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Case Report

Schimke immunoosseous dysplasia: a multisystem disorder

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ABSTRACT

Schimke immunoosseous dysplasia is an autosomal recessive disorder characterized by spondyloepiphyseal dysplasia, lymphopenia with defective cellular immunity, and renal insufficiency. It is caused by a biallelic mutation in SMARCAL 1 gene. In this study, we described clinical and genetic diagnosis of a 5 years old girl who presented to our centre with short stature and repeated infections in the past. She had one episode of stroke in the past due to infarction and she was diagnosed with hypertension 1 year back. Last admission in the hospital, she had new stroke episode and found to have steroid resistant nephrotic syndrome.

Keywords: Schimke immunoosseous dysplasia, Renal insufficiency, Skeletal dysplasia, Stroke

INTRODUCTION

Schimke immunoosseous dysplasia (SIOD) is a rare autosomal recessive multisystem disorder, firstly described in 1971.[1] Approximately 55 cases have been reported in the literature so far, without any sex, ethnic or geographic predilection. The disease is caused by a biallelic mutation in the SMARCAL1 gene. It is estimated that the incidence of SIOD is 1 in every 13,000,000 live births in Western world.[7]

Typical clinical and laboratory findings in SIOD include steroid resistant nephrotic syndrome (SRNS) with focal segmental glomerulosclerosis (FSGS), spondylo-epiphyseal dysplasia with disproportionate growth failure, typical facial appearance, pigment naevi, T-cell immunodeficiency, progressive renal failure, and hypothyroidism.[2] The SIOD phenotype may range from severe variant with in utero onset to a milder form with later onset.

Transient ischaemic attacks, cerebral infarction, atherosclerosis and migraine like headache are common neurological manifestations of SIOD.[3-6] In this article, we described a 5 years old girl who presented with headache, stroke and short stature from Maharashtra state.

CASE REPORT

This child was born of 3rd degree consanguineous union and was 5th by birth order. The 1st male sibling died at 9 months of age due to some developmental issues and 2nd female child was intrauterine fetal demise at 8 months of gestation.

This child was a preterm born at 32 weeks of gestation, normal vaginal delivery and the birth weight was 1.3 kg. She was admitted in neonatal intensive care unit for 21 days in view of low birth weight. At 3 months of age she was admitted for pneumonia and received intravenous antibiotics and 2 more admissions for lower respiratory tract infection in the past. At 2 years of age was evaluated for failure to thrive but no conclusion was made.

On general examination, she had tachypnoea and tachycardia and her blood pressure was >95th centile (hypertension) and hemiparetic posture on left side with normal intelligence. On physical examination she was short statured with short trunk (weight=10 kg, height=81

cm, head circumference=45 cm and upper to lower segment ratio=1:1, sitting height: leg length ratio <0.78), with triangular face, short neck, low set ears, thin upper lip, prominent root of nose, pectus carinatum, hyperpigmented macule over flank.

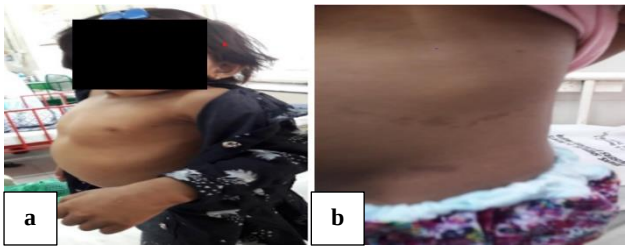

Figure 1: (a) Typical chest deformity; (b) hyperpigmented macule.

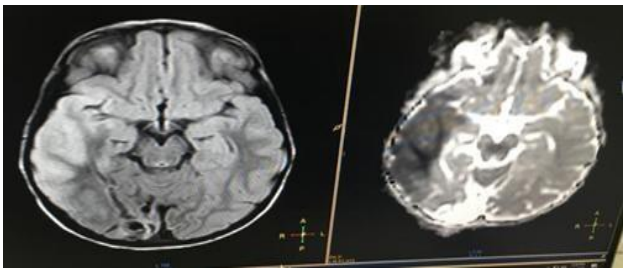

Figure 2: MRI brain showing ischaemic changes in the brain.

She had left sided hemiparesis with extensor plantar on left side and bilateral crepitations on respiratory examination. Laboratory data showed nephrotic range proteinuria, lymphopenia (800), hypophosphatesia (alkaline phosphatase of 82 for 8.4 calcium 1and 4 of phosphorus), vitamin-D deficiency (25-OH vitamin D≤3.4), hypercholesterolemia (204) and proteinuria (4+). Skeletal radiograph revealed mildly flattened vertebral bodies which was consistent with the diagnosis of SIOD.

The 2-D echocardiography was normal, ultrasound abdomen was suggestive of hepatomegaly with liver parenchymal disease and medical renal disease.

CT scan chest

The CT scan chest was suggestive of patchy areas of consolidation involving middle and lower lobe bilaterally.

MRI brain

Acute non haemorrhagic infarcts in right middle cerebral artery and another in left frontal lobe along with gliosis and cystic encephalomalacic changes in right occipital lobe suggestive old infarct was found.

Gradually her hemiparesis improved but hypoxia was persistent and she was comfortable with oxygen saturation of 84%.

On the basis of clinical and laboratory findings, a diagnosis of SIOD was suspected. After obtaining informed consent for genetic studies, mutational analysis of SMARCAL1 gene was performed. Sequence analysis revealed that this patient was homozygous for SMARCAL1 gene mutation.

DISCUSSION

SIOD is a rare autosomal recessive disorder caused by mutation in SMARCAL1 gene.[1] So far, around 60 mutations in SMARCAL1 gene have been identified in SIOD patients. The pathogenesis of this disease is largely unknown. SMARCAL1 gene encodes HepA-related protein, acting as chromatin remodelers within multiprotein complex.[8] This protein is involved in wide range of biological functions, including transcription, DNA replication and DNA repair.

SIOD patients can present with mild to severe disease. The severe form is characterised by intrauterine growth retardation, severe growth failure after birth, recurrent infections, cerebrovascular disease (stroke) and often death in second decade.[5,11] But, in the presented study, the child died in the first decade as the severity of the disease was more. Mild form generally had growth failure and renal dysfunction without infections or cerebrovascular disease.

We presented a 5 years old girl with failure to thrive, steroid resistant nephrotic syndrome, stroke, migraine like headache, skeletal dysplasia in favour of SIOD.[2,4] The exact etiology of SIOD was generally unclear, however, the mutations of SMARCAL1 gene were detected in about 50-60% of patients with SIOD, which turned out to be the etiology in the presented study as well.

The diagnosis of SIOD was made on clinical findings. The most definitive findings were: skeletal dysplasia (mildly flattened vertebral bodies); urinary protein loss (persistent 4+ proteinuria); T lymphocyte deficiency (lymphopenia-800 cells/cmm^3); hyperpigmented macule; dysmorphic facies (triangular face, fine hairs, prominent nasal root, short neck, increased anteroposterior diameter of the chest, disproportionate short stature with short neck and trunk).[3]

Anthropometry helps to distinguish SIOD from other forms of chronic kidney disease.[12] Sitting height: leg length ratio <0.83; >1.01 is indicative of non SIOD chronic kidney disease.

In the presented study, the sitting height:length ratio was 0.78 which was consistent with SIOD related chronic kidney disease.

DNA mutation in the SMARCAL1 gene was available to confirm the diagnosis but it was found in only 50-60% of cases of SIOD. Of note, our patient fulfilled all the clinical as well as genetic criteria for diagnosis of SIOD.

CONCLUSION

The paediatricians should be aware of this disease associated with a typical phenotype as identification of SIOD is of utmost importance for further therapy. The management of SIOD is challenging, as the majority of affected children suffer from severe complications limiting their quality of life and longevity. Our study highlighted the importance of detailed clinical evaluation, appropriate genetic counselling, and molecular testing, to provide timely treatment and more accurate prognosis of the patients with SIOD.

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