A.K, B.D.K; Critical Review– M.B., A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Supplementary: https://www.balkanmedicaljournal.org/img/files/SUPPLEMENTARY-2025.10-27.pdf

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