

A Case of Schimke Immunoosseous Dysplasia Caused by Large Deletion of *SMARCA1* Gene

Sir,

Schimke immunoosseous dysplasia (SIOD) is a rare autosomal recessive multisystem disorder with an estimated incidence of 1 in 1–3 million live births.^[1] It is a pleiotropic disorder characterized by growth failure, spondyloepiphyseal dysplasia, proteinuria with progressive renal failure, lymphopenia with recurrent infections, and a characteristic phenotype. Hypothyroidism, bone marrow failure and episodic cerebral ischemia have also been reported in severely affected patients. The underlying genetic cause is biallelic loss of function mutation in the *SMARCA1* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1) gene.^[2] We present a 5-year-old boy with SIOD phenotype and homozygous deletion of exon 1 to 4 in *SMARCA1* gene. To the best of our knowledge, only two patients with this deletion have been described earlier.^[1]

A 5-year-old male child, product of non-consanguineous marriage, was brought by parents in view of inability to gain height since 2 years of age. Their concern had further increased as his 1-year-old younger sibling had started looking taller than him. He was born by full-term normal vertex delivery to a 26-year-old woman who was booked and immunized in the antenatal period. She gave a history of two spontaneous first-trimester abortions and an intrauterine fetal demise (IUID) at term before this conception. The birth weight of the neonate was 1.5 kg and the birth length was 42 cm at

39 weeks 2 days period of gestation. There was no evidence of intrauterine growth restriction (IUGR) in the antenatal ultrasound done at the beginning of the third trimester as per the mother, though no records were available. The baby did not require any resuscitation after birth or admission to the neonatal intensive care unit. He was exclusively breastfed till 6 months of age and complement feeding was started at 6 months.

On examination, the child was 80 cm tall (<3rd centile), weighed 10 kg (<3rd centile) (World health organization growth charts), upper to lower segment (US: LS) ratio: 1.03 (normal for age: 1.08), suggestive of disproportionate short stature with a short trunk. The arm span was 84 cm. The mid parental height was 174.5 cm and the child's height was far below the 3rd centile of the target height. His head circumference was 45 cm (<3rd centile). Head to toe examination revealed sparse fine hair, bulbous nose, microdontia, short neck, abdominal protuberance, and multiple hyperpigmented macules on the trunk [Figure 1]. His vitals were stable with a blood pressure of 90/58 mmHg (50th centile for age). Systemic examination was unremarkable.

Baseline laboratory results were essentially normal except for hypoalbuminemia, nephrotic range proteinuria, and dyslipidemia [Table 1]. The ultrasound of the kidney was normal. His bone age was the same as chronological age (by Guerlich and Pyle atlas). The radiograph of the spine revealed dorsally flattened vertebral bodies. The pelvic radiograph



Figure 1: Child with Schimke immuno-osseous dysplasia (SIOD) phenotype (a) Bulbous nose (b) Microdontia (c) Disproportionate short stature with short trunk dwarfism (d) Pigmented macules on the trunk

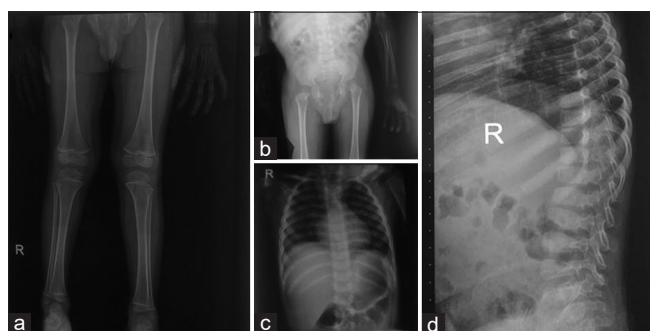


Figure 2: Skeletal Survey of the child with SIOD phenotype (a) Radiograph of both knees is essentially normal (b) Anteroposterior hip radiograph showing small, laterally displaced capital femoral epiphysis, hypoplastic ilia and upslanting and poorly formed acetabula (c) Spine radiograph anteroposterior view showing platyspondyly and (d) Lateral view showing dorsal flattening of vertebral bodies

showed small and laterally displaced capital femoral epiphysis, hypoplastic ilia, and poorly formed acetabula suggestive of spondyloepiphyseal dysplasia [Figure 2]. Radiographs of the skull, hands, and knees were essentially normal. Kidney biopsy for confirmation of renal pathology was planned, but could not be done as the parents refused to give consent.

Databases search including Online Mendelian Inheritance in Man (OMIM) suggested SIOD as an important differential diagnosis. Next-generation sequencing of medically relevant OMIM genes was performed to identify any pathogenic variants which were suggestive of homozygous deletion of exon 1 to 4 in the *SMARCAL1* gene, as the contiguous region corresponding to exons 1 to 4 of *SMARCAL1* gene which is usually well covered, were not covered in this patient's sample. This variant has previously been reported as pathogenic. Confirmation of the variant by an alternate method like Multiplex ligation-dependent probe amplification (MLPA) or Chromosomal microarray (CMA) and parental testing

Table 1: Laboratory results

| Laboratory test | Result | Normal range |
|--|--------------------------------|---------------------|
| Hemoglobin, g/L | 123 | 115-135 |
| Total leucocyte count, 10 ⁹ cells per liter | 6200 | 4000-11000 |
| Differential leucocyte count, % | P62%L32% | P: 40-75, L: 20-45 |
| Platelet count, 10 ⁹ per liter | 280 | 150-400 |
| Blood urea nitrogen, mmol/l | 2.86 | 2.5-7.14 |
| Serum creatinine, µmol/l | 26.53 | 17.68-114.95 |
| Fasting blood glucose, mmol/L | 3.94 | 4.11-5.55 |
| Serum albumin, g/L | 23 | 34-50 |
| Total protein, g/L | 49 | 63-82 |
| Serum calcium, mmol/L | 2.02 | 2.1-2.6 |
| Serum phosphate, mmol/L | 1.29 | 0.81-1.45 |
| Serum ALP, IU/L | | |
| Total cholesterol/ Triglycerides, mmol/L | 7.37/3.99 | 3.36-5.17/0.56-1.69 |
| LDL/HDL, mmol/L | 4.68/0.85 | 2.06-3.33/1.03-1.55 |
| Urine routine examination | pH-7.0, Prot 3+, WBC- 8-10/hpf | Prot – nil, WBC-nil |
| Urine culture | Sterile | Sterile |
| 24 hour urine protein, g/day | 3.2 | <0.15 |
| Immunoglobulin G, g/L | 4.48 | (7-14) |
| Immunoglobulin A, g/L | 1.4 | (0.7-4.0) |
| Immunoglobulin M, g/L | 1.31 | (0.4-2.30) |
| CD4/CD8 lymphocyte ratio | 0.2 | >2 |
| FT4, pmol/L | 13.12 | 10.29-21.88 |
| TSH, mIU/L | 2.8 | 0.30-3.60 |
| 25 (OH) vitamin D, nmol/L | 36.6 | 74.8-249.6 |

LDL=Low density lipoprotein; HDL=High density lipoprotein; FT4=Free thyroxine; TSH=Thyroid stimulating hormone; ALP=Alkaline phosphatase

was suggested, but parents did not opt for it due to financial constraints.

The child was worked up for other pleiotropic effects of *SMARCAL1* mutation. His immunoglobulin profile revealed low IgA levels and CD4 count (CD4/CD8 ratio: 0.2). There was no hematological abnormality, central nervous system involvement, hypothyroidism, or history of recurrent infections.

The child has been started on angiotensin II receptor blockers (ARBs) and a low dose of statins. He is on outpatient follow up and is being monitored for the progression of the disease.

Short stature in SIOD is attributed to spondyloepiphyseal dysplasia with primary involvement of the vertebrae and proximal epiphyseal centers resulting in short-trunk disproportionate dwarfism.^[3] Bone age is not grossly delayed and GH dynamics

is normal. Growth failure usually precedes renal dysfunction by 1-5 years.^[4] Renal dysfunction in SIOD begins with mild protein loss and progresses to nephrotic range proteinuria. It is typically resistant to steroids or other immunosuppressive agents.^[2] Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARBs) help in reducing the proteinuria. The disease is usually progressive with poor response to renal transplantation.^[4] Immunodeficiency in SIOD is characterized by T-cell lymphopenia and reduced immunoglobulin levels making them prone to recurrent fungal, viral and bacterial infection.^[4] Bone marrow failure and its complications is a well-described cause of mortality in these patients. Approximately 50% of the patients with severe disease also have cerebral infarcts or transient ischemic attacks.^[4] The underlying pathology in most of these cases is arteriosclerosis. The disease is usually progressive with poor response to renal transplantation.^[5]

To conclude, we have described a rare case of skeletal dysplasia with multisystem involvement. It is important to recognize this condition early for appropriate genetic counseling, as SIOD is refractory to medical therapy and management options are very limited.

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Conflicts of interest

There are no conflicts of interest.

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