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 uterus 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 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 conventional medical therapy in selected patients.
BILATERAL LAPAROSCOPIC ADRENALECTOMY

TABLE 1. Comparison of Preoperative and Postoperative Hormonal Profile

<table>
<thead>
<tr>
<th>Normal Values for Adult Females</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-OH-progesterone, ng/dL</td>
<td>150 ± 20</td>
<td>2280</td>
</tr>
<tr>
<td>Testosterone, ng/dL</td>
<td>40 ± 22</td>
<td>57</td>
</tr>
<tr>
<td>Δ4-Androstenedione, ng/dL</td>
<td>140 ± 56</td>
<td>159</td>
</tr>
<tr>
<td>Dehydroepiandrostosterone, ng/dL</td>
<td>442 ± 220</td>
<td>72</td>
</tr>
</tbody>
</table>

RESULTS

Both patients underwent uneventful transperito-neal laparoscopic bilateral adrenalectomy. There was a significant reduction in serum androgens and 17-OHP in both patients after adrenalectomy. Table 1 summarizes these results.
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 (baseline: 528 ng/dL), Δ4-androstenedione 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. Case 2 currently shows no signs of virilization and was maintained on hydrocortisone 13.3 mg/m²/day and Fludrocortisone 0.1 mg/day. Case 2 currently shows no signs of virilization and was maintained on hydrocortisone 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.15,17

**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 retroperito-
eal 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 andro-
gens. 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-

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spite elevated doses of dexamethasone. If performed early in life, as advocated by some,\textsuperscript{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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**REFERENCES**

1. Ritzen EM, Wedell A. Adrenals of patients with severe forms of congenital adrenal hyperplasia do more harm than good! J Clin Endocrinol Metab. 1996;81:3182–3184
2. Migeon CJ. Can the long range results of the treatment of congenital adrenal hyperplasia be improved? J Clin Endocrinol Metab. 1996;81:3187–3189
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