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Two Siblings with Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD II)

Emregül Işık¹, Andrew Jackson²

¹Gaziantep Children's Hospital, Gaziantep, Turkey

²University of Edinburgh, Institute of Genetics and Molecular Medicine, Edinburgh, UK

We aimed to identify the genetic cause of severe short stature and microcephaly in two siblings.

A ten-year-old boy presented with short stature. He was born with a birth weight of 1300 grams (-2.7 SDS) at 34 weeks of gestational age. On physical examination, height was 86 cm (-8.9 SDS), weight 8.4 kg (-7.9 SDS), BMI 11.4 kg/m² (-5.6 SDS), and head circumference was 37.7 cm (-9.1 SDS). Development was delayed. He started walking at 3 years, speaking with single words at 2 years, and he cannot make sentences yet. He had prominent nose, microcephaly, micrognathia, and microdontia. There were areas of hypo- and hyperpigmentation, cutis marmorata, and few cafe au lait spots on skin. Parents were first-degree cousins. Height of father was 177.5 cm (0.2 SDS) and height of mother was 159 cm (-0.7 SDS); target height was 161.8 cm (-0.2 SDS). His sister presented at 9 months of age and her height was 50.1 cm (-7.1 SDS), weight 3.8 kg (-6.3 SDS), and head circumference was 33.5 cm (-8.1 SDS). She was born with a birth weight of 1135 grams (-2.5 SDS) at 33 weeks of gestational age. Routine laboratory tests, serum levels of free triiodothyronine, free thyroxine, thyroid-stimulating hormone, insulin-like growth factor 1, and insulin-like growth factor binding protein 3 were normal.

Genetic analysis showed homozygous pericentrin mutation c.3109G > T, p. Glu1037 in both siblings. Parents were heterozygous for this mutation.

MPOD II is characterized by severe intrauterine and postnatal growth retardation, microcephaly, and distinctive face; patients with this disorder should be screened for cerebrovascular abnormalities.

⁴Yale Program on Neurogenetics, Yale Faculty of Medicine, New Haven, Connecticut, USA

⁵T.C. İstanbul Bilim University Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey

H syndrome (OMIM # 602782), first described in 2008, is a rare autosomal recessive genodermatosis which is multisystemic and is primarily characterized by cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, hearing loss, heart anomalies, hypogonadism, short stature, hyperglycemia (insulin-dependent diabetes mellitus), and hallux valgus/flexion contractures. It is caused by mutations in the solute carrier family 29 (SLC29A3) gene. A 23-year-old female patient who had the characteristic clinical features of H syndrome was referred to our medical genetics outpatient clinic to confirm the clinical diagnosis through molecular testing, to arrange the clinical follow-up and treatment support programme, and to provide the patient with suitable genetic counselling.

Clinical examination was performed. Related tests and imaging methods were planned. All coding exons of SLC29A3 gene were sequenced.

Physical examination revealed cutaneous hyperpigmentation on the body/on lower and upper extremity skin except knees and elbows, bilateral hypertrichosis on lower extremity (proximal), hepatosplenomegaly (splenomegaly), bilateral sensorineural hearing loss, heart anomalies, hyperglycemia (insulin-dependent diabetes mellitus), hallux valgus/flexion contractures (flexion contractures on bilateral hands/feet). Homozygote nonsense mutation causing premature stop codon (p.Y428*) in SLC29A3 gene exon sequencing was detected.

H syndrome is a rare genetic disease which requires multidisciplinary treatment because of its multisystemic involvement. Molecular genetic testing is important to confirm the diagnosis, to provide appropriate genetic counselling and to estimate prenatal diagnosis possibilities for the following pregnancies. As far as we are concerned, there are two more cases reported except ours in Turkey until now. More than 100 patients and 20 mutations in SLC29A3 gene have been described in the world. We find it convenient to present this rarely observed case in order to discuss the clinical findings and the mutation found in our case.

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A Rare Genodermatosis: H Syndrome

Özlem Sezer¹, Düriye Sıla Karagöz Özen², Mehmet Derya Demirağ³, İsmail Toto², Hacer Pınar Öztürk², Fatih Toy⁴, A. Gülhan Ercan Şençiçek⁴, Ahmet Okay Çağlayan⁵

¹Samsun Training and Research Hospital, Clinic of Medical Genetics, Samsun, Turkey

²Samsun Training and Research Hospital, Clinic of Internal Medicine, Samsun, Turkey

³Samsun Training and Research Hospital, Clinic of Romatology, Samsun, Turkey

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Non-Genetic Factors Altering Birth and Fertility Rates

Dilara Çelebi

Bahçeci BIH IVF Center

The purpose of this project was to understand how Bosnian war affected the fertility and birth rates.

I selected two countries, namely Bosnia and Herzegovina and Turkey and researched and analyzed the results of the national statistical institute of the countries.

Turkey has a higher BMI score for females compared to Bosnia and Herzegovina, but the difference is only 1.9 points in BMI scores. Both countries fall into the average weight category in the index which is above underweight and above overweight and obese category. Total fertility rates of Turkey and Bosnia and Herzegovina show that Turkey has 0.86 higher fertility rates in average when compared with Bosnia and Herzegovina from year 2011 to 2014.

The lower fertility rates may be due to the negative agents on the adults but also post-war trauma on Bosnians. The pronounced reduction in fertility can be linked to particular circumstances in Bosnia and Herzegovina following the war and subsequent economic stagnation and instability accompanying changes in societal behavior.

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A Rare Cause of Obesity: ROHHAD Syndrome

Gülay Can Yılmaz¹, Cengiz Kara¹, Filiz Serdaroğlu²,
Haydar Ali Taşdemir², Murat Aydın¹

¹Ondokuz Mayıs University Faculty of Medicine, Department of Pediatric Endocrinology, Samsun, Turkey

²Ondokuz Mayıs University Faculty of Medicine, Department of Pediatric Neurology, Samsun, Turkey

ROHHAD syndrome is a rare syndrome with rapid-onset obesity (RO), hypoventilation (H), hypothalamic (H), and autonomic dysfunction (AD). Rapid weight gain usually begins after the age of 2-3, while hypoventilation occurs in more advanced age. We report the case of a patient who developed hypoventilation at very early age and subsequently obesity, and was diagnosed at the age of 1.5 years.

A male patient developed progressive neurologic deterioration and epilepsy following hypoxic encephalopathy due to sudden respiratory arrest at five months old. At the age of 1.5, he was evaluated for sudden-onset obesity which occurred in the last few months. He received treatment for constipation as well as epilepsy. The weight was 15 kg (+1.4 SD), height 82 cm (-1.0 SD), and BMI 22.3 kg/m² (+3.1 SD). Spontaneous breath rate and heart rate were varying between 6-10/min and 45-55/min, respectively. The patient was spastic quadriplegic and had no pupillary reflex. Brain MRI revealed cortical and white matter atrophy. Laboratory values were as follows: serum Na 150 mEq/L, serum osmolality 310 mOsm/kg and urine osmolality 101 mOsm/kg, serum adrenocorticotrophic hormone <5 pg/mL, and cortisol 1.01 µg/dL. Other pituitary functions were normal. Treatment with desmopressin and hydrocortisone was initiated for central diabetes insipidus and adrenal insufficiency. All the findings (obesity, pituitary hormone deficiencies, hypoventilation, bradycardia, absence of pupillary reflex, constipation) indicated diagnosis of ROHHAD syndrome.

ROHHAD syndrome should be kept in mind in children with rapid-onset obesity and pituitary hormone deficiencies. These children should be monitored in terms of accompanying findings such as hypoventilation and autonomic dysfunction.

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Osteogenesis Imperfecta: Case Report

Nilüfer Özdemir Kutbay¹, Banu Şarer Yürekli², Hatice Özışık²,
Halit Diri³

¹University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Clinic of Endocrinology, Diyarbakır, Turkey

²Ege University Faculty of Medicine, Department of Endocrinology and Metabolism Diseases, İzmir, Turkey

³University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

Osteogenesis imperfecta is a genetic disorder characterized by osteoporosis, recurrent bone fractures and, consequently, deformities. In many cases, it is chiefly caused by a dominant mutation in the *COL1A1* or *COL1A2* genes that encode type I procollagen.

The medical history of our 41-year-old female patient revealed an earlier diagnosis of osteogenesis imperfecta and 4 fractures. She was diagnosed with the disease in her childhood. She was treated with zoledronic acid twice, once per year. In the clinical examination, she reported that she had no new fractures and her pain reduced after zoledronic acid treatment. Blue sclera was present in her physical examination. The laboratory results were as follows: AST 20 U/L, ALT 22 U/L, ALP 81, Ca 8.8 mg/dL, P 3.0 mg/dL, 25 OH vitamin D 35 ng/mL, TSH 0.995 µIU/mL, fT₄ 1.26 ng/dL, and PTH 40.81 pg/mL. Before zoledronic acid treatment, DEXA lumbar total T score was -2.9 and Z score was -2.7. One year after the second zoledronic acid administration, DEXA lumbar total T score was -2.5 and Z score was -2.2. The patient was treated with zoledronic acid for the third time by our team.

The target of the treatment of the cases with osteogenesis imperfecta is to reduce the fractures and pain and to prevent long-term bone deformities thus improve the patient's functional capacity and mobilization. Recently, no new bone fractures have been observed in our patient treated with zoledronic acid. Bearing drug compliance in mind, zoledronic acid could be an alternative to bisphosphonate treatment for suitable patients with osteogenesis.