Schimke immuno-osseous dysplasia

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ABSTRACT

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive disorder characterized by steroid resistant nephrotic syndrome, immune deficiency, and osseous dysplasia. SW/SNF2 related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1 (SMARCAL 1) is the gene responsible for SIOD but the underlying pathophysiologic mechanism is unclear, therefore, there is limited therapeutic options. To our best knowledge, less then 50 cases of SIOD have been published and we report 2 more cases with typical clinical and laboratory features from South of Iran. It is emphasized that this disorder should be considered in children with steroid resistant nephrotic syndrome and bone dysplasia.

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Schimke immuno-osseous dysplasia (SIOD, MIM 242900) is a rare multisystem disorder characterized by spondyloepiphyseal dysplasia (SED) resulting in disproportionate short stature, progressive nephropathy, and defective cellular immunity.[1] Although the pathogenesis of this autosomal recessive osteochondroma dysplasia is not known, the causative gene has been recognized recently and SWI/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like1 (SMARCAL 1) is the only gene known to be responsible for SIOD.[2] This article presents 2 cases from Iran with clinical and radiological abnormalities consistent with this rare genetic disorder to mention that it should be considered in children with growth retardation, steroid resistant nephrotic syndrome, and bone abnormalities.

Case Reports. ***Patient One.*** She was the only child of healthy consanguineous parents and product of premature delivery at 33 weeks of gestation due to placenta abruptio (birth weight = 1500 g, length = 45 cm, head circumference = 31 cm). Her postnatal development was unremarkable except for poor growth rate despite a normal provocative growth hormone test. At the age of 6.5 years, she developed nephrotic syndrome with no response to steroid. Kidney biopsy showed minimal change nephrotic syndrome (MCNS) on light microscopy with negative staining on immunofluorescence (IF). So, she remained on angiotensin converting enzyme inhibitor (ACEI) and Atorvastatin. Serial complete blood count documented episodic lymphopenia, but there was no evidence of recurrent infections. Three years later, she developed hypocalcemia leading to generalized tonic clonic convulsion, and brain MRI showed a small area of ischemic white matter. Physical examination revealed all growth indices below 3rd percentile (weight = 14 kg, height = 98 cm, head circumference = 46 cm). Blood pressure was within normal limits. She had characteristic peculiar facies with wide nasal bridge, bulbous nose tip, short neck, hyperpigmented macules on face and trunk, protruded abdomen, and lumbar lordosis (**Figure 1**). The radiographs documented ovoid flat vertebrae, hypoplastic pelvis, abnormal femoral head, and generalized osteopenia. Laboratory data are shown on **Table 1**. At the age of 10.5 years, she had end stage renal failure (ESRF) and while on hemodialysis, expired due to sudden onset of severe respiratory distress of unknown cause.

Patient 2. The third child of consanguineous parents and product of normal vaginal delivery at term, presented with cough and abdominal protrusion at 4 years of age. On physical examination he had peculiar facies, short neck, disproportionate short stature, low growth indices (weight = 10 kg, height =82 cm), and hypertension (**Figure 2**). Physical examination showed diffuse

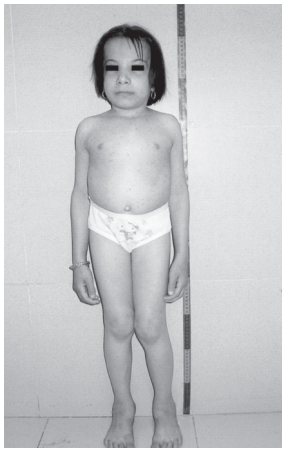

Figure 1 - Patient one with characteristic features of Schimke immuno-osseous dysplasia. Peculiar face with broad nasal bridge, bulbous nasal tip, short neck, and multiple lentigines.

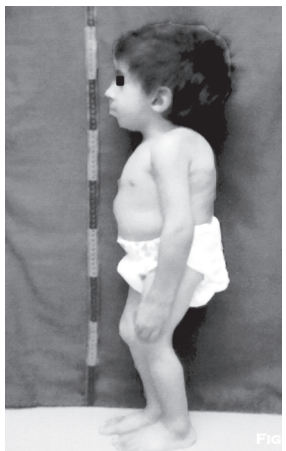

Figure 2 - Patient 2 with Schimke immuno-osseous dysplasia

rales, scattered wheezing, moderate ascites, and lower extremity edema. Laboratory investigations are shown in **Table 1**. Bone survey revealed platyspondyly of cervical spines, beaking of thoracolumbar vertebrae, epiphyseal dysgenesis of femur, shallow acetabulum, and generalized osteopenia (**Figures 3a to 3c**). In hospital, his respiratory symptoms did not respond to antibiotics and high resolution computerized tomography (HRCT) of the chest showed early stages of bronchiectasis, which responded well to inhaled corticosteroid and ß2 agonist. Considering proteinuria, hypoalbuminemia, and hyperlipidemia nephrotic syndrome was diagnosed as a component of SIOD, although kidney biopsy was not conclusive. Patient remained on Enalapril and Atorvastatin without systemic steroid and was discharged in good condition.

Table 1 - Laboratory data.

Test	Measured level		Normal values
	Patient 1	Patients 2	
Hemoglobin (gr/dl)	9.5	8.7	12-17
White blod cells (10^3 /µl)	4.5	2.7	4-10
Polymorph (%)	80	86	
Lymphocyte (%)	13	12	
Monocyte (%)	6	1	
Eosinophil (%)	1	1	
Platelet (10^3 /µl)	332	320	150-450
ESR (mm [1 hr])	64	124	
CRP	Negative	Negative	
BUN (mg/dl)	6	44	5-22
Creatinine (mg/dl)	0.6	1.8	0.9-1.6
Ca^{++} (mg/dl)	7.8	6.9	8.1 - 10.4
P (mg/dl)	3.2	7	3.5- 5.5
Alk Phosphatase (unit)	177	373	80 – 290
Na+ (meq/l)	138	144	135- 145
K + (meq/l)	4.5	5.6	3.5 – 5.5
TG (mg/dl)	293	473	50-150
Cholesterol (mg/dl)	307	216	125- 200
Albumin (mg/dl)	2.2	204	3.8-5.1
IgG (mg/dl)	260	1650	800-2100
IgM (mg/dl)	280	240	120-320
IgA	-	118	130-460
TSH (mIu/ml)	7.6	19	0.4-6.2
T4 (ng/dl)	3	5.7	4-12.5
T3 (ng/dl)	0.8	1.2	0.8-1.9
24 hours urine protein (mg)	2626	1371	< 150
B cell (CD^+_{19}) (%)	48	31	15-39
T cell (CD^+_3) (%)	32	54	54 -76
T cell (CD^+_4) (%)	12	26	31-54
T cell (CD^+_8) (%)	33	30	12-28
(CD_4/ CD_8)	0.36	0.87	1.3-3.9

ESR - erythrocyte sedimentation rate, CRP - C-reactive protein, Ca^{++} - calcium, Alk phosphatase - Alkaline phosphatase, Na - Sodium, K - potassium, TG - triglyceride, IgG - immunoglobulin G, IgM - immunoglobulin M, IgA - immunoglobulin A, TSH- thyroid-stimulating hormone, T4 - thyroxine

Discussion. Two rare cases of SIOD from 2 different consanguineous parents from South of Iran are described. Schimke immuno-osseous dysplasia is a disorder of chromatin remodeling caused by mutation in SMARCAL1 gene which is located on chromosome 2q34-q36 and encodes HARP, aSNF2 subfamily member. SNF2 related proteins participate in the DNA-nucleosome restructuring during gene regulation and replication but until now the precise function of HARP is not clear.[3] Recently Elizondo et al,[4] hypothesized a cell autonomous function for SMARCAL1 and tissue specific mechanism for the pathophysiology of SIOD.

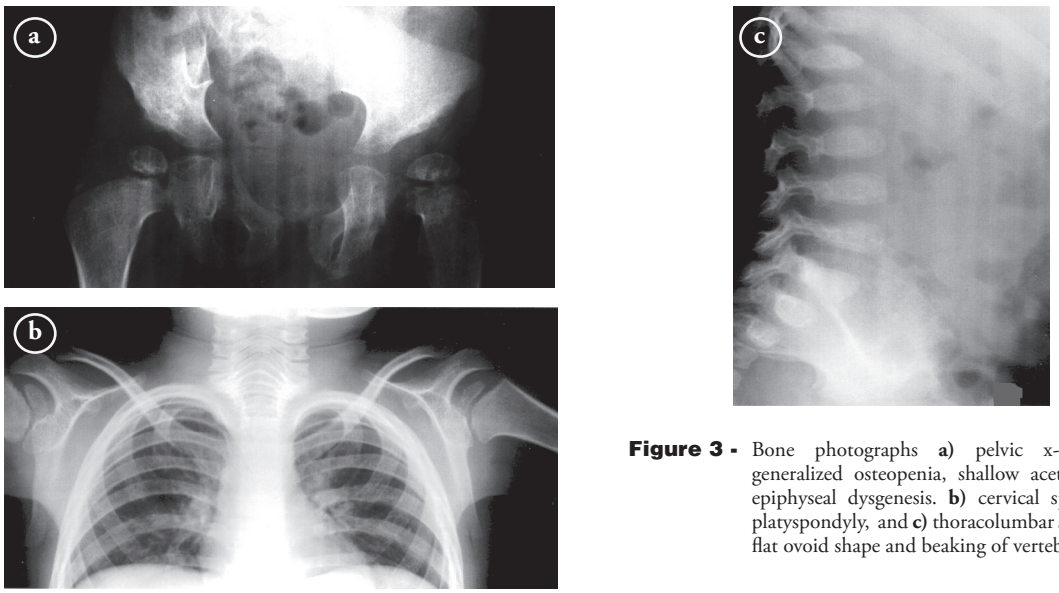

Figure 3 - Bone photographs **a)** pelvic x-ray showing generalized osteopenia, shallow acetabulum, and epiphyseal dysgenesis. **b)** cervical spine showing platyspondyly, and **c)** thoracolumbar spine showing flat ovoid shape and beaking of vertebrae.

Lucke et al,[5] tested the hypothesis of mitochondrial dysfunction as an underlying mechanism of disease but they found no evidence for that. Schimke immuno-osseous dysplasia was first described by Schimke et al, in 1974 as chondrotin-6-sulfate mucopolysaccharidosis,[6] but later reports showed chondroitin sulfaturia in 3 other cases[7] in addition to present cases.

In 1991 Spranger et al,[8] described 5 patients with progressive nephropathy, lymphopenia, hyperpigmented macules, spondyloepiphyseal dysplasia, facial dysmorphism with broad and depressed nasal bridge, and bulbous nasal tip. This disorder was called SIOD.[8] Our patients presented with clinical pictures of nephrotic syndrome. In a review article by Boerkoel et al,[1] all 39 patients with SIOD had proteinuria and 27 of 31 patients had focal segmental glomerulosclerosis (FSGS) in histopathological examination. Although the majority of patients with SIOD demonstrated FSGS in pathology but MCNS, nephronophthisis, mesangeal proliferative glomerulonephritis,[1] and membranous nephropathy (MGN)[9] have also been reported. The kidney biopsy of the first case has shown MCNS, but she progressed to ESRD within few years. The renal biopsy of the second case was not conclusive and it was not repeated because it would not have changed the treatment plan because of unresponsiveness to a variety of drugs.[3] Although the progression of renal disease to ESRD is inevitable, but the recurrence of the disease in grafted organ has not been reported.[10] There is no routine clinical diagnostic test for SIOD and it is based on clinical criteria. Sequence analysis of the SMARCAL 1 gene is available on the research basis only. Schimke immuno-osseous dysplasia should be considered in patients with disproportionate short stature, spondylo epiphyseal dysplasia (SED), T cell deficiency (CD4 and CD8), and nephropathy.[8] Although gene analysis could not be performed in present cases, but they had physical (dysmorphic features), growth (short stature), endocrine (hypothyroidism), skeletal (SED), hematologic (periodic lymphopenia), immunologic (low CD4 and abnormal CD4/CD8 ratio), and renal (nephrotic syndrome) features compatible with the diagnosis of SIOD.

There are 2 forms of SIOD, severe or infantile and mild or juvenile. Patients with severe form have early onset of symptoms such as intrauterine growth retardation (IUGR), nephropathy, neurologic symptoms such as transient ischemic attack (TIA), seizures, stroke, short life span, and they have at least one null allele (nonsense, frame shift, deletion).[3] On the other hand, patients who survive past 15-16 years have mild form and do not suffer from hypothyroidism, recurrent infections, bone marrow failure, neurological symptoms, and have missense mutation.[11] Although our patients presented early in life, they do not have some aspects of the severe form of SIOD such as TIA and recurrent infections. It may be because of weak genotype-phenotype correlation in SIOD[12] or lack of enough time to survive to show full pictures of early onset variant.

In conclusion, we reported 2 cases of SIOD from Iran with clinical characteristic and laboratory findings. We hope that continuing improvement in determining the underlying pathophysiology of disease could help to identify management options.

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