A Rare Presentation of Friedreich's Ataxia in Pediatric Case: Diabetes Mellitus

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Introduction: Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder resulting from a mutation of a gene locus on chromosome 9. The most common molecular abnormality is a GAA trinucleotide repeat expansion in intron 1 of the frataxin (*FXN*) gene; normal individuals have 5 to 30 GAA repeat expansions. FA is characterized by progressive gait and limb ataxia with associated limb muscle weakness, absent lower limb reflexes, extensor plantar responses, dysarthria, and decreased proprioception. Patients are at risk of getting glucose intolerance and 20% progress to overt diabetes. The cause of diabetes in FA is poorly understood. Diabetes can result from a shortage in insulin secretion, from a poor response to insulin (insulin resistance), or from a combination of both.

Case: A 15.5-year-old girl was admitted to the hospital with weakness, vomiting, weight loss, polyuria, and polydipsia in the last 1 month. History revealed the presence of gait disturbance and pain in soles for 3 years. On physical examination, cachexia, dehydration, and ketonemic odor were noted. Thyroid gland was soft and bilaterally 4 cm on palpation. Neurological examination demonstrated ataxic gait pattern, pes cavus, intentional tremor, lower limb areflexia, and flexor plantar response. Blood glucose was 390 mg/dL with ketonuria but without acidosis. Insulin and c-peptide levels were 1.53 µIU/mL and 1.08 ng/mL, respectively, and HbA1c was 13.4%. She was treated with subcutaneous insulin. Glutamic acid decarboxylase, insulin, and antiislet cell antibodies were negative. No cardiomyopathy was detected by echocardiography. Hyperthyroidism was detected [thyroid-stimulating hormone (TSH) 0.03 µU/mL (0.34-5.6), free thyroxine 1.79 ng/dL (0.61-1.12), free triiodothyronine 4.57 pg/mL (2.5-3.9)] with negative thyroid autoantibodies. *FXN* gene analysis revealed more than 66 GAA trinucleotide repeats in intron 1 which is a homozygous state and consistent with FA.

Conclusion: FA must be considered in patients who presented with diabetes and ataxia. In our case, for the first time, non-autoimmune hyperthyroidism was detected in FA.

Key words: Friedreich's ataxia, diabetes mellitus, frataxin, hyperthyroidism

Central Precocious Puberty in a Patient with Multiple Pituitary Hormone Deficiency Due to *POU1F1* (*PIT1*) Gene Mutation

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Background: Multiple pituitary hormone deficiency (MPHD) associated with central precocious puberty (CPP) has been widely reported in cases of arachnoid cyst, septo-optic dysplasia, brain tumors, or after cranial irradiation. However, MPHD due to deficiency of transcription factors that regulate the development of hypothalamo- pituitary system is rarely reported in combination with CPP. CPP may delay the diagnosis of growth hormone (GH) deficiency and adversely affects adult height. In this report, a patient with MPHD due to *POU1F1* (PIT1) deficiency and CPP is described because of its rarity.

Case: A 20-month-old boy presented with short stature. He had the diagnosis of central hypothyroidism and has been receiving L-thyroxin therapy since the age of 3 months. He was born at 34 gestational weeks [birth weight 0.6 standard deviation (SD), birth length -1.2 SD], and had no perinatal asphyxia. Severe short stature (length 62 cm, -6.6 SD) was detected. There was no dysmorphic features. Testicles were scrotal and pre-pubertal. GH deficiency and prolactin deficiency were detected and there were no abnormalities in cranial and pituitary magnetic resonance imaging except for pituitary hypoplasia. While he was on GH (started at age 2 years) and L-thyroxin therapy, puberty started at $7^{9/12}$ years. Gonadotropin-releasing hormone (GnRH) analogue was started at 8 years due to rapid progression of puberty and continued up to 11 years of age. In the patient who had thyroid-stimulating hormone, prolactin, and GH deficiencies, a new point mutation was detected in the *POU1F1* gene (homozygous p.I244S); the parents were carriers for this mutation.

Conclusion: In humans, the relation between *POU1F1* gene and CPP is not exactly known. In animal studies, it was shown that *POU1F1* gene has effects on the *GATA2* gene which has an important role on gonadotropin production and also plays a role in GnRH receptor gene functions, regulation of gonadotropin production, and in prevention of excess gonadotropin production. Further clinical and experimental studies are needed to detect the relation between *POU1F1* functions and CPP.

Key words: *MPHD, CPP, POU1F1, GATA2*