Lipoid Congenital Adrenal Hyperplasia (CAH): Patient Report and a Mini-Review

Erick J. Richmond, MD[1]
Charles J. Flickinger, MD[2]
Jay A. McDonald, MD[3]
Mark A. Lovell, MD[4]
Alan D. Rogol, MD[1]

Introduction

Congenital lipoid adrenal hyperplasia (lipoid CAH) is the most severe of the CAH syndromes, preventing synthesis of almost all adrenal and gonadal steroid hormones.[1] Although there is substantial variability in the clinical presentation, the typical patient has adrenocortical insufficiency within the first 2 weeks of life with poor feeding, lethargy, dehydration, hyponatremia, hyperkalemia, hypoglycemia, and acidosis. Patients have female external genitalia regardless of chromosomal sex. This condition has received greater attention since the discovery that lipoid CAH is caused by mutations in the gene for the steroidogenic acute regulatory protein (StAR)[2] and the demonstration that the disease is common in Japanese children.[3]

We report a 6-year-old individual with lipoid CAH, whose affected tissues were used for the genetic studies that led to the identification of StAR deficiency as the cause of lipoid CAH.[2]

Patient Report

The child was a 2.76 kg female, born by spontaneous vaginal delivery near term (36 wk) to a 21-year-old white primigravida. The parents were not related. The infant fed poorly during the first 24 h of life. Despite adequate nasogastric alimentation, hypoglycemia and apneic episodes developed on day 3 of life. A sepsis workup was performed and antibiotic therapy was instituted; all culture results subsequently proved negative. Results of a cranial computed tomography scan were normal.

At 1 week of age, the baby was lethargic, hypotonic, and a bronzed skin color was noted. On day 8, hyperkalemia developed to 6.5 mEq/L, and the serum sodium subsequently dropped to 128 mEq/L. Because of the concern of adrenal insufficiency, two morning serum cortisol levels were obtained; they were 3.5 and 2.8 μg/dL (normal, 2–11 μg/dL) with a simultaneous 17-hydroxyprogesterone level of 28 ng/dL (normal, 7–77 ng/dL). The child was treated with intramuscular cortisone acetate and deoxycorticosterone and with oral sodium chloride supplementation. There was clinical improvement with adequate weight gain and normalization of the serum glucose and electrolyte concentrations. The child was discharged to home on day 19. Follow-up serum electrolyte levels obtained by her pediatrician were normal.

When seen at age 1 month in the Pediatric Endocrinology Clinic at the University of Virginia Health Sciences Center, the in-

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[1]Pediatric Endocrinology, [2]Department of Cell Biology, University of Virginia, Charlottesville, Virginia; [3]General Pediatrics, Sewanee, TN; [4]Department of Pathology, The Children's Hospital, Denver, CO.

Reprint requests and correspondence to: Erick J. Richmond, MD, Pediatric Endocrinology, Department of Pediatrics, Box 800-386, University of Virginia, Health Sciences Center, Charlottesville, VA 22908.

fant was noted to be wasted in appearance, although vigorous and alert. There were no dysmorphic features. The skin was markedly hyperpigmented. The genitalia were those of a normal female infant, without palpable gonadal tissue, posterior labial fusion, or clitoromegaly.

Parenteral corticosteroid replacement was continued during infancy, and the child was eventually switched to oral cortisone acetate and fludrocortisone acetate. The early child developmental milestones were normal; however, at age 3 years a mild learning deficit was diagnosed that required speech therapy. Despite the normal linear growth velocity, moderate exogenous obesity developed. There were several hospitalizations for intravenous fluid therapy and glucocorticoid supplementation during severe viral or bacterial illnesses.

Since the patient was well controlled on the medical regimen, it was decided with the agreement of her parents, to wait until age 3 years before performing further workup to determine the cause of the adrenal insufficiency. At age 3.2 years, an abdominal sonogram did not depict either gonads or Müllerian structures. Serum levels of 17β-estradiol, testosterone, and 17-hydroxypregnenolone were undetectable. Although the serum lutenizing hormone (LH) level was normal (6.2 IU/L), follicle-stimulating hormone (FSH) concentration was elevated (29.3 IU/L). A peripheral lymphocyte karyotype was 46,XY. A tentative diagnosis of lipoid congenital adrenal hyperplasia was made, and the parents were informed of the child's need for future gonadectomy.

At age 6.3 years, the patient was admitted to the University of Virginia General Clinical Research Center for evaluation before surgery. One week before admission, the oral cortisone acetate was switched to dexamethasone at a physiologic replacement dose; the fludrocortisone dose was not changed. Blood was obtained on admission and again after a 7-day course of simultaneous intramuscular adrenocorticotropic hormone (ACTH) and human chorionic gonadotropin (hCG) stimulation of adrenal and gonadal steroid hormone biosynthesis. Baseline unstimulated values for serum ACTH, LH, FSH, prolactin, insulin-like growth factor 1 (IGF-1), T4, and thyroid-stimulating hormone (TSH) were all within normal limits. Serum Müllerian inhibiting substance (MIS) levels of 0 and 1 ng/mL were normal for a prepubertal female (normal, 0–9 ng/mL), but they were low for a prepubertal male (normal, 3–182 ng/dL).[4] The results of analyses for steroid hormones are shown in Table 1.

At surgery, two intraabdominal gonads were found, each approximately 1.5 × 0.7 × 0.4 cm; a short, blind vaginal pouch with no evidence of Müllerian structures was noted. The gonads were orange and uniformly solid on cut section. Light microscopy revealed focal microcalcifications within immature testicular tubules. The Leydig cells stained intensely for lipids. Electron microscopy showed intracellular lipid vacuolization in Leydig cell cytoplasm (Figure 1). Testicular tissue and blood were sent to the metabolic research unit at the University of California, San Francisco, where a mutation in the gene for the steroidogenic acute regulatory protein (StAR) was found (specifically, the patient was homozygous for the Arg^{193}→stop mutation). The previous finding as well as similar mutations in two other patients led to the conclusion that lipoid CAH was caused by mutations in the gene for the steroidogenic acute regulatory protein (StAR).[2] Lack of functional StAR causes markedly impaired gonadal and adrenal steroid hormone synthesis.

Our patient had a 46,XY karyotype, but female external genitalia, consistent with deficient fetal testicular steroidogenesis. Although the MIS levels at age 6.3 years were low for a prepubertal male, the fact that no Müllerian structures were found during surgery indicates that the patient's testes were able to produce adequate amounts of MIS during fetal life.

She is doing well on replacement therapy, which includes cortisone acetate and fludrocortisone. We anticipate the need for estrogen replacement for breast development in the near future.

Congenital Lipoid Adrenal Hyperplasia: Mini-Review

Congenital lipoid adrenal hyperplasia was described as an autosomal recessive disorder of adrenal and testicular steroidogenesis by Prader and associates[5-7] between 1952 and 1962. This condition was characterized by severe, often fatal, salt-wasting crisis in infancy and female external genitalia in children of both sexes. Because these patients apparently produced no steroid hormones and because their adrenal glands accumulated cholesterol, it was assumed that lipoid CAH was caused by a defect in one of the enzymes involved in the conversion of cholesterol to pregnenolone.[8] The conversion of cholesterol to pregnenolone was thought to require at least three

Table 1

BASELINE AND ACTH STIMULATED HORMONE CONCENTRATIONS OF A 6-YEAR-OLD GENETIC MALE WITH LIPOID CAH

Serum Compound Assayed	Baseline Level (upright posture)	Stimulated Level (upright posture)	Normal Range* (prepubertal upright, unstimulated)
cholesterol	192	205	<175 mg/dL
pregnenolone	32	70	20–110 ng/dL
progesterone	<10	16	7–52 ng/dL
17–OH-pregnenolone	<10	<10	15–221 ng/dL
17–OH-progesterone	<5.0	<5.0	3–90 ng/dL
dehydroepiandrosterone	<20	<20	20–150 ng/dL
DHEA sulfate	<10	<10	5–57 µg/dL
Δ^4-androstenedione	<10	<10	8–50 ng/dL
testosterone	<3.0	<3.0	3–10 ng/dL
estradiol	<0.5	<0.5	<1.0 ng/dL
11-desoxycortisol	<10	<10	20–155 ng/dL
cortisol	<1.0	1.0	3–21 µg/dL
deoxycorticosterone	3.9	3.8	2–34 ng/dL
corticosterone	<20	21	70–620 ng/dL
18-OH-corticosterone	<5.0	<5.0	6–85 ng/dL
aldosterone	<1.0	2.2	5–80 ng/dL

*Ranges of values measured from normal prepubertal children (Endocrine Sciences, Calabasas Hills, CA).

enzymes, a 20 α-hydroxylase, a 22-hydroxylase, and a 20-22 desmolase,[9] and lipoid CAH was considered to result from inactivity of one of these enzymes.

Work between 1965 and 1973 showed that the conversion of cholesterol to pregnenolone was catalyzed by a single mitochondrial P450 enzyme termed P450scc (where scc denotes side chain cleavage). Thus, although Degenhart and co-workers[10] concluded in 1972 that lipoid CAH was due to a specific lesion in a 20-hydroxylase, Zoizumi and associates[11] reported in 1977 that affected tissues lacked spectroscopically detectable P450scc. The basis for lipoid CAH was thereafter assumed to be a mutation of P450scc, just as the more common forms of CAH were believed due to mutations in other steroidogenic P450 enzymes.[1] This hypothesis was not seriously questioned until 1991.

In 1991 Lin and associates[12] found that the P450scc gene was expressed in affected tissue from children with lipoid CAH and that the expressed gene (cDNA) sequences were entirely normal, thus ruling out P450scc deficiency as a potential cause of lipoid CAH. Therefore, it was hypothesized that lipoid CAH might be due to disruption of a factor involved in the transport of cholesterol from lipid droplets to mitochondria or from the outer mitochondrial membrane to the inner leaflets, the locus of the P450scc. The cause of lipoid CAH remained indetermined until recently.

Analysis of three unrelated patients with lipoid CAH by Lin and

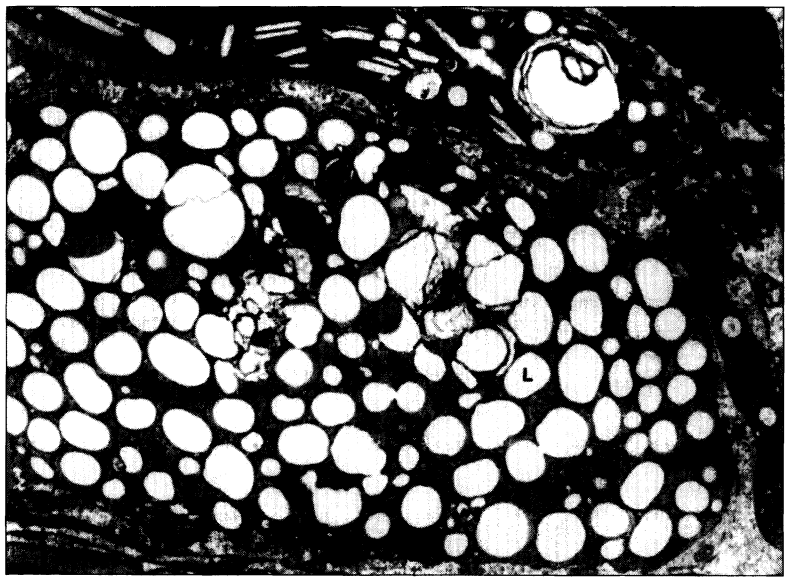

Figure 1. Electron micrograph of a portion of the interstitial tissue of the patient's testis. A large Leydig cell appears distended with multiple lipid droplets (**L**), to the near exclusion of most cytoplasmic organelles except for a few mitochondria (**M**), small vesicles, and ribosomes. The interiors of the lipid droplets are electron lucent because most of their content has been extracted during preparation. The smaller cell at the top of the field (**X**) contains a few lipid droplets and angular profiles (**A**), possibly representing areas from which crystalline material was extracted. C-collagen fibers. The bar represents 2 μm.

co-workers in 1995[2] (including the patient in this report) revealed mutations in the gene for the steroidogenic acute regulatory protein (StAR), which is now considered to be the cause of lipoid CAH. Moreover, these observations established that StAR functions to increase the flow of cholesterol into mitochondria and provided the first evidence for StAR-independent steroidogenesis.

Subsequently, Bose and associates[13] described the two-hit model that accounts for most of the clinical observations in lipoid CAH. In brief, StAR mutations initially eliminate only the StAR-induced steroidogenesis that occurs in response to tropic hormone stimulation. In the absence of StAR-dependent steroidogenesis (the first hit), the high levels of tropic hormone induce intracellular cholesterol accumulation (Figure 1). With time this accumulated cholesterol proves toxic to the cell and causes the loss of StAR-independent steroidogenesis (the second hit). In a recent review,[14] it was concluded that the mechanism of action of StAR is still unknown. However, StAR apparently functions by mediating the transfer of cholesterol from the outer to the inner mitochondrial membrane where it is transformed to pregnenolone, the first steroid synthesized.

The detailed study of several 46,XX females with lipoid CAH reinforced the pathophysiologic mechanism described as the two-hit model. In contrast to affected 46,XY subjects, whose testes cannot produce sufficient testosterone in-utero to masculinize the external genitalia and who cannot go through spontaneous puberty, 46,XX females do go through spontaneous puberty and secondary sexual development, including menarche.[15] The postpubertal females studied to date have abnormal patterns of gonadotropin secretion, with elevated LH levels that result in anovulatory cycles and the development of multicystic ovaries. The evident sparing of some ovarian function reflects the presence of modest StAR-independent steroidogenesis in follicles that is sufficient to promote estradiol synthesis. Because the ovary is essentially steroidogenically quiescent during fetal life and because follicles only produce steroids when they are recruited to mature, most follicles are spared from the ravage of cholesterol engorgement, leaving a source of vi-

able, albeit impaired, steroid-producing cells at the time of puberty.

In summary, patients with lipoid CAH require mineralocorticoid and glucocorticoid replacement therapy. Men additionally need exogenous testosterone to go through puberty and most females need oral contraceptives or medroxyprogesterone to prevent the formation of large ovarian cysts.[16]

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