Pediatric INSIGHTS

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An Update From the Division of Endocrinology, Diabetes, and Metabolism

DIAGNOSE IT!

For decades, the experts of the Division of Pediatric Endocrinology, Diabetes, and Metabolism at Children's Hospital of Pittsburgh of UPMC have played a major role in the care of children with diabetes and all types of hormone-related disorders. • Children's Hospital has one of the largest pediatric endocrine clinics in North America and is a leader in both clinical care and research in many of the issues surrounding childhood diabetes mellitus and endocrine issues. • We offer this case presentation to help educate other health care professionals about our most interesting and complex cases.

Case Presentation

A 14-year-old female was referred to endocrinology for growth retardation and delayed puberty. She had short stature (height 144.4 cm, < 3rd percentile), no breast development, and Tanner stage 2 pubic hair. Past history showed delayed developmental milestones and ataxia noted at age 28 months. Apart from delayed puberty, short stature, and ataxia, the patient's physical evaluation was normal.

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Initial Laboratory Values

	Level	Ref Range
FSH (mIU/mL)	144.8	1.0 – 9.2
LH (mIU/mL)	26.9	0.02 – 4.7
E2 (pg/mL)	<2	25 – 150
TSH (uIU/mL)	0.912	0.7 – 5.7
F T4 (ng/mL)	0.98	0.8 – 1.8
IGF-1 (ng/mL)	305	261 – 1096

Additional Studies

Bone age	11–12 y (Greulich-Pyle method; chronological age 14 y, 2 mo)
Karyotype	46 XX, normal female
Pelvic sonogram	Infantile uterus, small ovaries
MRI	Diffuse cerebellar atrophy, with no progression on subsequent imaging up to age 6 y

What steps would you take next to diagnose this patient?

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Differential Diagnosis

The most common cause of premature ovarian failure (POF) is due to deletion of X-chromosomal material **(Turner syndrome)**.

Acquired causes: Surgery, ovarian tissue damage from radiation or chemotherapy, and autoimmunity.

Rare genetic causes of POF: Autosomal gene defects, such as galactosemia, mutations in FSH receptor gene, and phosphomanno-mutase 2 (PMM2) gene.

DIAGNOSE IT!

- Screening test for Congenital Disorders of Glycosylation (CDGs) showed abnormal isoelectric focusing pattern of serum transferrins.
- PMM2 gene testing showed the patient to be double heterozygous for previously described missense mutations of the PMM2 gene (Exon 4; c.323 C>T and Exon 8; c.710 C>G), compatible with a diagnosis of CDG-1a.

Treatment

- Induction of puberty was initiated using an estrogen patch (estradiol 0.025 mg/24 hr, 1/2 patch twice weekly).
- The patient has responded well, with improved growth velocity and development of breasts. She had menarche after 2 years of increasing doses of estrogen therapy. Now maintained on combined oral contraceptives.

Discussion

- CDGs are rare metabolic disorders that affect multiple endocrine systems and may cause hypothyroidism, hyperinsulinemic hypoglycemia, short stature, and premature ovarian failure (POF).
- CDG-1a (PMM2 gene mutation) is the most common defect in the group of N-glycosylation defects.
- CDG-1a–related POF is believed to stem from hypoglycosylation of FSH and its receptor. The combination and severity of clinical features are widely variable. Mortality in infancy due to severe multi-organ involvement can be as high as 20%. Ataxia-developmental delay is frequently present during childhood. Cognitive status stabilizes in adolescence and adulthood.
- POF associated with neurodevelopmental abnormalities should alert the clinician to consider CDG.
- Rare genetic conditions are important to consider once common causes have been ruled out and are diagnosed with increasing frequency due to the availability of targeted genetic testing. •

Video Rounds

Video Rounds is a series of short, informative, and educational videos created for physicians that cover a variety of medical and surgical disciplines.

The Clinical Approach to Disorders of Sex Development

Presented by Selma Witchel, MD

Diagnosing and treating disorders of sex development can often be challenging for physicians, and may present difficult situations for family members. However, consistent communication and a comprehensive team approach can help physicians appropriately counsel parents and family. Dr. Witchel explains how a clinical approach of effective communication and individualized treatment can help physicians give families the tools they need to make educated and informed treatment decisions.

To watch this video or to access the full library, visit **UPMCPhysicianResources.com/VideoRounds**.

Online CME

UPMC Physician Resources brings free educational CME opportunities to your computer and tablet device.

Type 1 Diabetes Complications: 30 Year Pittsburgh Perspective

Presented by Trevor Orchard, MD

Dr. Orchard presents the 2016 Kenny Drash lecture, highlighting some of the work that has been done over the past 30 years in the Pittsburgh EDC study.

Hidden in Plain Sight: Adipose Tissue as an Endocrine Organ

Presented by Radhika Muzumdar, MD

Dr. Muzumdar presents on the endocrine role of adipose tissue and the effects of adipose tissue on health, and discusses the role of adipose tissue dysregulation in obesity.

To view this course or to view more resources, visit **UPMCPhysicianResources.com/Pediatrics**.

For the latest information, follow @**UPMCPhysicianEd** on Twitter.

RECENT GRANTS AND AWARDS

Kara S. Hughan, MD
Assistant Professor of Pediatrics
Division of Pediatric Endocrinology, Diabetes, and Metabolism

Dr. Hughan has provided dedicated outpatient cystic fibrosis endocrine care over the last three years, in addition to inpatient CF endocrine consultation within Children's Hospital of Pittsburgh Cystic Fibrosis Care Center. Dr. Hughan is one of 16 recipients nationally of the Cystic Fibrosis Foundation CF EnVision Award: Emerging Leaders in CF Endocrinology Program. This three-year training award provides Dr. Hughan the opportunity to expand her CF Endocrine practice and to address the unique endocrinologic needs of pediatric patients with CF. Greater than 25% of the 280 pediatric CF patients followed at the CF Care Center have glucose abnormalities. Dr. Hughan and the CF Care Center team have initiated a project to examine factors, including glycemic control, that determine successful recovery of pulmonary exacerbations in cystic fibrosis. Additionally, Dr. Hughan is developing a clinical research proposal in collaboration with another Cystic Fibrosis Foundation CF EnVision junior faculty member at UT-Kids in San Antonio, Texas. Their multicenter cross-sectional study aims to investigate the overlap of CF liver disease (CFLD, as determined by liver stiffness using transient elastography) and glucose abnormalities, free fatty acid flux, and hepatic handling of glucose (as determined by OGTT) in children with CF, and to determine the relationship of transient elastography with other measures of CFLD, including liver ultrasound, direct liver function markers, and novel indirect biomarkers of liver fibrosis.

H. Henry Dong, PhD
Associate Professor of Pediatrics
Division of Pediatric Endocrinology, Diabetes, and Metabolism
Title: Hepatic Insulin for Diabetes
Funding source: American Diabetes Association
Fund year: 2017-2019

Type 1 diabetes results from autoimmune destruction of insulin-producing beta-cells in the pancreas. Dr. Dong's research goal is to reconstitute a glucose-coupled insulin release system in the liver for improving blood sugar control in type 1 diabetes. He has provided proof-of-principle that insulin production in the liver is sufficient to abate body weight loss, stop ketonuria, prevent ketoacidosis, and reduce hyperglycemia to a normal range for months in diabetic animals. To couple insulin production with blood sugar, Dr. Dong has integrated glucose-responsive elements into the system for controlling insulin production, such that insulin secretion from the liver will be turned on in response to blood sugar elevation and switched off in response to blood sugar decline. This system has been validated for glucose-dependent insulin production in liver cells and for blood sugar control in diabetic mice. Dr. Dong will conduct preclinical trials of this tightly glucose-regulated insulin production system for determining its efficacy and safety for life-long blood sugar control in diabetic animals. Liver cells are non-beta cell type and are refractory to autoimmunity. Unlike beta-cells that are difficult to obtain, liver cells are renewable due to their native regenerating capacity. Liver cell transplantation has been used in clinics for treating liver diseases in humans. Dr. Dong's project will address whether insulin-producing liver cells can be a cell source for transplantation for improving blood sugar control in type 1 diabetes. It will answer whether liver insulin will provide life-long blood sugar control in type 1 diabetes. •

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ABOUT THE DIVISION

The Division of Pediatric Endocrinology, Diabetes, and Metabolism at Children's Hospital of Pittsburgh of UPMC provides diagnostic and therapeutic services for children with diabetes mellitus, hypoglycemia, and disorders of physical growth, sexual maturation, thyroid function, pituitary function, and calcium and phosphorous metabolism, as well as other gender disorders. Patients are evaluated in collaboration with multidisciplinary teams to come to a unifying diagnosis and provide the best outcomes for patients and families. •

For a referral or consultation, please contact us at **412-692-5170**. Visit us online at **chp.edu/our-services/endocrinology**.

ABOUT CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists.

Children's is consistently recognized for its research and clinical achievements, including ranking 10th among children's hospitals and schools of medicine (FY15) in NIH funding for pediatric research, and being named to the 2016-17 *U.S. News & World Report* Honor Roll of America's Best Children's Hospitals.

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