Abnormal Glycerol Metabolism in a Child with Global Developmental Delay, Adrenal Insufficiency, and Intellectual Disability

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CLINICAL HISTORY AND BACKGROUND

After an uncomplicated birth and initial symptom-free period, a 7-day-old male infant presented with poor feeding, hypotension, hyponatremia (123 mmol/L; reference interval, 135–148), hyperkalemia (9.0 mmol/L; reference interval, 3.5–5.5), and increased blood urea nitrogen. A diagnosis of primary adrenal insufficiency was made following an adrenal ultrasound remarkable for no discernable adrenal tissue. Subsequent fluorescent in situ hybridization studies revealed deletions in the region containing the NR0B1, IL1RAPL1, and GK genes in both the patient (for which he was treated with adrenocorticosteroids) and his asymptomatic mother. At approximately 4 years of age, he experienced a hypoglycemic episode (plasma glucose, 42 mg/dL). Fasting triglyceride level was also increased at 465 mg/dL (reference interval, <250). Approximately 1 year later, he presented again to the emergency room with vomiting, headaches, lethargy, cramps, and diarrhea. Clinical examination showed a developmentally delayed child with hypotonia and strabismus. He had iatrogenic Cushing syndrome. There was evidence of microorchidism, mental stenosis, congenital hydroceles, and bilateral inguinal hernia. As part of follow-up studies, an array comparative genomic hybridization was performed. A urine specimen was also collected for organic acid analysis using GC-MS (Fig. 1).

DIAGNOSIS AND SUMMARY

This patient has a complex form of glycerol kinase deficiency (GKD) caused by a contiguous gene deletion (2.7 MB in size) within the short arm of chromosome X [arr[hg18] Xp21.3-p21.2 (27868256–30610575) ×0], detected by array comparative genomic hybridization. This nonrecurrent deletion includes NR0B1 (associated with adrenal hypoplasia congenita (AHC)), GK (associated with GKD), and IL1RAPL1 (associated with X-linked mental retardation). Deletions that include these genes have been reported in patients with and without mental retardation and complex GKD (1). NR0B1 encodes DAX1, required for the development of the adrenal gland, pituitary, and gonads. Thus, the adrenocortical failure in X-linked AHC is largely owing to the impairment of adrenal cortex organization into cords because of DAX1 deficiency. Patients with X-linked AHC typically present with neonatal primary adrenal failure and an intact minipuberty. At puberty, these patients develop both primary gonadal failure and hypogonadotropic hypogonadism, a hallmark of AHC (2–4). In some boys, transient precocious sexual development may occur during childhood, which progresses to hypogonadism (2). Although patients with hypogonadism clearly have hypogonadotropic disease, they do not respond to gonadotropin therapy, thus implicating primary gonadal failure (3).

GKD is an X-linked recessive disorder caused by pathogenic variants or contiguous gene deletions that in-
clude the GK gene. With variable expressivity (depending on the molecular etiology), GKD may be isolated, as in those with pathogenic variants in the GK gene, or complex, as in those with nonrecurrent Xp21 contiguous gene deletions that involve the GK and NR0B1 genes with or without genes like DMD or IL1RAPL1 (4). The phenotype of the isolated form ranges from life-threatening childhood metabolic crisis to asymptomatic, with only a biochemical phenotype of hyperglycerolemia. The clinical phenotype in the complex form of GKD may include short stature, severe developmental delay, and dysmorphic features, in addition to adrenal insufficiency and mental retardation linked to other deleted genes, as observed in our patient.

Glycerol kinase (GK) (EC 2.7.1.30), the rate-limiting enzyme in glycerol utilization, catalyzes the phosphorylation of glycerol to glycerol-3-phosphate (G-3-P). GKD results in accumulation of glycerol in blood and urine, the latter of which may be detected by organic acid analysis (Fig. 1). Glyceroluria per se is most often detected by organic acid analysis with the use of emollients and suppositories. Several additional metabolic disorders are associated with glycerol excretion, including fructose-1,6-bisphosphatase and malonyl-CoA decarboxylase deficiencies. Hypoglycemia is also a feature of GKD, as observed in this case (5). After phosphorylation by GK, the majority of G-3-P is oxidized to dihydroxyacetone phosphate, a substrate for hepatic gluconeogenesis (Fig. 2).

Hyperglycerolemia per se may negatively affect other gluconeogenic substrates, such as alanine, and can act as an inhibitor of gluconeogenic enzymes, such as fructose-1,6-bisphosphatase and phosphoenolpyruvate carboxykinase. Hypertriglyceridemia is also a biochemical hallmark of GKD; in the adipocyte, G-3-P combines with fatty acyl-CoA to ultimately form triglyceride, which undergoes hydrolysis to fatty acids and glycerol, the latter of which is used as a substrate for GK. Most triglyceride assays measure glycerol in a hydrolysis reaction using a microbial lipase. In pre-

Fig. 1. Organic acid analysis of patient urine using GC-MS.
Urine organic acids were extracted into ethyl acetate/ether and converted to trimethylsilyl derivatives before analysis using a GC 6890N/MS 5975 system equipped with a DB-1 column (Agilent).
Previous years, the potential for "pseudohypertriglyceridemia" in cases of GKD was a concern, whereby endogenous glycerol caused falsely increased triglyceride concentrations. However, the widespread adoption of "blanking" for background glycerol in triglyceride assays has largely resolved this problem.

Currently, there is no curative treatment for GKD, although early treatment in the complex form of GKD prevents life-threatening complications (5). The current treatment approach includes medical emergency alert identification, a low-fat diet, combined glucocorticoid and mineralocorticoid steroid hormone replacement therapy, and management of chronic hypoglycemia with frequent feedings. To address hypogonadotropic hypogonadism, treatment regimens should incorporate administration of testosterone at the time of puberty to aid the development of secondary sexual characteristics. Our patient is currently receiving testosterone (25 mg, intramuscular, quarterly), hydrocortisone (15 mg daily), fludrocortisone (0.15 mg daily), sertraline, and a multivitamin. He underwent a successful and uncomplicated bilateral inguinal hernia repair and meatotomy.

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Fig. 2. Metabolism of glycerol in adipocytes and the liver. DHAP, dihydroxyacetone phosphate; HSL, hormone-sensitive lipase; G3PD, glycerol-3-phosphate dehydrogenase.

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References


