International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Family History of Schimke or Immuno-Osseous Dysplasia: Clinical Features and Management

N. Hazzab[1], A. Mehdaoui[2], S. Eddaoudi K[3], Khabbach[4], Y. Elboussadni[5], A. Oulmaati[6]

[1,2,3,4,5,6]Pediatric Department, Mohammed VI University Hospital

Abstract

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive disorder characterized by spondyloepiphyseal dysplasia, progressive nephropathy, immunodeficiency, and distinctive ectodermal features. We report two affected siblings born to consanguineous parents. The first case is a 4-year-old girl presenting with severe disproportionate short stature, lumbar lordosis, facial dysmorphism, coarse hair, hyperpigmented macules, and persistent lymphopenia, with normal renal function. The second case is her 3-year-old brother, who presented with growth retardation, facial dysmorphism, thoracic kyphosis, lumbar lordosis, steroid-resistant nephrotic syndrome, secondary hypothyroidism, and marked T-cell deficiency. An older sibling had previously died from chronic kidney disease, and molecular testing in the family confirmed a SMARCAL1 mutation.

These observations illustrate the phenotypic variability and severity of SIOD and emphasize the importance of early diagnosis, monitoring of immunological and renal functions, and multidisciplinary management to improve outcomes.

Keywords: Schimke immuno osseous dysplasia, familial case, growth retardation, rare genetic disease, pediatric nephropathy

Introduction

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive spondylo-epiphyseal dysplasia characterized by progressive nephropathy leading to renal failure, lymphopenia with impaired cellular immunity, and hyperpigmented macules [1].Less common manifestations include premature atherosclerosis, dental and other ectodermal abnormalities, neurologic complications such as transient ischemic attacks and chronic headaches, autoimmune diseases, and malignancies including non-Hodgkin lymphoma and osteosarcoma[2].Without stem cell and/or renal transplantation, SIOD is typically fatal during adolescence, although survival into adulthood has been reported. The pathogenesis remains incompletely understood. Boerkoel et al. demonstrated that biallelic mutations in the chromatin-remodelling protein **SMARCAL1** cause SIOD [3].

Case Report

We report a family in which one child died at the age of 7 years from chronic kidney disease. The parents

are first-degree consanguineous and have normal stature. They have three other children.

Case 1

The oldest child is a 4-year-old girl born at term after an unremarkable pregnancy. At birth, she was small for gestational age (weight 2 kg, <3rd centile). Her intellectual and neurological development was normal. Clinical examination revealed a short trunk, height **85 cm** (–4 SD), weight 9 kg (–4SD), short neck, and accentuated lumbar lordosis. She had a characteristic facial appearance with a broad, depressed nasal bridge and slightly elongated upper lip, coarse fine hair, and a high-pitched voice. **(Figure 1 and 2)**. Cutaneous examination shows hyperpigmented macules were present on the upper limbs.

X-rays showed : Ovoid, flat and biconvex with progressive flattening more pronounced at dorso lumbar and lumbar levels, bilateral hypoplasia of femoral heads associates with acetabular dysplasia, proximal femoral epiphyses are small and irregular.

Laboratory results demonstrated lymphopenia (700/mm^3), and proteinuria was negative with a normal renal function She receives cotrimoxazole prophylaxis, and renal function and proteinuria are monitored regularly.

One year later she developed minimal proteinuria, and ACE inhibitor was started

Figure 1: characteristic facial features

Figure 2: Thoracic kyphosis, and lumbar lordosis

Case 2

Her 3-year-old brother was admitted for edema and growth retardation. Clinical examination showed a weight of 8 kg (–4 SD) and height 70cm (–4 SD). Facial dysmorphism (depressed nasal bridge and broad nasal tip) (Fig 3 and 4), disproportionate short stature with short trunk, thoracic kyphosis, and lumbar

lordosis were noted (Fig 5). And he had also Hyperpigmented macules, and he presented facial and limb edema.

He had nephrotic-range proteinuria, hypoalbuminemia, hypoproteinemia, and secondary hypothyroidism. Renal function was normal. Lymphopenia was present (400/mm³). Peripheral lymphocyte evaluation (Table I) revealed decreased T cells : reduced CD4 and CD8 counts.

His nephrotic syndrome was steroid-resistant. He is currently receiving nephroprotective therapy with thyroid hormone replacement and albumin infusion .

During one year, he presented recurrent respiratory infections, three of which required hospitalisation, and he needs albumin infusion regularly because of his nephrotic syndrome no controlled.

Lymphocyte	CD3	CD4	CD8	CD4/CD8
481/mm3	163/mm3	35/mm3	88/mm3	0,4

Table 1: subpopulations lymphocytes numeration

Figure 3: characterized facial features

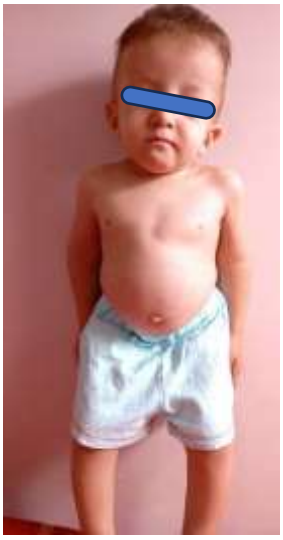

Figure 4: thoracic kyphosis, and lumbar lordosis

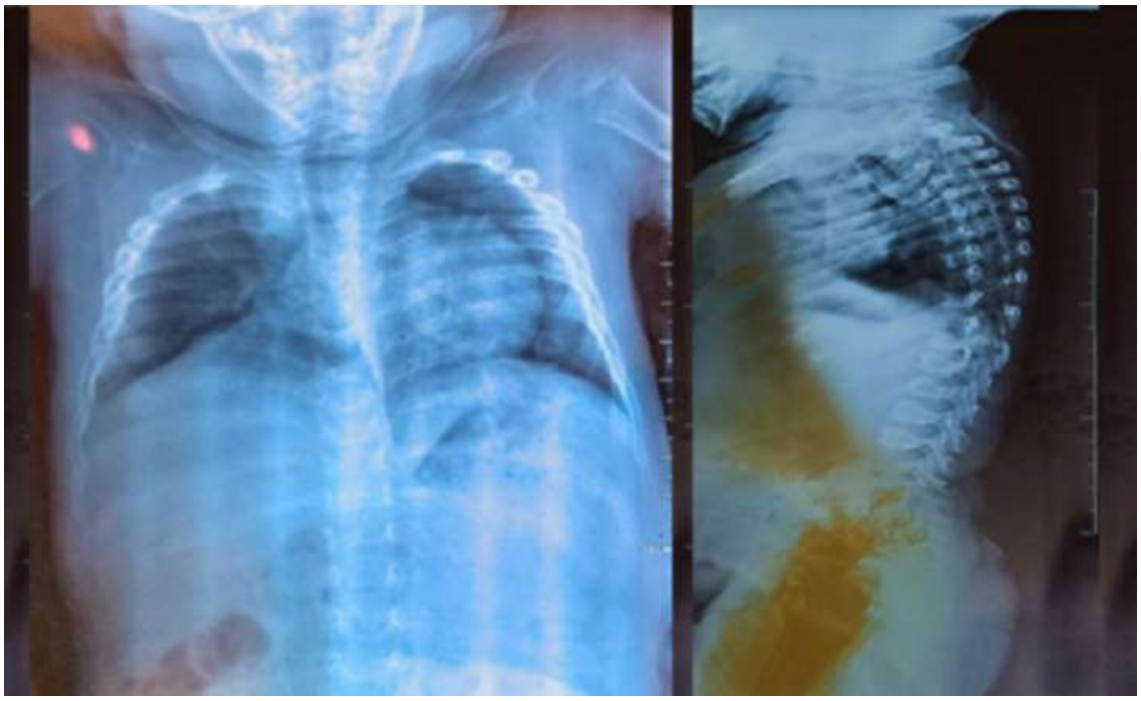

Figure 5: Thoracic kyphosis

Discussion

Spondyloepiphyseal dysplasia, renal dysfunction, immunodeficiency, and facial dysmorphism are consistent features of SIOD **[1].**Other manifestations include growth failure, episodic lymphopenia, cerebral ischemia, ectodermal abnormalities, hypothyroidism, ocular abnormalities, autoimmune diseases, and bone marrow hypoplasia. Although SIOD is often sporadic, consanguinity is common, The incidence is estimated at 1:1,000,000 to1:3,000,000 live birth, approximately half of SIOD patients carry biallelic **SMARCAL1** mutations **[4,5].**

Schimke immuno-osseous dysplasia is caused by biallelic variants in SMARCAL1, encoding the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A-like protein-1 (SMARCAL-1) from the SWI2/SNF2 family of ATP-dependent chromatin remodelling proteins . Disease severity inversely correlates with residual SMARCAL1 activity—mild and severe forms of SIOD are associated with missense and predicted loss-of-function (LOF) variants (nonsense, frameshift, or splicing), respectively **[6,7,8]**.

SMARCAL1 plays an important role in DNA stabilization and its deficiency leads to the impairment of cellular function due to the accumulation of DNA damage, resulting in a progressive systemic disease. It is still not clear how functional impairment of SMARCAL1 causes such a specific SIOD phenotype represented by alterations in the bones, kidney, and immune system, however it has been shown that proteins encoded by SMARCAL1 orthologs bu_er fluctuations in gene expression and that alterations in gene expression contribute to SIOD manifestations [9,10].

Clinical manifestations include:

- Disproportionate short stature (prenatal onset in 70%)
- Characteristic facial features (wide, depressed nasal bridge; broad nasal tip)
- Hyperpigmented macules

- Recurrent infections (60–80%)
- Dental anomalies
- Neurologic events (migraine, TIA, stroke)
- ocular manifestations (photophobia, macular hypoplasia, partial atrophy of the optic nerveexcavation of the optic discs, congenital cataract) **[11,12].**

Laboratory features include progressive steroid-resistant nephropathy and T-cell deficiency (reduced CD4 and CD8 counts). Radiographic features include ovoid vertebral bodies, endplate irregularities, small ilia, and dysplastic femoral epiphyses **[11].**

In our family, the deceased brother had confirmed **SMARCAL1** mutation, and the two surviving siblings showed characteristic clinical and biological features of SIOD:

- Short stature
- Facial dysmorphism
- Hyperpigmented macules
- Proteinuria
- T-cell deficiency
- Vertebral abnormalities (kyphosis/lordosis)

SIOD varies in severity, ranging from prenatal growth deficiency with death in the first few years of life to a slowly progressive course with survival into adulthood if ESRD is treated with renal dialysis and/or renal transplantation. The major cause of morbidity and mortality in SIOD is severe or recurrent infection related to T-cell deficiency (23%). Other causes of death include stroke (13%), pulmonary hypertension and congestive heart failure (13%), renal failure (11%), complications of organ transplantation (9%), lymphoproliferative disease (4%), gastrointestinal complications (4%), respiratory failure (4%), bone marrow failure (2%), non-Hodgkin lymphoma (2%), pancreatitis (2%), and other causes not reported (13%) **[13,14**].

SIOD management:

Renal management

Progressive nephropathy leads to end-stage disease, treated with dialysis or transplantation using minimal immunosuppression. **[13,15].**ACE inhibitors, cyclosporin or tacrolimus may reduce proteinuria temporarily

Immunodeficiency management

Prophylaxis includes antivirals like acyclovir, no live vaccines, and pneumocystis prevention, with bone marrow transplant for severe cases **[13,15].**

Skeletal and endocrine support

Hip arthroplasty addresses dysplasia, thyroid replacement manage hypothyroidism, growth hormone shows no benefit **[15].**

Vascular and other care

Pentoxifylline, aspirin or anticoagulants target arteriosclerosis, multidisciplinary support includes nutrition and therapy **[15].**

In our cases, they developed renal complications, recurring infections, skeletal abnormalities without vascular complication, which requires multidisciplinary management.

Conclusion:

Schimke immune osseous dysplasia is a rare and severe multisystem genetic disorder with significant clinical variability. This family history illustrates the challenges of early diagnostic and highlights the importance of considering this condition in patients presenting with growth failure, renal involvement, and immunodeficiency. Management remains mainly supportive and requires a multidisciplinary approcach, while prognosis is often limited by renal and infectious complications.

References:

1. Boerkoel CF, O'Neill S, Andre JL, Benke PJ, Bogdanovic R, Bulla M, et al. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and review of the literature. *Eur J Pediatr*. 2000;159:1–7.
2. Carroll C, Carroll R, Rypkema J, Son MBF, Nigrovic PA. Schimke immuno-osseous dysplasia associated with undifferentiated carcinoma and a novel SMARCAL1 mutation in a child. *Pediatr Blood Cancer*. 2013;60(9):E88–E90.
3. Boerkoel CF, Takashima H, John J, Yan J, Stankiewicz P, Rosenbarker L, et al. Mutant chromatin-remodelling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. *Nat Genet*. 2002;30:215–20.
4. Özdemir N, Düzova A, Yalçinkaya F, Şimşek E, Aydin Z, Öner A. Membranous nephropathy in Schimke immuno-osseous dysplasia. *Pediatr Nephrol*. 2006;21:870–2.
5. Lippner E, Lücke T, Salgado C, et al. Schimke's immunoosseous dysplasia [Updated March 30, 2023]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. Gene reviews ®. Seattle (WA): University of Washington, Seattle; 2002 Oct 1. p. 1993e2023 [Internet].
6. Bansbach, C.E.; Bétous, R.; Lovejoy, C.A.; Glick, G.G.; Cortez, D. The annealing helicase, SMARCAL1 maintains genome integrity at stalled replication forks. Genes Dev. 2009, 23, 2405–2414. [CrossRef]
7. Elizondo, L.I.; Huang, C.; Northrop, J.L.; Deguchi, K.; Clewing, J.M.; Armstrong, D.L.; Boerkoel, C.F. Schimke immuno-osseous dysplasia: A cell autonomous disorder? Am. J. Med. Genet. A 2006, 140, 340–348. [CrossRef] [PubMed]
8. Elizondo, L.I.; Cho, K.S.; Zhang, W.; Yan, J.; Huang, C.; Huang, Y.; Choi, K.; Sloan E, A.; Deguchi, K.; Lou, S.; et al. Schimke immuno-osseous dysplasia: SMARCAL1 loss-of-function and phenotypic correlation. J. Med. Genet. 2009, 46, 49–59. [CrossRef] [PubMed]
9. Baradaran-Heravi, A.; Raams, A.; Lubieniecka, J.; Cho, K.S.; DeHaai, K.A.; Basiratnia, M.; Mari, P.O.;Xue, Y.; Rauth, M.; Olney, A.H.; et al. SMARCAL1 deficiency predisposes to non-Hodgkin lymphoma and hypersensitivity to genotoxic agents in vivo. Am. J. Med. Genet. A 2012, 158, 2204–2213. [CrossRef] [PubMed]
10. Dekel, B.; Metsuyanim, S.; Goldstein, N.; Pode-Shakked, N.; Kovalski, Y.; Cohen, Y.; Davidovits, M.;Anikster, Y. Schimke immuno-osseous dysplasia: Expression of SMARCAL1 in blood and kidney provides novel insight into disease phenotype. Pediatr. Res. 2008, 63, 398–403. [CrossRef] [PubMed]

11. Lippner E, Lücke T, Salgado C, Boerkoel C, Lewis DB. SMARCAL1-Related Immuno-Osseous Dysplasia (Schimke Type). *GeneReviews*. 2002 (revised 2023).
12. Anastasiia pMilovanova and Al. Genetic and Clinical Features of Schimke Immuno-Osseous Dyslasia: Single-Centre Retrospective Study of 21 Unrelated Paediatric Patients over a Period of 20 Years. Int. J. Mol. Sci. 2025, 26, 1744
13. Zieg J, et al. Schimke immuno-osseous dysplasia: an ultra-rare disease. A 20-year case series from a tertiary hospital in the Czech Republic. *Ital J Pediatr*. 2023;49:11.
14. Lippner E. SMARCAL1-Related Immuno-Osseous Dysplasia (Schimke Type). *GeneReviews*. 2023.
15. Kshamta B Hunter and al. Schimke immune osseous dysplasia: defining skeletal features.Eur J Pediatr.2009 Dec 15;169 (7)