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Monogenic Diabetes Case Presented with Symptomatic Hyperglycemia and Atypical Mutation

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We report this case to emphasize that appropriate genetic analysis for MODY should be done in young diabetics not coinciding with type 1 or 2 diabetes.

An 18-year-old female patient referred to our clinic with symptoms of dry mouth, polyuria, polydipsia, fatigue, and weight loss (decrease from 58 kg to 51 kg in one month). No chronic diseases or continuous drug usage were noted; her mother had type 2 diabetes. On physical examination, vital signs were stable and systemic examination was normal. In laboratory results, FPG was 261 mg/dL, HbA1C 9.58%, C-peptide 0.9 ng/mL, urine ketone and glucose were positive, blood count and biochemical parameters were normal.

As regards to patient age and clinical findings, pre-diagnosis of type1 diabetes mellitus was established. We started aspart insulin 3x8 unit and detemir insulin 1x12 unit by monitoring blood glucose; then blood glucose stabilized. Anti-GAD and anti-insulin antibodies measured for diagnosis were negative. Due to absence of autoantibodies and positive family history of diabetes, we performed genetic analysis for maturity-onset diabetes of the young (MODY). Compound heterozygous mutation of Ile27Leu/Ser487Asn in *hepatocyte nuclear factor 1α (HNF-1α)* gene was detected and diagnosis of MODY3 was made.

MODY3 revealed by *HNF-1α* defect is the most frequently seen MODY type and composes 50-65% of all MODY cases. Many different mutations were defined in *HNF-1α* gene and clinical findings may differ according to detected mutation. To our knowledge, for the first time in the literature, compound heterozygous mutation of Ile27Leu/Ser487Asn in *HNF-1α* gene was detected in our case. The mutation possibly had contributed to the aggressive clinical pattern in our patient.

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Case Report of Leri-Weill Dyschondrosteosis Caused By *SHOX* Gene Deletion

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Short stature is one of the most frequent causes of referral to the children's endocrine outpatient clinics. Short stature affects 2-3%

of the general population. The short stature homeobox (*SHOX*) gene is located in the pseudo-autosomal regions of the short arms of the X and Y chromosomes. Deletions or mutations on the gene cause Turner's syndrome, idiopathic short stature, and Leri-Weill dyschondrosteosis (LWD). Here, we present a case with *SHOX* gene deletion detected in a genetic study that was performed due to LWD findings.

A 4-year 3-month-old girl presented to our clinic because of shortness. There was no family history. Her arms were short and curved.

Height was 96 cm (3-10p/-1.47 SDS), body weight 15.3 kg (25-50p, -0.43 SDS), the right upper arm was 13 cm, the right forearm 13 cm, the upper left arm 10.5 cm, and the right forearm was 10 cm. The distance between the fingers was 92 cm. Other system examinations were normal. Complete blood count, biochemical parameters, and thyroid function tests were normal. Madelung deformities were observed in the radiographs of the upper extremity. LWD was considered in patients with present findings. Karyotype analysis revealed 46,XX. *SHOX* (Xp22.3) gene deletion was detected in the patient who underwent advanced genetic examination.

We wanted to emphasize the importance of genetic studies in the etiology of short stature by presenting our case with LWD findings and *SHOX* gene deletion.

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A Case of Marfan Syndrome Presenting with Transverse Striae of the Back

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Marfan syndrome is an autosomal dominant genetic disorder resulting from fibrillin gene mutation. The connective tissue in heart, eyes, skeletal, lungs, and central nervous system is affected.

A girl from non-consanguineous family was referred to pediatric endocrine department because of tall stature, joint pain for six months, and transverse striae of the back. It was learned from her family history that two uncles had tall stature and very long extremities. This 12-year-old girl was born with weight of 4000 g by caesarean section. On physical examination, height was 182.3 cm (>97p), height SDS 3.92, weight 67.1 kg (75-90p), weight SDS 1.75, body mass index 20.19, body mass index SDS 0.54, arm span 186 cm (>97p), and arm span SDS +4.5. On physical examination, the patient with the long-facial appearance had high-arched palate, long limbs and legs, purple-guinea-colored transverse striae of back, arachnodactyly, genu recurvatum, joint laxity, hypermobility, pes planus, scoliosis, and pectus excavatum. The Beighton score 7/9 for hypermobility and Tanner 4 for puberty were detected.

Full blood count, biochemical analysis, thyroid function, and pubertal hormone tests were found to be normal in terms of tall stature. Serum levels of IGF-1 and IGFBP-3 ranged from 0 to +1 SDS. Echocardiography revealed mitral valve prolapse. The eye examination was normal in terms of lens subluxation.

In this report, Marfan syndrome with tall stature and transverse striae of the back was presented. Early diagnosis and appropriate treatment will prevent the development of complications.

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Diagnostic Algorithm in Two Different Cases with Subclinical Endocrinologic Problems

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Incomplete form of Di George syndrome (DGS) which is characterized by hypoparathyroidism, thymic aplasia, facial dysmorphism, and cardiovascular anomalies may present with subclinical endocrine problems and may result in delay in diagnosis.

Case 1: A 2-year-old girl born to unrelated healthy parents was consulted due to mild hypocalcemia before angiographic evaluation for tetralogy of Fallot. Anthropometric evaluation was appropriate for her age. She had perioral cyanosis, mild hypertelorism, high palate, and minor anomaly in her toe. She had borderline hypocalcemia, low parathormone, and high TSH levels in biochemical and hormonal evaluation. Thymus was absent in her chest X-ray. CD3, CD4, CD8, CD19 were low, total complement level, quantitative immunoglobulin levels, and in vitro lymphocyte transformation tests were normal.

Case 2: A 31-day-old female patient born to unrelated healthy parents was consulted due to high TSH levels. Anthropometric evaluation was appropriate for her age. She had clubfoot, low-set ears, micrognathia, and high palate. In laboratory evaluation, hypocalcemia and high TSH level were determined. Ostium secundum ASD and bilateral hydronephrosis were observed in echocardiography and renal ultrasonography. Thymus gland was present in chest X-ray.

DOUBLE FISH analysis was performed. Case 1: Heterozygote 22q11 mutation was determined and the patient was diagnosed as having incomplete DGS. Case 2: Homozygote 22q11 deletion was determined and the patient was diagnosed as having DGS.

It's important to perform DOUBLE FISH analysis in cases with subclinical endocrine problems if incomplete DGS is suspected. Thus, major problems (such as graft versus host disease due to transfusion), which may patient face in the future, might be prevented.

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A Novel *De Novo* Missense Mutation in HNF4A Resulting in Sulfonylurea-Responsive MODY

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Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes with autosomal dominant inheritance and usually develops before 25 years. Heterozygous inactivating hepatocyte nuclear factor 4A (HNF4A) mutation is a rare subtype of MODY.

A 14-year-old girl was admitted to our clinic due to fatigue and polyuria, and hyperglycemia was detected afterward. She was born full term with birth weight of 5500 g (4.9 SD score) and had no postnatal hypoglycemia. Her parents were not relatives and family history revealed no diabetes. Physical examination revealed a height of 163 cm (SD score 0.29), weight 64.7 kg (SD score 1.2), and body mass index of 24 kg/m² (SD score 1.2). Neither acanthosis nigricans nor striae were found. Laboratory analyses showed C-peptide 1.66 ng/mL (normal, 0.9-7.1 ng/mL), glycated hemoglobin (HbA1c) 8.8%, normal lipid profile, and negative autoantibodies regarding diabetes. Urine analysis showed 2+ glycosuria and no ketosis. We started only insulin glargine (0.2 unit/kg/day) with most probable diagnosis of MODY. Normal glycemia was improved and no hypoglycemia was seen with this treatment. HbA1c was decreased to 6.3%.

Genetic analysis revealed a *de novo* p.C93Y (c.278G>A) heterozygous novel change in the HNF4A. Insulin treatment was stopped and low-dose sulfonylurea (5.0 mg/day) initiated when the diagnosis of MODY 1 was proved. After five months of the treatment onset, fasting glucose was 111 mg/dL, insulin 11 IU/mL, C-peptide 2.2 ng/mL, and HbA1c was 5.8%.

Genetic testing should be considered to establish an accurate diagnosis and provide an opinion to determine the appropriate type of treatment.