CLINICAL CASE SEMINAR

Fertility and Body Composition after Laparoscopic Bilateral Adrenalectomy in a 30-Year-Old Female with Congenital Adrenal Hyperplasia

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ABSTRACT

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is caused by an inborn defect in the 21-hydroxylase gene (CYP21; Refs. 1–3). This gene is normally expressed in the adrenal glands. The genetic defect causes a deficit in functionally active enzyme, leading to the inability to synthesize mineralo- and glucocorticosteroids. Depending on the type of defect, the level of residual enzyme can range from a subtle reduction to complete absence. The decreased synthesis of cortisol results in increased secretion of ACTH from the pituitary, with subsequent adrenal hyperplasia and overproduction of 21-hydroxylase substrates, which can be further metabolized to androgenic steroids, leading to virilization of female patients and causing ambiguous genitals in the majority of female infants. Growth is initially accelerated, followed by early epiphysial closure and short stature in both sexes (4–6). Hyperandrogenism of adrenal origin can induce precocious puberty in boys. The medical treatment of 21-hydroxylase deficiency has not been substantially altered since 1950 (7).

Glucocorticoid replacement aims to reduce virilization by suppression of ACTH stimulation. The reported prescribed dosages frequently exceed 15 mg cortisol/m²/day, whereas the normal daily secretion rate is about 7–8 mg/m² (8, 9). Despite frequent monitoring and dose adjustments these supraphysiological dosages have been shown to lead to adverse effects like attenuation of growth, obesity, and decreased bone mineral density (10–13). In adult life sexual functioning is often impaired, both biologically and psychologically (14). Women still suffer from loss of libido, irregular or absent cycles, and reduced fertility (6, 15–17). In males suppression of gonadotrophic hormones may induce poor spermatogenesis (4).

These problems have stimulated the search for alternative treatment modalities (9, 18). It is now possible to carry out prenatal fetal genotyping in women known to be at risk of having offspring with 21-hydroxylase deficiency, and affected female fetuses can be treated in utero to prevent virilization. Also, bilateral adrenalectomy has been used in patients where medical suppression of adrenal precursors was difficult to achieve or was accompanied by serious side effects (19–22). Patients without any remaining enzyme activity, the so-called double null mutation carriers, are supposed to be the most eligible candidates for this approach (9). This invasive treatment has become more accessible because the patients can be identified easily by genotyping of the CYP21 gene, and also by the introduction of laparoscopic adrenalectomy. This procedure is safe, less mutilating, and well tolerated (23–25). We present a typical adult female patient with CAH as a result of complete loss of 21-hydroxylase activity, who was difficult to treat medically and whose clinical situation was markedly improved by laparoscopic bilateral adrenalectomy.

CONGENITAL ADRENAL hyperplasia (CAH) due to 21-hydroxylase deficiency is caused by an inborn defect in the 21-hydroxylase gene (CYP21; Refs. 1–3). This gene is normally expressed in the adrenal glands. The genetic defect causes a deficit in functionally active enzyme, leading to the inability to synthesize mineralo- and glucocorticosteroids. Depending on the type of defect, the level of residual enzyme can range from a subtle reduction to complete absence. The decreased synthesis of cortisol results in increased secretion of ACTH from the pituitary, with subsequent adrenal hyperplasia and overproduction of 21-hydroxylase substrates, which can be further metabolized to androgenic steroids, leading to virilization of female patients and causing ambiguous genitals in the majority of female infants. Growth is initially accelerated, followed by early epiphysial closure and short stature in both sexes (4–6). Hyperandrogenism of adrenal origin can induce precocious puberty in boys. The medical treatment of 21-hydroxylase deficiency has not been substantially altered since 1950 (7).

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Postoperatively the elevated serum progesterone and 17-hydroxysterone levels, as well as the undetectable LH levels, normalized. The procedure resulted in marked clinical improvement. Within 12 months after surgery she lost 11 kg in weight. This weight loss consisted mainly of adipose tissue. Acne disappeared, and she had a regular 4-week menstrual cycle, with progesterone levels that are compatible with a luteal phase. The introduction of laparoscopic techniques may give an impulse to the application of surgical therapy at a larger scale in patients with 21-hydroxylase deficiency who are difficult to treat with adrenal suppression therapy. (J Clin Endocrinol Metab 86: 482–484, 2001)
The patient

The patient, now a 31-yr-old female, from nonconsanguineous parents, was born with ambiguous genitalia. She went through a salt-losing crisis shortly after birth and was diagnosed as having classical CAH on clinical grounds. At 2 yr of age a nephropyleotomy and a meatoectomy of the urethra were performed to relieve her from recurrent urinary tract problems. When she was 4 yr old a clitoral reduction and correction of the labia were performed, followed by an introitoplasty and vaginoplasty at age 13 and 16, respectively. She visited the hospital three to four times each year, and on these occasions circulating hormone levels were checked. The results were used to adjust the glucocorticoid dose to keep androstenedione and 17-hydroxyprogesterone levels within the normal range using as little medication as possible. Despite this frequent monitoring and frequent dose adjustments, she experienced many problems that can accompany the treatment of these patients: she did not feel feminine, had a masculine build, was obese, had irregular menses with long amenorrhoic periods, and a seborrhoic skin with acne. Her weight was 79 kg, and her height was 168 cm, whereas her mother and father measured 174 and 180 cm, respectively. She was normotensive (110/70 mm Hg).

Using allele-specific PCR (26) it was determined that the patient was homozygous for a splice-site mutation in intron 2, which by itself would have resulted in a very low residual activity of 21-hydroxylase activity (27). In addition, however, the patient was heterozygous for the five most C-terminal mutations in the protein: V28I L, InsT, Q318ter, R356W, and P453S. At the age of 29 she used dexamethasone at a dose varying between 0.5 and 1 mg per day in two divided doses taken at 0900 and 2100 h and 0.0625 mg/day fludrocortisone. With those treatment regimens serum progesterone and 17-hydroxyprogesterone concentrations remained well above the reference levels in our laboratory, whereas serum ACTH levels were normal. A representative hormonal profile is shown in Table 1. Furthermore, the LH was suppressed, which might contribute to the disturbance of her menstrual cycle (Table 1). A computed tomography scan showed bilateral hyperplasia of both the adrenals.

<table>
<thead>
<tr>
<th>Table 1. Laboratory results</th>
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<tr>
<td><strong>FSH (IU/L)</strong></td>
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<td>1–7</td>
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<tr>
<td><strong>LH (IU/L)</strong></td>
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<tr>
<td><strong>Progesterone</strong></td>
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<td>(nmol/L)</td>
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<tr>
<td><strong>Oestradiol</strong></td>
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<tr>
<td><strong>17-OH-progesterone</strong></td>
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<td><strong>Serum ACTH</strong></td>
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<td><strong>Medication</strong></td>
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F. Follicular phase of the menstrual cycle; L, luteal phase of the menstrual cycle.

a One hormonal profile is presented preoperatively, which is representative of many measurements over a period of 6 yr under variable doses of dexamethasone (0.5–1 mg/day).

b Serum LH, FSH, progesterone, and oestradiol concentrations measured preoperatively, as well as 3 and 6 months after operation, were not related to the menstrual cycle, which was abnormal. However, menstrual cycles had normalized 12 months after bilateral adrenalectomy, and the serum gonadotropin and steroid hormone concentrations at that time were drawn on day 24 of the menstrual cycle.

Laparoscopic biadrenalectomy was offered as alternative treatment, with the objective to restore the menstrual cycle, reduce masculinization, and make medical (supplementation) therapy easier and less intensive.

Adrenalectomy was performed using a standard laparoscopic procedure (22–24). The operation and postoperative recovery were uncomplicated, and discharge from hospital followed after 3 days. Replacement therapy was started with 10 mg hydrocortisone three times daily and 0.0625 mg fludrocortisone once daily. Hydrocortisone replacement was later tapered to 20 mg daily without adverse effects. However, early morning serum ACTH levels turned out to be increased. Therefore, hydrocortisone replacement therapy was increased to 25 mg/day, after which ACTH levels normalized (data not shown). Postoperative laboratory data (Table 1) revealed that the serum progesterone and 17-hydroxyprogesterone levels had normalized and that LH levels became measurable again. The procedure resulted in marked clinical improvement. Within 12 months after surgery she had lost 11 kg in weight, her acne had disappeared, and she had a regular 4-week menstrual cycle, with progesterone levels that are compatible with a luteal phase. This strongly suggests that she ovulated during her menstrual cycles. Subjective improvement was reported in terms of increased feeling of well being and femininity. Her physical activity and capacity were unaltered, subjectively. Body composition and bone mineral density were assessed by dual-energy x-ray absorptiometry using a Lunar DPX-L densitometer (Lunar Corp., Madison, WI) before and after surgery (Table 2). The results show that loss of fat completely accounted for her weight loss. Lean body mass and bone mineral density did not change.

Discussion

Here, we report the excellent clinical effect of bilateral laparoscopic adrenalectomy in an adult female with classical CAH. The patient, like many of her fellow patients, had experienced virilizing and masculinizing effects from birth to adulthood, despite intensive follow-up and variable doses of medical treatment. Recently, laparoscopic adrenalectomy

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was introduced as a new modality for surgical treatment. The availability of ample local expertise with this procedure for different indications (24) helped us with the decision to offer our patient bilateral adrenalectomy as the alternative for the medical treatment of the sequelae of her CAH. This procedure would completely deprive her of all adrenal steroid hormone precursors and their (masculinizing) effects. Earlier studies have shown that the hyperplastic adrenal is not helpful in times of stress. It has been demonstrated that adrenal steroid precursors promote salt wasting under stress conditions in both patients and healthy volunteers (28). On the other hand, clinically beneficial effects of steroid precursors have recently been reported for dehydroepiandrosterone (DHEA): suppletion of DHEA restored libido in DHEA-deficient women (29, 30). These findings necessitate careful follow-up of adrenalectomized women to determine whether suppletion to physiological dosages of steroid precursors is indicated to further improve their quality of life. Follow-up is also required because failure of surgical therapy with recurrence of virilization several years later has been reported (20). Virilization in those patients was driven by either ovarian steroidogenesis or hormone production in ectopic adrenal tissue (20, 21). To date, the frequency and clinical importance of these failures in adrenalectomized patients have not been determined. Procedure-related complications are impressively low in experienced hands (23, 24).

In our patient, a good short-term result was obtained. All preoperative goals were met, without any complications either related to the procedure or to the hormonal replacement therapy afterward. This is in line with the data reported on patients with classic adrenal hyperplasia who were treated by adrenalectomy by different techniques or earlier in their lives (9, 18–21). The introduction of laparoscopic techniques may give an impulse to the application of surgical therapy at a larger scale in cases that are difficult to treat with adrenal suppression therapy.

References