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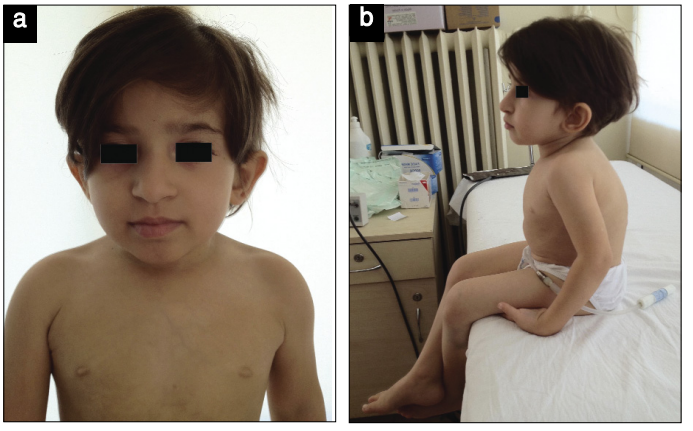
A severily affected case with Schimke immuno-osseous dysplasia

To the Editor,

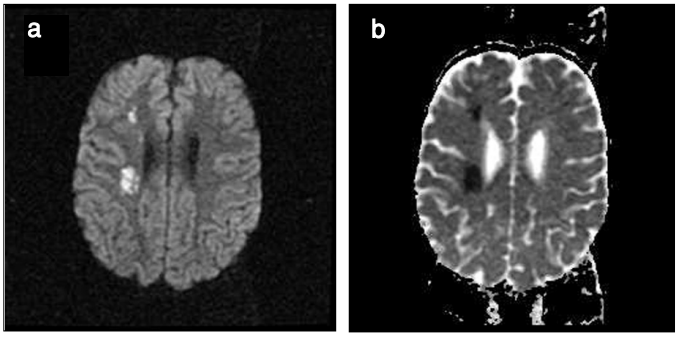
Schimke immuno-osseous dysplasia (SIOD; MIM 242900) is a multi-system syndrome with autosomal recessive inheritance caused by a rare mutation in chromatin remodeling protein (SMARCAL 1) characterized by disproportional short stature with truncal shortness due to spondyloepiphysial dysplasia, steroid resistant nephrotic syndrome progressing to end stage renal failure (ESRD), recurrent infections caused by cellular immune deficiency and typical phenotypic characteristics (1,2). Ischemic attacks in the brain, migraine, ectodernal abnormalities and hypothroidism are observed frequently in SIOD (2,3). In this article, a patient who was referred with a clinical picture of steroid-resistant nephrotic syndrome in the early childhood and who was diagnosed as SIOD with growth failure and typical phenotypic characteristics was presented. Treatment administered to this patient who rapidly progressed to ESRD and underwent peritoneal dialysis (PD) and developed treatment-resistant migraine attacks and severe recurrent ischemic attacks in the brain was summarized.

A three-year-old female patient was referred to our clinic because of swelling in the eyelids, abdomen and legs. Her personal medical history revealed that she was born from the 3rd pregnancy of a 24-year-old mother as the first living baby by cesarean section at the 34th gestational week which was performed because of oligohydramniosis and intrauterine growth failure determined in the 6th month of pregnancy with a birth weight of 1780 g and a height of 46 cm. The family recognized that her body weight and height were retarded compared to her peers after she was 1,5 years of age. The mother and the father were double-cousins. On physical examination, the height was found to be compatible with -4 SD and the body weight was found to be compatible with -2.4 SD. The blood pressure was found to be compatible with the 95th percentile. Brown discolorations with a diameter of 3-8 cm were found on the whole body (especially on the groins and trunk). The hair was fine, the nose root was prominent and the nose had a bulleous structure. Her teeth were small, her neck was short and the antero-posterior diameter of her chest was increased (Picture 1a,b). Abdominal ascites and pretibial edema were present. A diagnosis of nephrotic syndrome was made in the patient who had hypoalbuminemia and hyperlipidemia. Since she did not respond to oral prednisolone treatment, renal biopsy was performed and a diagnosis of focal segmental glomerulosclerosis (FSGS) was made. Since no response to cyclosporine A and steroid treatment could be obtained, immunsuppressive treatment was discontinued at the end of 6 months and the patient was followed up with angiotensin converting enzyme inhibitor, angiotensin receptor blocker and statin treatment. ESRD developed 15 months after the first diagnosis and the patient was included in PD program. The patient's blood pressure was maintained in normal ranges with dual antihypertensive drug therapy. 4 months after peritoneal dialysis was started the patient developed headaches (which were pulsative, lasted for a few hours and recurred during the day) recurring 3-4 times a day which responded to oral

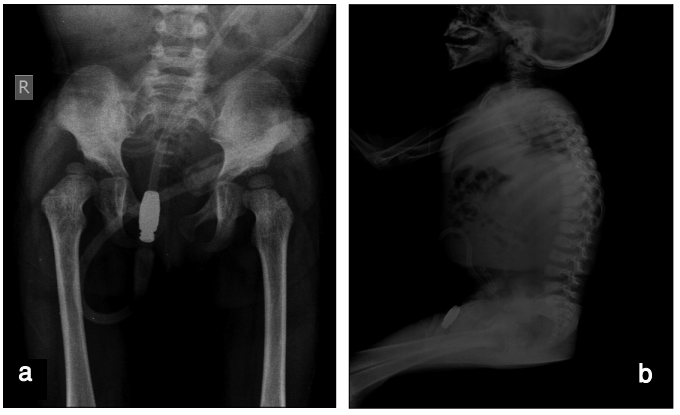


Picture 1a) Triangular face, fine hair, prominent nasal root and bullous nose structure, 1b) Short neck, increased antero-posterior diameter of the chest, disproportionate short stature with short trunk

Address for Correspondence: Cengiz Candan MD, SB İstanbul Medeniyet University Göztepe Education and Research Hospital, Pediatric Nephrology, İstanbul, Turkey
E-mail: cengizcandan@hotmail.com **Received:** 10.10.2012 **Accepted:** 10.15.2012



Picture 2 a-b). Acute infarction areas in the anterior and middle cerebral artery in the deep white matter in the right half of the brain



Picture 3a). Hypoplastic pelvis, narrowing in the basal part of the acetabulum, right hip dislocation, 3b) flattening in the vertebrae

analgesics initially, but did not respond to treatment later and gradually became more severe. One month after this she presented to the emergency department with left central facial paralysis and weakness in the left lower and upper extremity. An area of acute ischemia was observed in the right half of the brain on diffusion magnetic resonance (MR) imaging (Picture 2). Low molecular weight heparin, acetyl salicylic acid and levetiracetam treatment was started and the neurologic findings started to improve from the second day of treatment. 5 days after the attack neurologic examination was found to be normal. Digital angiographic imaging revealed 20-50% narrowing in the first segments of the anterior and middle cerebral arteries bilaterlly. At this time, a diagnosis of SIOD was considered in pediatric genetic consultation with the clinical findings. DNA sample was planned to be obtained for molecular diagnosis. Our patient had most of the dysmorphic and phenotypic characteristics described in the literature for SIOD. Direct graphies revealed flattening in the vertebrae and hypoplastic pelvis (Picture 3a,b). Total lymphocyte count was found to be 570/mm^3 (10.6%) and CD3$^+$ (34%), CD3$^+$/CD4$^+$ (25%) and CD3$^+$/CD8$^+$ (9%) were found to be low, but a severe clinical picture of infection was not observed. The patient was discharged with levetiracetam and acetyl salicylic acid. Three weeks later she presented to our hospital with acute ischemic attack in the brain. It was learned that migraine type headache attacks continued at this time. In the period following the second attack levetiracetam was changed with sodium valproate and enoxaparine was started again. 10 days later a third ischemic attack developed and severe headaches continued. After the dose of valproic acid was increased to 20 mg/kg/day a marked improvement was observed in migraine attacks. While our patient was being followed up with this treatment without any neurologic findings, she was lost following the stroke attack she had 3 months later.

In 50-60% of the patients with Schimke immuno-osseous dysplasia, a mutation in SMARCAL1 has been found (4). While some of the patients have early-onset and severe disease, some others have a late-onset and milder disease. However, some early-onset patients reach their mid-twenties and clinical variance has been shown even in siblings (5,6). Failure to establish a relation between genotype and phenotype and clinical variance have been explained by affection of mutation in SMARCAL1 by environmental, genetic and epigenetic variables and occurence of the clinical picture in patients in whom no mutation can be found has been explained by non-allelic heterogeneity (7). However, no difference could be found between the patients in whom mutation could be found and could not be found in terms of clinical and radiologic characteristics (8).

In Schimke immuno-osseous dysplasia, the disease is due to ESRD, recurrent infections and cerebrovascular complications. The patients frequently have steroid-resistant nephrotic syndrome and the typical renal pathology is FSGS and results in ESRD in a short time (9). Although a decrease in proteinuria has been found with immunosuppressive drugs in some patients, the disease is resistant to treatment (3,9). In our patient, FSGS did not respond to immunosupressive drugs, progressed to ESRD rapidly and requirement for dialysis occured. High blood pressure in our patient was controlled with enalapril and amlodipine. Interestingly, it was reported that glomerulosclerosis did not recur after renal transplantation in this patient (9,10).

In approximately half of the patients with Schimke immuno-osseous dysplasia, cerebrovascular events including transient ischemic attacks and stroke and severe migraine attacks are observed (11). In some patients, heath intolerance and increase in cerebrovascular events in summer have been reported (12). Our patient had all her ischemic attacks in August and September, but she had no heath intolerance. It has been reported that diffuse and progressive atherosclerosis is the basic cause of cerebrovascular events in patients with Schimke immuno-osseous dysplasia (7,10). Although hypertension, hyperlipidemia, proteinuria and ESRD which were also found in our patient are significant risk factors for atherosclerosis, symptoms of cerebrovascular ischemia have been observed in patients with SIOD even before renal disease started (13). In fact, it is difficult to explain cerebral vascular narrowing reaching

a ratio of 50% related to atherosclerosis with traditional risk factors in a 5-year-old patient. In addition, progression of systemic hypertension and vascular disease without recurrence of glomerulosclerosis after renal transplantation suggested that other causes accelerated atherosclerosis. Morimoto et al. (13) showed elastin mRNA and protein levels decreased as a result of dysfunction of SMARCAL1 and thus defect in elestogenesis which has a critical role for vascular structure was the cause of progressive arteriosclerosis in SIOD. On the other hand, the reason of migrain attacks have not been explained yet. Kılıç et al. (11) suggested that migraine attacks may occur because of an intrinsic neuroimmune and neurovascular disorder caused by dysfunction in SMARCAL1 gene. The drugs tried until the present time have not shown a significant effect in treatment of migraine. We observed that migraine attacks improved to a great extent with sodium valproate in our patient at the time when we could not obtain a response with analgesics and levetiracetam.

Conclusively, SIOD should be considered especially in patients with steroid-resistant nephrotic syndrome displaying disproportionate growth failure and other common and life-threatening findings should be investigated. Sodium valproate may be en efficient option in patients with migraine attacks.

Cengiz Candan[1], Yüksel Yılmaz[2], Yasemin Alanay[3], Pınar Turhan[4], Fatma Candan[5], Müferet Ergüven[6]

[1]SB İstanbul Medeniyet University Göztepe Education and Research Hospital, Pediatric Nephrology, İstanbul, Turkey
[2]Association of Cardiac Health and Brain Health, Pediatric Neurology, İstanbul, Turkey
[3]Acıbadem University Medical Faculty, Pediatric Genetic Unit, İstanbul, Turkey
[4]SB İstanbul Medeniyet University Göztepe Education and Research Hospital, Pediatric Nephrology Unit, İstanbul, Turkey
[5]SB İstanbul Medeniyet University Göztepe Education and Research Hospital, Neurology Clinic, İstanbul, Turkey
[6]SB İstanbul Medeniyet University Göztepe Education and Research Hospital, Department of Pediatrics, İstanbul, Turkey

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