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A Novel Mutation in *INSR* Gene in a Child Presenting with Acanthosis Nigricans

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Rabson-Mendenhall syndrome (RMS) is an autosomal recessive disorder resulting in severe insulin resistance due to defects in signaling through the insulin receptor. Symptoms of RMS include diabetes mellitus due to severe insulin resistance, acanthosis nigricans, impaired adipose tissue, and growth restriction. Herein, we report a case with RMS presenting with acanthosis nigricans due to a novel mutation in the *INSR* gene.

According to the past medical history, the patient was born with a birth weight of 3500 g. She was the first child of consanguineous parents. On physical examination, her weight was 18.7 kg (-0.08 SDS) and height was 98.7 cm (-2.6 SDS). Initial clinical findings showed severe acanthosis nigricans of the neck, axillae, the external genitalia and antecubital regions, generalized lanugo, abnormalities of the teeth, and dysmorphic face.

Initial laboratory tests showed normal fasting glucose (78 mg/dL), normal postprandial glucose (102 mg/dL), and extremely elevated fasting insulin (129 µIU/mL). After an overnight fast, an oral glucose tolerance test was performed and impaired glucose tolerance was detected. Sequence analysis of the *INSR* gene in the patient revealed a homozygous missense mutation in exon 11 at the nucleotide position c.861 (c861 C > A) resulting in a premature stop codon instead of tyrosine at codon 287 (p.Y287). Screening of relevant mutation was performed in the remaining family members. The father, mother, and a sibling were heterozygous.

We thought that our patient may have RMS due to her mild clinic signs and a novel mutation in *INSR* gene detected in molecular analyses.

(P-43)

Thyroid Hormone Resistance P453A Mutation

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Thyroid hormone resistance is a disease characterized by reduced sensitivity to thyroid hormone in cell membrane, altered

metabolism and nuclear receptor. The clinic signs of thyroid hormone resistance are goiter, sinus tachycardia, attention deficit hyperactivity disorder; the laboratory signs are high level of free T4 and normal level of TSH.

A 10-year-old girl was admitted to our clinic with complaints of palpitation and nervousness. Her weight and height were 27 kg (3-10p) and 132.8 cm (3-10p), respectively. On physical examination, heart rate was 84 beats/min, blood pressure was 90/60 mmHg, and her thyroid was stage 1. Her thyroid function tests were as follows: total T₃ 2.4 ng/mL (0.9-2.3), free T₃ 6.17 pg/mL (1.7-3.7), total T₄ 12.9 µg/dL (5.9-12.9), free T₄ 2.33 ng/dL (0.7-1.48), TSH 3.29 µIU/mL, thyroglobulin 15.2 ng/mL (0.2-70), and negative antibodies of thyroglobulin and thyroperoxidase. In the genetic analysis of the patient suspected of having thyroid hormone resistance, the P453A c.1357C > G mutation was detected to be heterozygous on the exon 10 of the *THRB* gene. Beta-blocker therapy was initiated in the patient who was still complaining of palpitations and tachycardia.

Among *THRB* gene mutations, 453 mutation is the most common one. In our case, the receptor affinity of T₃ was reduced to 17% as a result of alanine substitution of proline amino acid due to guanine transversion instead of cytosine in codon 453 at exon 10. This mutation has been reported in six patients in the literature and it is noteworthy that four of the patients are of Turkish origin.

(P-45)

A Case of Vanishing Testis Syndrome

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Gender differentiation results from the interaction of hormonal and genetic factors. According to the sex chromosomes of the individual and the effect of transcriptional factors, testis or ovary develop from the embryonic bipotential gonads.

A boy from non-consanguineous family was admitted to pediatric endocrine department because of non-palpable testes in the scrotum. A 7-year and 2-month-old boy was born with weight of 2500 g by vaginal delivery. It was learned from his previous history that he had undergone laparoscopy and no testes had been found in the abdomen. On general examination, height was 133.6 cm (97p), height SDS 2, weight 27 (75-90p), and weight SDS was 0.89. The patient was conscious, oriented, and well-nourished with normal secondary sexual characteristics for his age. On local genital examination, he had 5 cm stretched penile length, 1 cm penile width, no axillary and pubic hair. Right and left scrotal sac appeared empty.

For finding location of testes, ultrasonography and MRI were done and no testes was found in abdomen, inguinal canal, or scrotum. Karyotyping revealed a normal 46,XY karyotype. Serum follicle-

stimulating hormone, luteinizing hormone, and total testosterone levels were 33.02 mIU/mL (normal reference range <6.7), 0.54 mIU/mL (normal reference range 0.3-6.0), and 5.19 ng/dL (normal reference range <7), respectively. Serum testosterone levels were not increased in response to 1500 units/dose HCG stimulation test for 3 days. The diagnosis of vanishing testis was confirmed and hormone replacement therapy was planned to start during puberty.

Early diagnosis and appropriate treatment will prevent the development of hypogonadism complications.

(P-46)

Warburg Micro Syndrome: A New Case from Consanguineous Parents

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Warburg micro syndrome (WARBM) is a rare autosomal recessive disorder characterized by postnatal severe intellectual disability, microcephaly, ocular findings such as congenital cataract, microcornea, microphthalmia and optic atrophy, and hypogonadism. *RAB3GAP1* mutations are mostly causative. This child was presented because of having two patients from the same family. First son of the family had WARBM and he died.

A 12-month-old boy was admitted to our clinic because of congenital cataracts, micropenis, and cryptorchidism. Parents were second cousins. Birth weight was 2800 g. At 2 months of age, he underwent bilaterally phacoemulsification. His weight was 6.8 kg (<3p), length 75.5 cm (25-50p), and head circumference was 41 cm (<3p). He had low-set and large ears, a prominent nasal root, ptosis, high-arched palate, and micrognathia. Ophthalmological examination revealed hypotelorism, microphthalmia, and microcornea. He had truncal hypotonia, increased muscle tone in both legs, poor head control, and was unable to sit without support. He had bilateral cryptorchidism, a micropenis (stretched penile length of 20 mm), and scrotal hypoplasia. USG revealed both testicles within the inguinal canals. Karyotype was 46, XY, inv(9)(p12q13). Failed to get visual message as a result of Flash VEP. Cranial MRI showed atrophy of the corpus callosum and cerebral cortex. Sequence analyses of the *RAB3GAP1* gene revealed that he was homozygous for the splice donor mutation c.748+1G>A. His deceased brother possessed the same mutation. Both parents were heterozygous for the mutation.

WARBM is rarely presented in siblings. The importance of pre-conception genetic counseling in the family who has children with same disorders is highlighted.

(P-47)

Williams Syndrome Associated with Isolated Growth Hormone Deficiency: Is It Just a Coincidence?

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Williams-Beuren syndrome (WBS) is a rare disorder caused by chromosome 7q11.23 deletion. Clinical manifestations are a happy looking dysmorphism, moderate mental retardation, growth retardation, and congenital heart defects (CHD). Short stature is found in about 50% of children with WBS, however, it is generally not severe. Here, we report a case of WBS associated with growth hormone deficiency (GHD).

The patient was the first child of healthy, non-consanguineous parents. He was born at term with weight of 2500 g (3p), length 48 cm (3p), and head circumference (HC) of 33 cm (3p). At age 3 years, he was referred for the first time because of dysmorphism and CHD. Serum calcium levels were elevated. He had severe growth retardation. His height was 73.6 cm (≤3p), weight 7300 g (≤3p), and HC was 43.5 cm (below -2 SDS). The karyotype was normal. FISH analysis showed hemizygotously deleted 7q11.23. Measures yielded during endocrine evaluation were indicative of severe GHD. Treatment with hGH 1 U/day was started to which our patient responded well.

Short stature is found in about 50% of children with WBS. It is usually not severe and the postnatal overall growth is frequently along the 3p. For some WBS patients on the contrary, growth retardation is severe. To the best of our knowledge, there are only 3 patients with WBS reported to have associated GHD. The pathogenesis of GHD is unclear. A hypothalamic rather than pituitary defect is suggested. We recommend evaluation of growth hormone or at least screening by IGF-I measurements in all patients with microdeletions and unexplained short stature.