Bilateral Laparoscopic Adrenalectomy as a Treatment for Classic Congenital Adrenal Hyperplasia Attributable to 21-Hydroxylase Deficiency

Glenn A. Gmyrek, MD*; Maria I. New, MD, FAAP‡; R. E. Sosa, MD*; and Dix P. Poppas, MD, FAAP*‡

ABSTRACT. Objective. Current medical therapy for congenital adrenal hyperplasia (CAH) attributable to a complete 21-hydroxylase deficiency is not optimal. Difficulties in adequate adrenal androgen suppression are common, causing short adult stature, infertility, and hyperandrogenism. We report the use of laparoscopic bilateral adrenalectomy as a definitive therapy for this condition and argue that it is superior to conventional medical therapy in selected patients.

Methods. Participants were 2 adult females with classic, salt-wasting CAH and a history of poor adrenal control were selected for adrenalectomy: case 1 was a 22-year-old woman with mild hirsutism and primary amenorrhea; case 2 was a 28-year-old woman with severe hirsutism, acne, and amenorrhea. Preoperative and postoperative hormonal profiles were performed. Both underwent laparoscopic bilateral adrenalectomy with a mean follow-up of 37 months.

Results. Bilateral laparoscopic adrenalectomy was performed in both patients with no complications and an uneventful recovery. Maintenance medications of glucocorticoid and mineralocorticoid replacement were reduced compared with preoperative doses. Three years postoperatively, however, rising adrenal steroid precursor levels in case 1, presumably caused by adrenal rests, prompted an increase in replacement therapy dose. Hirsutism and acne improved in both patients, and regular menstruation began 5 months (case 1) and 2 months (case 2) postoperatively. Pregnancy 3 years postoperatively was successful in case 2, who delivered an unaffected infant, full-term via Cesarian section.

Conclusions. Surgical adrenalectomy should be considered in females with classic CAH attributable to 21-hydroxylase deficiency and a history of poor hormonal control. Adrenalectomy may prove to be superior to current medical therapy for these patients. Pediatrics 2002; 109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e28; congenital adrenal hyperplasia, treatment, laparoscopy, adrenalectomy.

ABBREVIATIONS. CAH, congenital adrenal hyperplasia; ACTH, adrenocorticotropic hormone; 17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase; CCRC, Children’s Clinical Research Center.

Congenital adrenal hyperplasia (CAH) is a family of inherited disorders of steroidogenesis in which enzymatic defects result in impaired synthesis of cortisol by the adrenal cortex. Over 95% of cases are owed to deleterious mutations in the gene coding for 21-hydroxylase, CYP21, which results in little to no 21-hydroxylase activity. Classic CAH occurs in 2 forms, simple virilizing and salt wasting, the latter causing a life-threatening deficiency of both cortisol and aldosterone. Lack of negative feedback to the anterior pituitary leads to excessive adrenocorticotropic hormone (ACTH) secretion and overproduction of adrenal androgens and cortisol precursors such as 17-hydroxyprogesterone (17-OHP) and Δ4-androstenediol. In affected females, the high circulating levels of adrenal androgens virilize external genitalia in utero and female pseudohermaphroditism results. Postnatal clinical features include precocious appearance of facial, axillary and pubic hair, and short adult stature from premature epiphyseal closure. During adolescence and childbearing years, elevated serum levels of adrenal androgens and progesterone in many women likely affect gonadotropin secretion causing the commonly observed delayed menarche, amenorrhea, and decreased fertility.

Medical treatment of females with a complete absence of the 21-hydroxylase (21-OH) enzyme has long been a source of frustration for both clinician and patient alike. The mainstay of treatment since 1950 has been exogenous glucocorticoid and mineralocorticoid replacement. Replacement therapy ideally serves to restore electrolyte homeostasis and suppress the hypothalamic-pituitary-adrenal axis. In the management of patients with significantly decreased or absent 21-hydroxylase activity, replacement therapy has enjoyed only limited success because complete suppression of the hypothalamic-pituitary-adrenal axis has proven difficult. The dose of glucocorticoid required to prevent hyperandrogenism in these females is often supraphysiologic and can result in iatrogenic hypercortisolism with its associated obesity and Cushingoid features. As a result, 21-OH−deficient females may endure, to varying degrees, effects of the adrenal androgens and the side effects of iatrogenic hypercortisolism.

Bilateral adrenalectomy has been reported as an alternative treatment for females with classic CAH who were poorly controlled with conventional steroid replacement therapy. Laparoscopic adrenal-
ectomy provides an efficient elimination of excess adrenal steroid precursors and the need to suppress the hypothalamic-pituitary-adrenal axis. Postoperatively, the glucocorticoid dose can be reduced and the side effects of iatrogenic hypercortisolism avoided.

We present our experience with 2 adult females with salt-wasting CAH attributable to a complete 21-OH deficiency who underwent laparoscopic bilateral adrenalectomy. Both patients had been managed with conventional steroid replacement therapy since birth with limited success. We discuss the advantages of this therapeutic modality, its potential shortcomings, and its future as a treatment for children with the most severe cases of CAH.

MATERIALS AND METHODS

Two females, ages 22 (case 1) and 28 (case 2), with the severe, salt-wasting form of CAH were selected from a cohort of 72 patients currently followed by the same pediatric endocrinologist at our institution. The patients were admitted to the Children’s Clinical Research Center (CCRC) of Weill Medical College of Cornell University 3 days (case 1) and 1 day (case 2) before the adrenalectomy.

Case 1 is a 25.5-year-old female born with ambiguous genitalia referred at 1 day of life to our CCRC where she was diagnosed with salt-wasting 21-hydroxylase deficiency based on hyperkalemia, elevated levels of serum 17-ketosteroids, adrenal androgens, and significantly low aldosterone levels. She has since been followed by the same pediatric endocrinologist every 3 months where baseline serum adrenal steroid concentrations are measured in the morning of each visit. At 1.5 years of age, a clitoral recession was performed, followed by opening of labial-scrotal folds at 3 years old; clitoroplasty and vaginoplasty occurred at 4.5 years of age. A urethral surgery was performed at age 3 and again at age 4.5 years because of kinking of the bladder neck. At 21 years of age, DNA analysis using allele-specific polymerase chain reaction and Southern blotting revealed the patient was heterozygous with an Exon 4 (Q318X) mutation on 1 chromosome and 1 large deletion of CYP21 on the other chromosome. Although the patient was compliant, throughout her childhood she had many periods of over and under adrenal suppression and frequent changes in prednisone and later dexamethasone dosage. Hirsutism and acne persisted despite adjustments in replacement therapy doses. Before adrenalectomy, case 1 had been maintained on hydrocortisone 13.3 mg/m²/day. After a year of adequate adrenal suppression at age 16, the patient remained amenorrheic while LH stimulation tests were consistent with Tanner stage IV puberty. Two attempts to induce menses at age 17 using high-dose conjugated estrogens (Premarin, Wyeth-Ayerst, Philadelphia, PA) for 28 days and progesterone (Provera, Pharmacia and Upjohn, conjugated estrogens (Premarin, Wyeth-Ayerst, Philadelphia, PA) for puberty. Two attempts to induce menses at age 17 using high-dose conjugated estrogens (Premarin, Wyeth-Ayerst, Philadelphia, PA) for 28 days and progesterone (Provera, Pharmacia and Upjohn, Kalamazoo, MI) on days 19 through 28 were unsuccessful. Levels of adrenal androgen precursors began rising at age 20 evidenced by 17-OHP level ranging from 1281 to 2887 ng/dL, and Δ4-androstanedione ranging from 44 to 215 ng/dL (Table 1).

Case 2 is a 28-year-old female born with ambiguous genitalia who developed hynapotremia and hyperkalemia over the first 2 weeks of life prompting the diagnosis of salt-wasting 21-hydroxylase deficiency. Glucocorticoid and mineralocorticoid replacement therapy was started and a clitorectomy and perineal repair performed at 1 month of age. After several salt-wasting crisis throughout her first 6 years of life she was referred to our CCRC to evaluate her medical treatment and was discharged on 25.7 mg/m²/day. She has since been followed by the same pediatric endocrinologist every 3 months at our institution. Human leukocyte antigens typing confirmed the diagnosis of CAH, and allele-specific polymerase chain reaction and Southern blotting revealed the patient was a compound heterozygote, with deletion of the CYP21 gene on 1 chromosome and Exon 1 (P30L), Intron 2(A/C→G) Exon 3 (8 base pair deletion) mutations on the other chromosome. Menarche occurred at age 14, followed by complaints of weight gain, acne, and dysfunctional bleeding (2–3 times within 28 days) beginning at age 18. A luteinizing hormone-releasing hormone test before dexamethasone suppression indicated a normal pubertal response, however, an abdominal ultrasound revealed bilateral ovarian cysts. The patient was started on oral contraceptives and regular menses ensued. The oral contraceptives were discontinued by the patient after 1 year because of weight gain (weight 75th percentile, height <5th percentile), and dysfunctional bleeding continued for 9 years after which she became amenorrheic. Serum adrenal androgen levels remained elevated throughout adolescence and early adulthood, and the patient complained of acne and hirsutism. To evaluate if elevated androgens were caused by poor compliance, the patient had several admissions to our CCRC where she was monitored for approximately 1 week taking the same medications as prescribed at home. The patient seemed to be compliant, because the androgen levels did not suppress sufficiently during these admissions. At age 26, 2 years before the adrenalectomy, Δ4-OHP levels ranged from 2248 to 8330 ng/dL, and Δ4-androstenedione ranged from 281 to 498 ng/dL.

Laparoscopic bilateral adrenalectomy was offered to both patients to prevent accumulation of adrenal steroid precursors; this would likely restore regular 4-week menstrual cycles, decrease virilization, and decrease dosage of replacement therapy. Preoperative and postoperative testosterone, Δ4-androstenedione, dehydroepiandrosterone (DHEA) and 17-OHP levels were obtained (Table 1), as well as plasma renin activity. Transperitoneal laparoscopic bilateral adrenalectomy was performed using a previously reported laparoscopic technique. The institutional review committee of our hospital approved the study and informed consent was obtained from the patients. Operative time was 370 minutes and 283 minutes in cases 1 and 2, respectively (mean 325 minutes). Estimated mean operative blood loss was 100 mL. Length of stay was 3 days for case 1. Case 2 required an additional day (length of stay: 4 days) because of postoperative pain and limited mobility. No complications occurred at the time of surgery or postoperatively. Both patients received 100 mg of hydrocortisone the morning of surgery and 50 mg of hydrocortisone per hour during the procedure. Slow tapering of hydrocortisone occurred over 3 days. After 3 days postoperatively, case 1 was discharged on 9.7 mg/m²/day hydrocortisone and case 2 was discharged on 19.2 mg/m²/day hydrocortisone. Both patients were discharged on 0.1 mg/day of Florinef.

Both patients have been seen postoperatively at 3-month intervals where a baseline serum adrenal steroid profile, plasma renin activity, and electrolyte evaluation are performed.

RESULTS

Both patients underwent uneventful transperitoneal laparoscopic bilateral adrenalectomy. There was a significant reduction in serum androgens and 17-OHP in both patients after adrenalectomy. Table 1 summarizes these results.

TABLE 1. Comparison of Preoperative and Postoperative Hormonal Profile

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<tr>
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<th>Normal Values for Adult Females</th>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
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<td>Preoperative (10 Months)</td>
<td>Postoperative (39 Months)</td>
<td>Preoperative (10 Months)</td>
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<td>17-OH-progesterone, ng/dL</td>
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<td>Testosterone, ng/dL</td>
<td>40 ± 22</td>
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<tr>
<td>Δ4-Androstenedione, ng/dL</td>
<td>140 ± 56</td>
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<td>44</td>
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<td>Dehydroepiandrosterone, ng/dL</td>
<td>442 ± 220</td>
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Follow-up is 39 months and 35 months for cases 1 and 2, respectively (mean: 37 months). Steroid requirements in both patients were reduced compared with preoperative requirements. Acne and hirsutism in case 2 had markedly decreased 5 months postoperatively. After 1 year, weight loss occurred in both patients, body mass index of case 1 was 27 kg/m² preoperatively and is currently 25 kg/m², and the body mass index of case 2 was 31.6 kg/m² and is currently 29 kg/m². Spontaneous menses at 28-day intervals commenced at 5 and 2 months postoperatively in cases 1 and 2, respectively, and have continued to date. During 2 follow-up visits, 33 and 39 months postoperatively, case 1 was found to have increasingly elevated serum levels of adrenal steroid precursors (Table 1) likely caused by adrenal rests in the ovaries or other tissue. An ACTH stimulation test revealed serum 17-OHP was stimulated to 609 ng/dL after 60 minutes (baseline: 528 ng/dl), Δ₄-androsteindione stimulated to 94 ng/dL (baseline: 88 ng/dL), dehydroepiandrosterone stimulated to 24 ng/dL (baseline: 18 ng/dL) and testosterone was 38 ng/dL after stimulation compared with 43 ng/dL at baseline. A pelvic ultrasound of ovaries and uterus to rule out polycystic ovarian disease was normal. The patient is asymptomatic and currently main- tained on hydrocortisone 12.5 mg/m²/day and Fludrocortisone 13.3 mg/m²/day and Fludrocortisone 0.1 mg/day, until she became pregnant, and her hydrocortisone dose was increased to 19 mg/m²/day, and Fludrocortisone was increased to 0.2 mg/day. The patient, a healthy, full-term infant weighing 3.5 kg with a birth length of 52.0 cm and a head circumference of 37.0 cm, was delivered by Cesarian section. The fetus was prenatally diagnosed as unaffected with CAH.5

DISCUSSION
Patients with the salt-wasting form of CAH suffer a potentially life-threatening deficiency of glucocorticoids and mineralocorticoids because of an absence of 21-hydroxylase activity. Lifelong steroid replacement has been the mainstay of treatment since 1950 when it first was shown that administration of exogenous glucocorticoids could not only maintain electrolyte homeostasis but also suppress the hypothalamic-pituitary-adrenal axis and minimize the excessive secretion of adrenal steroid precursors and androgens.18,19 Unfortunately maintaining adequate adrenal suppression with replacement therapy has found only moderate success.

Pituitary secretion of ACTH has been shown to be a complex, multifactorial process not solely dependent on the negative feedback of glucocorticoids.20,21 In addition, 21-hydroxylase deficient adrenals have been shown to be hypersensitive, oversecreting in response to a small ACTH challenge. Thus, the feasibility of complete adrenal suppression using conventional steroid replacement therapy has been questioned.5

Bilateral adrenalectomy has been proposed for some inadequately controlled classic CAH patients who may be better managed as an Addisonian patients.

Given inherent shortcomings and the suboptimal results produced with conventional steroid replacement therapy, we support bilateral adrenalectomy as a possible treatment for female salt-wasting CAH patients with severe symptoms in which conventional treatment has not been effective. Performed laparoscopically, it poses minimal risk and minimal morbidity with an acceptable postoperative recovery time and cosmetic result. Regular menstruation occurred in both patients, and fertility was documented in 1 patient who had a successful pregnancy 3 years postoperatively.

Genetic analysis of a large cohort of CAH patients has nearly characterized the mutational spectrum of the disease and has made it possible to identify the subset of females most likely to benefit from surgical adrenalectomy, ie, those with absent 21-OH activity attributable to null alleles which have 0% enzyme activity. The most common large deletion in CAH usually begins at a point between Exon 3 and Exon 8, and extends through the rest of the gene into the pseudogene, CYP21P.14,15 There are, however, approximately 25 other small deletions, conversions, and nonsense mutations that result in little to no 21-hydroxylase activity according to transfection studies.22 Genotype does not always predict phenotype in this disorder,23 thus adrenalectomy may be considered as a treatment option for the most severe cases of salt-wasting CAH regardless of genotype.

It is important to note that recurrence of elevated adrenal steroid levels occurred in case 1 and has been previously reported in other adult CAH patients who underwent bilateral adrenalectomy.7,8 Virilization or menstrual abnormalities have not reappeared in our patient who is followed closely in our clinic. Ablation of ectopic adrenal rests could be performed laparoscopically if indicated in the future. However, this would require potential extensive retroperitoneal exposure. Ectopic ovarian adrenal rests would be difficult to completely remove risking damage to the remaining ovary. Currently, there is not enough data to determine the significance and frequency of ectopic adrenal tissue in adrenalectomized female CAH patients.

Some authors argue that bilateral adrenalectomy renders a patient Addisonian, mandates lifelong steroid replacement, and increases susceptibility to adrenal crises in times of bodily stress.1,5 Patients with a complete 21-OH deficiency, however, are already committed to lifelong steroid replacement to prevent adrenal crises. Their 21-OH deficient adrenal glands produce little, if any, cortisol and aldosterone while secreting excessive amounts of undesirable androgens. Therefore, we feel that this argument against surgical adrenalectomy has little merit.

The appropriate time to perform adrenalectomy is controversial and must be further defined. In salt-wasting females with poorly controlled CAH, many disease manifestations develop during childhood and adolescence. Our patients were 22 and 28 years old at the time of adrenalectomy. They had already endured years of marginal adrenal suppression de-
spite elevated doses of dexamethasone. If performed early in life, as advocated by some,1,5,10,12 patients could avoid unnecessary virilization, precocious puberty, short stature, and irregular menses commonly seen using conventional medical therapy.

CONCLUSION

Bilateral adrenalectomy should be considered in females with classic CAH and a history of poor adrenal control. Virilization, hirsutism, and menstrual abnormalities can be improved and the adverse effects of conventional steroid replacement therapy can be avoided. When performed laparoscopically, surgical morbidity and postoperative recovery time are minimized, and the cosmetic result is excellent. Although it is a viable therapeutic option in those females with genetically proven complete 21-OH deficiency, the role of adrenalectomy as a definitive treatment for the salt-wasting form of CAH needs to be clearly defined through controlled clinical trials.

ACKNOWLEDGMENT

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