ADRENALECTOMY FOR CAH
Summary Research by
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Over 50 years ago Dr. Lawson Wilkins demonstrated that the administration of glucocorticoids (such as cortisol or cortisone) to patients with congenital adrenal hyperplasia (CAH) could suppress ACTH (the pituitary hormone that stimulates the adrenal cortex to overproduce virilizing hormones). Prior to then, most patients with the severe salt wasting form of CAH died at an early age, and females with the less severe forms of the disease became masculinized with deep voices, acne and amenorrhea. Since then, substitution therapy with adrenal steroids has saved the lives of countless patients and spared most of them from progressive virilization. Physicians with long experience in treating these patients, however, are often frustrated by difficulties in maintaining satisfactory adrenal suppression with physiologic dosages of adrenal steroids. When these patients are then given sufficiently high dosages to halt their progressive virilization, they display the many features of hypercortisolism including progressive obesity, growth arrest, and many other features that lead to poor self-image. Affected females have pregnancy rates that are far below normal, partly because of the psychological and anatomic problems that make heterosexual attachments difficult, and partly because their elevated progesterone levels act as contraceptives. It is often not clear how many of these problems are due to poor compliance with prescribed therapy and how many are due to our limited ability to control ACTH secretion through the feedback mechanism.

In 1996 we suggested that certain patients with CAH would profit from bilateral adrenalectomy, because children with Addison's disease (a condition in which the adrenal glands are destroyed by disease) present many fewer problems in management than do many patients with CAH. Since then, we have carried out adrenalectomy in 3 young children who were proved by genetic analysis to have no possibility of making beneficial amounts of adrenal steroids. These were part of a study to compare prophylactic adrenalectomy with conventional treatment in such severely affected children. In addition, we have identified 15 other patients with CAH who, during the past 7 years, were subjected to bilateral adrenalectomy. Thirteen of these patients have been reported as case reports in the literature. The average duration of follow-up of these 18 patients was 59 months, representing an aggregate of 90 post-operative years. This study, which was reported in the July 2003 issue of the Journal of Clinical Endocrinology and Metabolism, is the first long-term follow-up of patients with CAH treated by bilateral adrenalectomy.

Nine of the 18 patients were 8 years of age or younger at the time of surgery, and the others ranged from 14 yrs. to 44 yrs. Sixteen had 21-O hydroxylase deficiency, one of whom was late onset, and the other two had 11ß-O hydroxylase deficiency. Our 3 young patients were adrenalectomized prophylactically as part of an approved research protocol. The others were adrenalectomized because attempts to keep their adrenals suppressed had proven ineffective, and they were showing signs of androgen excess as well as obesity and other signs of hypercortisolism.

Safety of the Operative Procedure:
Thirteen of the patients were adrenalectomized by laparoscopic surgery and five had traditional flank incisions. No notable operative complications were encountered. The
patients operated on by laparoscopy had low post-operative morbidity and were discharged from the hospital within 1-4 days.

Responses to Adrenal Crises and Other Illnesses:

Our major emphasis in this review was to identify any immediate or long term adverse effects resulting from adrenalectomy. There were no deaths. Five patients had one or more incidents of crisis or other serious illness at some time following surgery, but all responded well to proper therapy.

One of the teenagers had an episode of "adrenal crisis" from laxness in taking medication. She responded well to regular medications.

A 30 yr old woman with Late Onset CAH (nonclassical, in the first 3 postoperative months lost 13 kgs. secondary to lowering of her cortisol dosage. She then had an adrenal crisis associated with a urinary track infection. She had no further problems after adjustment of her replacement medications.

One of the patients survived 2 crises postoperatively. She was poorly compliant and a known drug abuser who had suffered repeated crises before her adrenals were removed. Adrenalectomy had been performed because an adrenal tumor had been suspected.

Two of our younger patients had serious illnesses postoperatively. An 8 year old girl, who had been well controlled preoperatively on a hydrocortisone dose of 20 mg/M2 (20 milligrams per square meter of body surface) had been reduced to 8 mg/M2 postoperatively. Three months after adrenalectomy she developed acute gastroenteritis, missed her evening meal, and probably vomited her evening dose of hydrocortisone. The following morning she was found comatose in bed with severe hypoglycemia. No further episodes of hypoglycemia have occurred after her daily dose of hydrocortisone was increased from 8 mg/M2 to 12 mg/M2 and the need for increased doses during stress was reemphasized. She has been left, however, with epileptic seizures that are controlled by appropriate medication.

The youngest patient of this series, who was adrenalectomized at 16 months, also had a short episode of hypoglycemia with seizures during an illness in which she had been febrile for 4 days and had fed poorly. At that time her baseline dose of hydrocortisone was 8 mg/M2. While on the lower doses of HC she consistently had elevated levels of ACTH and 17OH-progesterone. Her ACTH and 17-OH-progesterone levels quickly fell when her HC dosages were increased to 11-13 mg/M2. She is now a healthy child leading a normal life 6 years after adrenalectomy.

The post-operative dosage of 8 mg/M2 in these patients (and in some of the others) was chosen because this has been reported to be the normal daily secretion rate of cortisol from normal adrenal glands. We have now learned that this dose is insufficient, possibly because of inherent inefficiencies in absorption from the intestine.

Activation of Ectopic Adrenal Tissue

Hyperpigmentation and elevated ACTH levels were observed in over half of the patients. This was often the result of attempts to reduce hydrocortisone (HC) dosages
to 10 mg/M2 or lower. When the dose of HC was increased to 11-13 mg/M2 the serum ACTH levels fell to normal and pigmentation disappeared. ACTH levels proved to be the most reliable indicator of substitution therapy, since ACTH levels rose to abnormally high levels when the dosage of hydrocortisone was too low.

One might anticipate that no adrenal steroids would remain after both adrenal glands were removed. We were surprised to find that significant elevations of steroid precursors remained postoperatively in 8 of the 18 patients. This incidence is probably an underestimate because postoperative steroid levels were not routinely measured in most patients. Presumably these circulating steroids arose from abnormally located adrenal tissue. Ultrasound studies have revealed ectopic adrenal tissue in 30% of testes in boys with CAH. Previous studies have documented adrenal tissue in the broad ligament of the uterus, along the spermatic cord, and in the celiac plexus. Although such adrenal remnants theoretically have the potential of eventually nullifying the beneficial effects of adrenalectomy, re-suppression of the adrenals in this series has not proven difficult, and recurrent virilism, if present, has been far less of a problem than it had been prior to surgery.

Benefits of Adrenalectomy

These patients and their parents were nearly unanimous in their enthusiasm for adrenalectomy. In virtually all patients, signs of androgen excess have greatly lessened, and although obesity has not miraculously disappeared, it has almost uniformly become less of a problem following reduction of the glucocorticoid dosage from the very high pre-operative levels. Many of the patients and their families commented on their relief from the need for frequent monitoring.

A 28 year old infertile woman with oligomenorrhea resumed menstruation and gave birth to a normal female child. Chabre reported excellent results in a man with 11βOH'ase deficiency who had developed severe hypertension. Adrenalectomy was carried out at the age of 44 because medical control of the severe hypertension had become increasingly difficult, and adrenal suppression could not be achieved without producing severe manifestations of hypercortisolism. Now, 4 years following adrenalectomy, his blood pressure is normal, and he faults his physician for not having removed his adrenals earlier.

The initial patient in this series was 3 years old at the time of her adrenalectomy. We have previously reported that prior to surgery, exogenous ACTH caused sodium loss in this patient, whereas ACTH caused sodium retention in her normal twin. This supported our thesis that in many patients with CAH the adrenals do more harm than good. Our patient has thrived in the 6 years since adrenalectomy. At the time of this report, she is a 9 year old 4th grader living a normal life. Mother responds quickly with stress doses of hydrocortisone in response to respiratory infections. She now returns to endocrine clinic only twice a year, more out of habit than necessity.

Discussion

Objections to adrenalectomy in CAH have been based primarily on surgical risk and deprivation of the protective actions of the adrenal. Although adrenalectomy by any procedure should not be taken lightly, the operative procedure carries no unacceptable risk if adequate provision has been made for exogenous steroids. With modern laparoscopic procedures the postoperative morbidity is very low, and in the hands of
skilled laparoscopic surgeons, the laparoscopic approach is clearly preferable to the open flank approach.

Following adrenalectomy we have found that glucocorticoid therapy can generally be maintained at replacement dosages that are lower than the suppressive dosages that were often required before adrenalectomy. Mineralocorticoid supplementation with mineralocorticoids such as fluodrocortisone is mandatory, but dosages rarely need adjustment, and can be easily monitored by infrequent renin measurements.

Bilateral adrenalectomy removes the adrenal medulla as well as the cortex. This deprives the patient of epinephrine and probably results in reduced ability to respond to stress. It has recently been shown by Merke et al, however, that patients with CAH on glucocorticoid substitution already have greatly reduced secretion of epinephrine. Thus they are no worse off in this respect than they were prior to surgery.

The present studies reinforce the necessity for preventing sustained high levels of ACTH. This is particularly important because many patients have adrenal remnants that are capable of responding to ACTH. In our patients ACTH suppression could usually be achieved with hydrocortisone dosages of 11-13 mg/M2. Most of the patients in this series were on much higher doses of glucocorticoid prior to surgery. It is difficult to overstate the importance of promptly instituting stress dosages of glucocorticoids at the onset of illnesses.

Summary

We believe that these long term studies document that bilateral adrenalectomy is a safe and efficacious method of managing patients with severe forms of congenital adrenal hyperplasia. It should be considered in patients who have repeatedly escaped from adrenal suppression and who are now suffering from progressive signs of both androgen and glucocorticoid excess. Adrenalectomized patients will require close medical supervision for life since they will remain at risk for serious consequences or death if not given adequate substitution therapy. Prophylactic adrenalectomy of young patients should be limited to academic centers with established research protocols. Most of the patients in this series report a better quality of life without adrenals than had been their experience prior to adrenalectomy.

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