Hyperadrenalism in Childhood and Adolescence

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Hyperadrenalism in childhood and adolescence has unique features that influence diagnosis and management. We reviewed our experience with 18 patients, ranging in age from 18 months to 18 years. Nine had bilateral adrenal hyperplasia, eight had adrenal neoplasms, and one had micronodular hyperplasia. Patients with congenital adrenal hyperplasia and hyperaldosteronism were excluded. Six patients with Cushing's disease diagnosed in earlier years were treated by total adrenalectomy and recently two patients underwent transsphenoidal removal of pituitary tumors. Bilateral adrenalectomy was carried out in one patient with micronodular hyperplasia and in a second because of elevated adrenocorticotrophic hormone (ACTH) levels from an undefined source. Eight patients had adrenal neoplasms, including five adenomas and three carcinomas. We found no reliable criteria to differentiate before surgery between adrenal adenomas and adrenal carcinomas. The most recognizable characteristic of malignancy was tumor size, specifically weight greater than 75 gms. Of the three patients with adrenal carcinoma, one expired 20 months after adrenalectomy and 8 months after receiving palliative partial hepatectomy for liver metastasis. Two patients are well with normal growth and development at 11 and 20 years following adrenalectomy. With the exception of one patient who died 6 years after surgery from a glioblastoma multiforme, all patients with adrenal adenomas are well. Eight patients underwent bilateral adrenalectomy for hypercortisolism. Five of the six who have reached their adult stature are significantly stunted. Four of six patients with Cushing's disease, treated by total adrenalectomy, have developed Nelson's syndrome at 2, 6, 10, and 12 years after surgery. Of the two patients undergoing transsphenoidal surgery, one had recurrent disease at 2 years and was treated by pituitary irradiation with recovery. The patients undergoing adrenalectomy for micronodular hyperplasia and ectopic ACTH are well at 2 and 4 years, respectively. Cushing's disease in children and adolescents is best treated by transsphenoidal removal of the pituitary adenoma. Adrenalectomy, once the most accepted approach, plays a secondary role and is indicated primarily in micronodular adrenal hyperplasia, in patients with ectopic ACTH production of an undefined source, and in recurrent Cushing's disease following prior pituitary irradiation. The high incidence of Nelson's syndrome in children treated by adrenalectomy mandates that patients at risk be monitored lifelong for the progression of a pituitary tumor. Irradiation should be considered in patients with recurrent Cushing's disease following transsphenoidal surgery and as an alternative to hypophysectomy in the prepubertal patient with Nelson's syndrome. Adrenalectomy remains the treatment of choice for adrenal tumors with the prognosis being excellent in neoplasms weighing less than 75 gms.

ADRENOCORTICAL HYPERFUNCTION in childhood and adolescence is an uncommon occurrence and has unique features that influence diagnosis and management. In children, hypercortisolism of pituitary origin (Cushing's disease) is manifest primarily by growth failure and other physical features of cortisol excess, whereas adrenal neoplasms may produce cushingoid features, growth acceleration, masculinization, feminization, or a combination of these features. Rarely is there an ectopic source of ACTH in this age group. While adrenalectomy plays a primary role in the treatment of adrenal neoplasms, the ability to remove pituitary microadenomas by the transsphenoidal approach has changed the indications for adrenalectomy in Cushing's disease. Children present a particular challenge in management because of the need to assure normal growth and development.

This study reviews our experience over the past 2 decades in the management of adrenocortical hyperfunction in children. It was designed to: (1) review the clinical and laboratory presentation of children with adrenal tumors or bilateral adrenal hyperplasia; (2) determine methods to aid in distinguishing adrenal from pituitary disease; (3) determine whether adrenal carcinomas could be differentiated from adrenal adenomas; (4) identify the incidence of Nelson's syndrome in patients who have undergone adrenalectomy; and (5) establish the indications for and results of adrenalectomy.

Presented at the Ninety-Fifth Annual Meeting of the Southern Surgical Association, December 5–7, 1983, The Homestead, Hot Springs, Virginia.

Supported in part by Training Grant AM07129-10, National Institutes of Health.

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Submitted for publication: February 16, 1984.

Materials, Methods, and Results

An examination of the records at the North Carolina Memorial Hospital revealed that in the last 20 years we have cared for 18 patients, ranging in age from 18 months to 18 years, with cortical hyperadrenalism exclusive of patients with congenital adrenal hyperplasia or hyperaldosteronism. Nine of these 18 children had bilateral adrenal hyperplasia (5 males, 4 females), eight had adrenal tumors (2 males, 6 females), and one girl had micronodular hyperplasia. The age distribution of these patients at the time of presentation is demonstrated in Figure 1. The patient with micronodular adrenal hyperplasia was 12 years old at the time of presentation.

Table 1 summarizes the clinical findings in our 17 patients with adrenal tumors or hyperplasia. One patient with micronodular hyperplasia is not included, although her clinical presentation was indistinguishable from that of patients with bilateral adrenal hyperplasia. In all patients with bilateral adrenal hyperplasia, linear growth deceleration antedated diagnosis by intervals up to 6 years. Conversely, linear growth acceleration was a prominent finding in five of six growing children with adrenal tumors. Normal growth was present in a 4-year-old girl with combined cortisol and androgen excess.

Patients with bilateral adrenal hyperplasia had classical signs and symptoms of Cushing's syndrome in contrast to those with adrenal tumors who presented primarily with inappropriate virilization and/or feminization. This distinction was not, however, complete. Although none of the patients with bilateral adrenal hyperplasia had inappropriate clitoral or penile enlargement, many showed mild hirsutism. Likewise, a few of the patients with adrenal tumors presented with mild to moderate cushingoid features.

Chemical and hematologic evaluation of our patients is summarized in Table 2. Data on one patient with micronodular hyperplasia and one patient with bilateral adrenal hyperplasia are not included. Data on the former patient (L.P.) will be presented (*vida infra*). The second patient (T.N.) may have a unique form of bilateral adrenal hyperplasia and will be reported elsewhere. Glucose intolerance was not observed in the patients included in Table 1, although T.N. developed both severe diabetes and metabolic alkalosis with associated renal stones.

The studies chosen to determine the presence of cortisol excess reflect the "state of the art" methodology at the time the patient was studied and included A.M., P.M., and midnight blood cortisol levels, 24-hour urine collections for 17-hydroxycorticosteroids or free cortisol and the dexamethasone suppression test. Although all eight patients with bilateral adrenal hyperplasia had an abnormality in one or more of these tests, the number studied with each test is inadequate to compare their respective reliabilities. Two patients with bilateral adrenal hyperplasia did not suppress with low dose dexamethasone, although the dose was appropriate for their size.

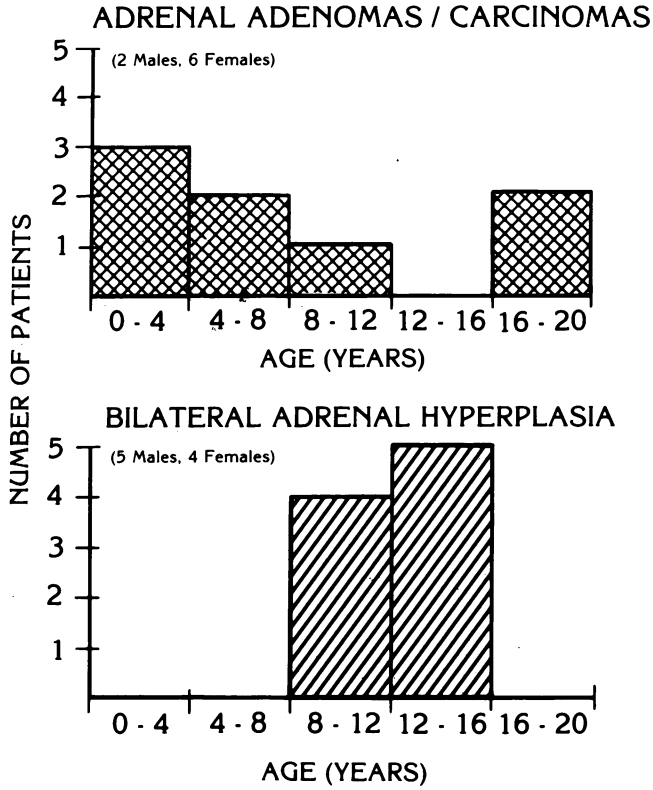

FIG. 1. Age distribution of patients with adrenal tumors and bilateral adrenal hyperplasia. Eight patients with Cushing's disease and one with ectopic ACTH of an undefined source are included in the latter group.

Evaluation of androgen excess primarily included urinary 17-ketosteroids and plasma testosterone levels. Four patients with bilateral adrenal hyperplasia had normal 17-ketosteroids and four had borderline levels. All eight patients with adrenal tumors had elevated urinary 17-ketosteroids. The elevation was markedly higher than those observed in our patients with bilateral adrenal hyperplasia.

Several additional tests were used to distinguish adrenal tumors from bilateral adrenal hyperplasia. Six of eight patients with adrenal tumors failed to show normal suppression of urinary 17-ketosteroids in response to high dose dexamethasone. Blood ACTH levels were elevated in two of three children with bilateral adrenal hyperplasia. A third patient had two normal determinations (55 and 105 pg/ml; normal < 130 pg/ml). Despite these normal values, this patient had a pituitary adenoma. Adrenocorticotrophic hormone stimulation tests were performed

TABLE 1. *Presenting Signs and Symptoms of Corticol Hyperadrenalism in Eight Children with Adrenal Tumors and Nine Children with Bilateral Adrenal Hyperplasia*

	Adrenal Tumors (8 Patients: 2 males, 6 females)				Bilateral Adrenal Hyperplasia (9 Patients: 5 males, 4 females)			
Sign/Symptom	Present No.	Not Present No.	Not Known if Present No.	Not Applicable No.	Present No.	Not Present No.	Not Known if Present No.	Not Applicable No.
Features of cortisol excess								
Linear growth deceleration	0	5	1	2	9	0	0	0
Hypertension	1	4	3	0	5	4	0	0
Truncal obesity	2	1	5	0	7	1	1	0
Moon facies	3	1	4	0	9	0	0	0
Plethora	1	1	6	0	7	1	1	0
Buffalo hump	0	2	6	0	7	2	0	0
Easy bruisability	0	3	5	0	5	2	2	0
Striae	0	3	5	0	7	1	1	0
Muscle weakness	0	3	5	0	4	1	4	0
Hyperpigmentation	0	0	8	0	5	0	4	0
Features of cortisol or androgen excess								
Emotional changes	4	1	3	0	2	4	3	0
Increased body hair	6	2	0	0	5	0	4	0
Acne	7	0	1	0	9	0	0	0
Menstrual changes	2	0	0	6	0	0	2	7
Features of androgen excess								
Linear growth acceleration	5	0	1	2	0	9	0	0
Inappropriately deep voice	3	1	4	0	0	0	9	0
Increased muscle mass	3	1	4	0	0	1	8	0
Inappropriate facial hair	4	1	3	0	3	1	5	0
Inappropriate sexual hair	6	0	0	2	2	5	2	0
Inappropriate clitoral or penile enlargement	4	1	3	0	0	6	3	0
Inappropriate feminization	1	5	0	2	0	9	0	0

on one patient with bilateral adrenal hyperplasia and three patients with adrenal tumors. As predicted, the patient with bilateral adrenal hyperplasia had an exaggerated response with significant elevation of urinary 17-hydroxycorticosteroids and the three patients with adrenal tumors had no significant change in 17-hydroxycorticosteroids excretion. There were no findings that differentiated before surgery between adrenal adenomas and carcinomas.

The radiologic findings in eight patients with adrenal tumors reflect the evolution of radiologic diagnosis during the two decades of this study. Plain films of the abdomen demonstrated a 19-cm carcinoma in one patient and a 4.5-cm adenoma in an 18-month-old boy. Intravenous pyelography was the most common roentgenogram examination and revealed an adrenal mass in all seven patients undergoing this examination. In two patients an arteriogram was performed, revealing a suprarenal mass without major vessel abnormality in one and a "tremendous partially cystic mass" in another. A hepatic arteriogram identified a "solitary" liver metastasis in the latter patient 9 months following adrenalectomy. In the one patient studied since the availability of ultrasound and computerized tomography, a 2-cm adrenal tumor (8 gm) was demonstrated by both techniques.[6] Computerized tomography demonstrated "nodules" in the patient with micronodular hyperplasia. However, this proved to be a false-positive interpretation since, although enlarged, the adrenals had no gross nodularity. Iodocholesterol scans and venograms were not used. Radiologic findings in patients with Cushing's disease demonstrated osteopenia in six of eight patients. Skull x-rays were normal in five of seven patients studied. One patient had sellar demineralization and one (P.S.) had sellar enlargement. Computerized topographic (CT) scans were positive in both patients studied (C.S. and P.S.; Fig. 3).

Seven patients with bilateral adrenal hyperplasia and one with bilateral micronodular hyperplasia underwent total adrenalectomy. Two patients with adrenal hyperplasia underwent transsphenoidal resection of a pituitary tumor. Unilateral adrenalectomy was performed in the eight patients with neoplasms. All adrenal tumors were approached anteriorly through a subcostal incision with a wide excision of the adrenal, surrounding fat, and areolar tissue. There was no extension to lymph nodes, kidney,

TABLE 2. *Chemical and Hematological Findings in Eight Children with Adrenal Tumors and Eight Children with Bilateral Adrenal Hyperplasia*

	Adrenal Tumors (8)				Bilateral Adrenal Hyperplasia (8)			
	Positive or Abnormal	Negative or Normal	Borderline Result	Not Determined or Not Applicable	Positive or Abnormal	Negative or Normal	Borderline Result	Not Determined or Not Applicable
Hematologic abnormalities								
Erythrocytosis	2	4	1	1	1	4	2	1
Eosinopenia	2	2	0	4	3	4	0	1
Electrolyte or glucose abnormalities								
Hypokalemia	0	7	0	1	0	8	0	0
Hypochloremia	0	7	0	1	0	7	0	1
Elevated fasting blood sugar	0	6	0	2	0	6	0	2
Glucosuria	0	6	0	2	0	7	0	1
Bone age determination								
Accelerated	3	1*	0	4				
Delayed					1	7	0	0
Evaluation of cortison excess								
Blood cortisol level								
A.M.	0	1	0	7	0	4	0	4
P.M.	2	0	0	6	3	0	1	4
Midnight	0	0	0	8	1	0	0	7
Lack of diurnal variation	1	0	0	7	2	2	0	4
24-hour urinary free cortisol	1	0	0	7	1	0	0	7
24-hour urinary 17-hydroxycorticosteroids	3	5	0	0	7	0	1	0
Dexamethasone suppression test								
Low dose	3	0	0	5	6	2	0	0
High dose	3	0	0	5	0	6	0	2
Evaluation of androgen or estrogen excess								
24-hour urinary 17-ketosteroids	8	0	0	0	0	4	4	0
Blood testosterone	6	0	0	2	4	1	0	3
Dihydroepiandosterone-sulfate (DHEAS)	0	1	0	7	0	0	0	8
24-hour urinary pregnanetriol	1	1	0	6	0	0	0	8
Estradiol	1	0	0	7	0	0	0	8
Miscellaneous differentiating tests								
ACTH Level	0	0	0	8	2	1	0	5
ACTH stimulation test	3†	1	0	4	1§	0	0	7
24-hour urinary 17-ketosteroid response to high dose dexamethasone suppression	6‡	0	0	2	2	4	1	1

* Bone age was not accelerated in the child with combined cortisol and androgen excess.

† Urinary 17 hydroxycorticosteroids did not increase significantly in response to ACTH in these three patients; one would expect this result in patients with an autonomous adrenal tumor.

‡ Urinary 17-ketosteroids did not decrease in response to high dose dexamethasone.

§ Hyperresponse as one would expect with bilateral adrenal hyperplasia. Normative data based on References 1, 2, 3, 4, and 5.

liver, or vena cava in any patient. Bilateral adrenalectomy was accomplished *via* bilateral posterior lumbar incisions in seven patients and *via* a midline incision in one.

With the exception of three carcinomas (weighing 1600, 440, and 130 gms), tumors were of modest size, for example, 8, 12, 25, 52, and 60 gms. Histopathologic findings in six of the tumors were similar. Large pleomorphic and multinucleated cells were frequently found. Many of these cells had bizarre nuclei with eosinophilic cytoplasmic intranuclear invaginations. All of the neoplasms showed sinusoidal vascular invasion and two (one adenoma and one carcinoma) showed tumor thrombi in a vein. The eighth and largest tumor (1600 gms) differed significantly from the others only in that frequent and atypical mitotic figures were found and distinctly spindled tumor cells were present. This lesion subsequently recurred and invaded the liver. None of the other lesions, even those classified as carcinoma on the basis of weight, had more than a rare mitotic figure.

In the absence of identifiable invasive or metastatic disease at the time of diagnosis, tumor mass appears to be the best criterion of malignancy and, in accord with

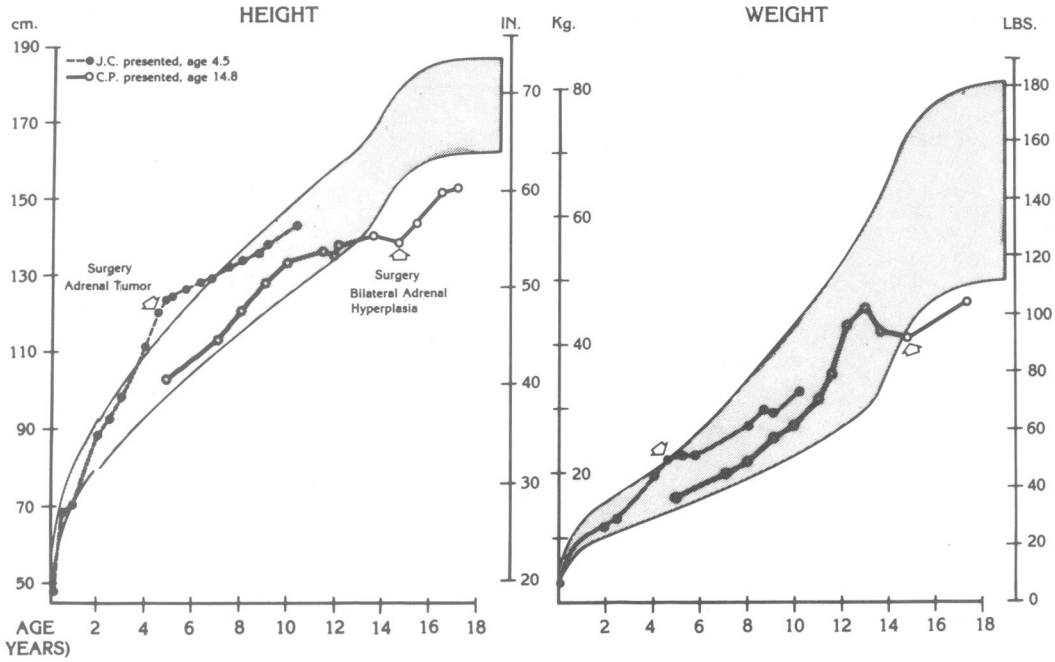

FIG. 2. Aberrations in growth of a boy with a virilizing/feminizing adrenal adenoma (Case Report 1) and a boy with Cushing's disease (Case Report 2). Note return of height velocity to normal following correction of abnormal adrenal hormone production.

published criteria, encapsulated lesions weighing over 75 gms were classified as carcinoma on the basis of weight alone.[7,8] In our study, intravenous thrombi, multiple nucleated giant cells, and large bizarre nuclei were not indications of malignancy in the absence of abnormal mitoses. The one clearly malignant lesion in our series was the only lesion that had abnormal and excessive mitoses and contained large numbers of bizarre spindled tumor cells. The pituitary lesions removed in two patients undergoing transsphenoidal surgery had histologic features of "basophilic adenoma."

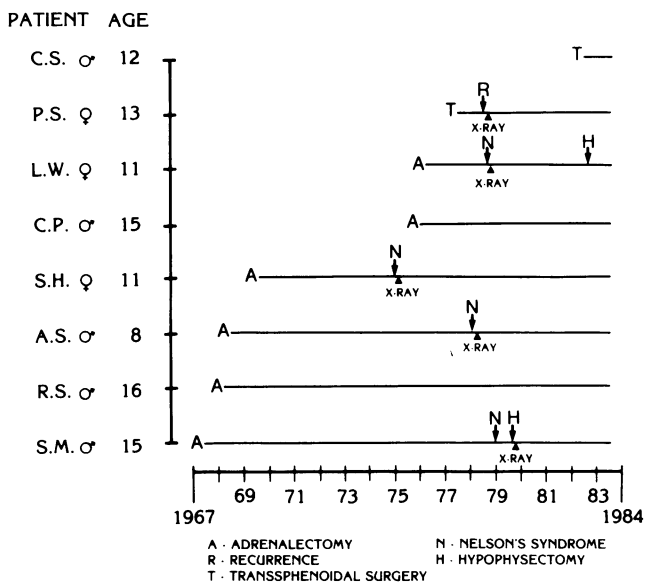

FIG. 3. Survivorship in patients with Cushing's disease is portrayed. Note that four of six patients developed Nelson's syndrome. X-ray therapy (4500–5000 R) using a cobalt source was utilized in the management of Nelson's syndrome and the one patient who had recurrence of Cushing's disease after transsphenoidal surgery.

The results of treatment of eight patients with adrenal tumors are depicted in Figure 4. Of the three patients with carcinoma, one expired of advanced disease 20 months after adrenalectomy and 8 months after partial hepatectomy for liver metastasis. The administration of O,p'DDD was poorly tolerated in this patient. Two patients are well with normal growth and development 11 and 20 years following adrenalectomy. The relatively good survivorship in these two patients with adrenal carcinoma may be related to the small size of their tumors (130 and 440 gms). With the exception of one patient who died 6 years after surgery from a glioblastoma multiforme, all patients with adrenal adenomas are well at 1, 9, 9, 10, and 11 years following operation. The association between brain tumors and adrenal tumors has been observed by others.[9]

The course of eight patients with Cushing's disease is presented in Figure 3. Of the seven patients who have reached their final adult stature, all but one have significant short stature (< third percentile). Two patients are otherwise well on replacement therapy at 15 and 16 years after bilateral adrenalectomy and one patient is well 1½ years after transsphenoidal surgery. Three patients de-

veloped Nelson's syndrome (cutaneous hyperpigmentation associated with a pituitary tumor) at 2, 6, and 12 years postadrenalectomy. The first patient (L.W.) was treated by 4800 R of external irradiation but required total hypophysectomy 5 years later. S.H. underwent irradiation therapy and remains well 9 years later. S.M. required total hypophysectomy followed by irradiation (4500 R) 12 years after adrenalectomy. His tumor had extended into the sphenoid sinus. A.S. was treated by 4800 R of external irradiation and remains well 6 years later. P.S., treated initially by transsphenoidal surgery, developed decreased visual acuity and a blind spot immediately after operation. One year later she received irradiation (4800 R) for recurrent Cushing's disease. Although her Cushing's disease has resolved, she has growth hormone deficiency and borderline gonadotrophic function.

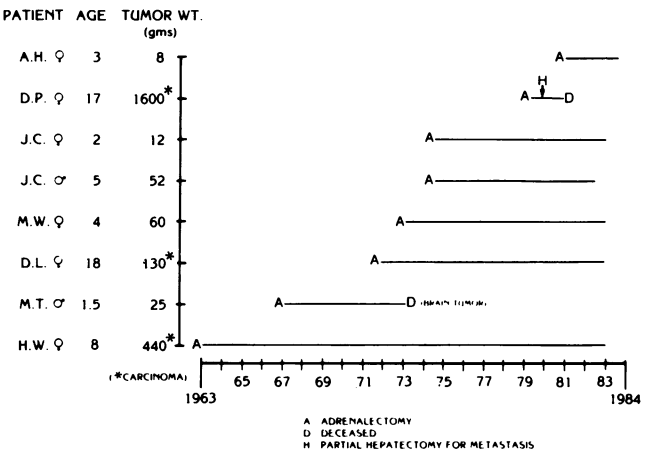

FIG. 4. Survivorship in eight patients with adrenal tumors revealed only one death from adrenal carcinoma. This patient was also treated with mitotane (O,p'DDD) which was poorly tolerated.

Case Reports

Case 1. J.C. presented at age 4.6 years with a 1-year history of breast enlargement, a 6-month history of acne and body odor, and a 3-month history of pubic hair development and penile enlargement. Physical examination revealed a virilized young boy with a deep voice. His height and weight were greater than the 97th percentile for age (Fig. 2). He was normotensive. There was bilateral glandular breast tissue, measuring 2.5 cm in diameter on the left and 2.2 cm in diameter on the right. There was sparse axillary hair and Tanner Stage 2 pubic hair. The scrotum was rugated and the testes measured 2.3 × 1.1 cm on the right and 2.1 × 1.1 cm on the left. Stretched penile length was 6 × 2.3 cm. There were no cushingoid features and the remainder of the examination was normal. Review of growth records revealed accelerated linear growth (Fig. 2). Bone age was 8 years and skull x-ray demonstrated a normal sella. Abdominal x-ray revealed no calcifications.

True precocious puberty was initially considered the most likely diagnosis since the testes were at the upper limits of normal prepubertal size, suggesting they were under gonadotrophic stimulation. Further evaluation, however, was not consistent with this impression. Electrolytes and the hemogram were normal. Baseline 24-hour urinary 17-hydroxycorticosteroids were 2.6 mg/m^2 (normal). Follicle-stimulating hormone (FSH) was 2.0 mlu/ml (prepubertal). Twenty-four hour urinary 17-ketosteroid excretion was 7.7 mg (normal ≤2 mg). Plasma testosterone was 145 ng/dl (normal: 4.1–8.1 ng/dl). Twenty-four hour urinary pregnanetriol was elevated at 7 mg (normal: 1 mg). Serum estrogen was 40.2 ng/dl (normal: 0). Seventeen-ketosteroid excretion did not decrease in response to high dose dexamethasone suppression. Adrenocorticotrophic hormone stimulation did not result in a significant rise in either urinary 17-ketosteroids or 17-hydroxycorticosteroids. An intravenous pyelogram revealed a 3 × 3 cm left suprarenal mass. Left adrenalectomy with excision of periadrenal fat was performed using a left subcostal approach. Pathological examination demonstrated a 52-gm encapsulated tumor with a small portion of normal adrenal at one margin. Microscopical evaluation showed sheets and trabeculae of cells with large, clear, finely vesiculated nuclei, many with one or more nucleoli. In some areas, tumor cells involved the inner layer of fibrous capsule but did not extend to outer layers. In other areas, tumor cells appeared to invade the walls of small veins and were also encountered in the lumen of vascular channels.

The immediate postoperative course was uncomplicated except for transient signs of hypocortisolism. This patient was most recently evaluated at age 11.9 years. He is on no medication except insulin for diabetes mellitus. Urinary 17-ketosteroids, androstenedione, testosterone, and estradiol were normal. Growth is at a normal velocity along the 75th percentile.

Comment

The clinical presentation and endocrinological findings in this patient are representative of a virilizing/feminizing tumor of the adrenal cortex. The microscopic findings were characteristic and, although tumor cells were present in veins, such a finding was also noted in other patients with adrenal adenomas. The tumor in this patient was regarded as an adenoma on the basis of weight.

Case 2. C.P. was referred at 14.8 years of age for evaluation of short stature. Growth data demonstrated deceleration of linear growth velocity beginning approximately 4 years prior and essentially no growth for 3½ years (Fig. 4). Height was well below the third percentile and weight was at the tenth percentile for age. He was normotensive. Findings included a suggestion of a moon facies, acne, a small "buffalo hump," moderate nontruncal obesity, a low hairline, striae, fine lanugo hair on the extremities, and thin skin over the knuckles. Hyperpigmentation was not present. There was Tanner Stage 3 pubic hair development. The electrolytes and hemogram were normal except for eosinopenia. The bone age was delayed by 2 years. Morning cortisol level was normal at 17 ug/dl, with an evening cortisol elevated at 26 ug/dl. Twenty-four urinary 17-hydroxycorticosteroids were elevated at 7.9 mg (6 mg/m^2/d; normal: 0.9–4.9 ng/m^2/dl). Cortisol levels suppressed only with high dose dexamethasone. Urinary 17-ketosteroids and plasma testosterone levels were normal. Radiologic examination revealed osteoporosis with compression fractures of T4-8. The skull x-ray was normal as was a nephrotomogram. Bilateral adrenalectomy was carried out with the right adrenal weighing 4.5 gms and the left 4 gms. Microscopic evaluation was consistent with bilateral adrenal hyperplasia. Although stunted (final adult height 5 feet), C.P. had done well on replacement therapy up

through the time of his last visit at age 21. However, he has subsequently developed headaches associated with vomiting and he is currently undergoing evaluation for Nelson's syndrome.

Comment

This patient illustrates a case of childhood Cushing's disease with associated growth failure and ultimate stunting. He demonstrates the need to monitor these patients indefinitely for the development of Nelson's syndrome.

Case 3. L.P., a 12-year-old female, was seen because of a 3–4 year history of cushingoid features including a decrease from the 25th to the third percentile in height. The patient had previously undergone repair of a patent ductus arteriosus and ventriculoseptal defect at age 4, placement of a ventriculoperitoneal shunt for obstructive hydrocephalus at age 6, and evacuation of a left chronic subdural hematoma at age 11. A maternal aunt had Cushing's syndrome secondary to an adrenal adenoma. Another maternal aunt had a parathyroid adenoma.

Physical examination revealed a pleasant cushingoid white girl. Height was less than the third percentile and weight was the 25th percentile for age. Blood pressure was 132/86. There was mild acne and striae but no bruising or hyperpigmentation. Breasts were Tanner Stage 2 and pubic development was Tanner Stage 4. The remainder of the examination was noncontributory.

Laboratory studies indicated a normal hemogram, urinalysis, and an SMA-6. Glucose was 83 mg/dl. There was loss of diurnal cortisol variation (8 A.M.—36.3 ug/dl; 4 P.M.—29.9 ug/dl). On venous catheterization the cortisol level from the left adrenal vein was 253 ug/dl, from the right adrenal vein 165–218 ug/dl, and from a peripheral vein 23.5 ug/dl. There was no suppression of urinary free cortisol, 17-OHCS or 17-KS, with low (20 ug/kg/day) or high (80 ug/kg/day) dose dexamethasone. The ACTH level was 30 pg/ml (normal: ≤130 pg/ml). A CT scan of the abdomen revealed two 1-cm nodules in the right adrenal and a 1-cm nodule in the left adrenal.

With the clinical impression of hypercortisolism secondary to bilateral nodular adrenal hyperplasia, the patient underwent bilateral adrenalectomy through flank incisions. Although there was no gross nodularity, both glands had micronodular changes. A grossly normal segment of the right gland was diced into 25 2 × 1 mm pieces that were implanted in the left volar forearm musculature. Pathological examination disclosed bilateral multiple nonencapsulated cortical nodules containing lipid-laden cells in compact arrangement. Many cells contained lipofuchsin. There was significant nuclear enlargement in a few cells within each nodule. There were no architectural changes to suggest malignancy.

The patient's postoperative course was unremarkable. She is currently maintained on cortisone acetate and fludrocortisone. During the 15 months since adrenalectomy, she has had a gradual change in overall body habitus to that of a normally proportioned adolescent girl. She is normotensive. Menses have started, linear growth has resumed, and she has a height prediction of 4 ft, 11 in–5 ft.

Comment

This patient's endocrinological and pathological findings are characteristic of micronodular adrenal hyperplasia. Micronodular adrenal hyperplasia appears to be a variant of nodular adrenal hyperplasia, which is a heterogeneous group of disorders varying from one or more nodules to diffuse nodular hyperplasia.[10–14] The pathogenesis of these disorders is unknown. In a few patients there appears to be pituitary dependence, although most demonstrate impaired suppression to dexamethasone.[11–13] Adrenocorticotrophic hormone levels are usually suppressed but may be elevated.[11] Although adrenalectomy has been the most common therapeutic approach, pituitary tumors have been observed with the development of Nelson's syndrome after surgery. Remission has been reported following pituitary surgery or radiation therapy.[11]

Discussion

Adrenocortical hyperfunction due to adrenal tumors and bilateral adrenal hyperplasia of pituitary or hypothalamic origin are rare conditions at any age. When these conditions present in children and adolescents, there are certain unique features that must be considered in terms of clinical presentation, evaluation, treatment, and outcome.

The clinical features and laboratory findings demonstrated by our patients are similar to those described by others.[15–23] Although female preponderance has been noted among adults with Cushing's disease,[10] no sexual predilection was observed in our children with Cushing's disease and none has been noted in the literature.[19,21,24–26] In contrast, there is a female preponderance among children with adrenal tumors.[20,23,26,27] This is illustrated by our series in which six of eight children with adrenal tumors were female. The literature indicates that children under age eight with Cushing's syndrome are more likely to have an adrenal tumor while those over this age are more likely to have Cushing's disease.[21] This generalization is consistent with our data in which the youngest of eight patients with Cushing's disease was 9.6 years at the time of presentation. Although the age of the child presenting with cortisol excess is useful in differentiation, about 15–25% of children with Cushing's disease present before 8 years of age[28] and Cushing's disease has even been demonstrated in infancy.[16]

Our patients presented with signs and symptoms that were typical and appropriate for their underlying disease. Nine patients with bilateral adrenal hyperplasia and one patient with micronodular hyperplasia had findings suggestive of significant cortisol excess and mild androgen excess. Six of our eight patients with adrenal tumors presented with virilization with or without mild signs of cortisol excess; one presented with mixed cortisol and androgen excess; and the last presented with virilization and feminization. An abnormality in linear growth was the single most constant sign of hyperadrenalism. Patients with androgen excess alone demonstrated linear growth acceleration, whereas patients with glucocorticoid excess

uniformly suffered growth arrest. Although androgen excess causes increased skeletal maturation regardless of glucocorticoid status, androgens cannot overcome the inhibitory effect of glucocorticoid excess on linear growth. Indeed, this inhibitory effect of glucocorticoid secretion on linear growth is so invariable that the finding of normal growth in an obese child excludes the possibility of underlying hyperadrenalism and eliminates the need for further evaluation.

Laboratory evaluation of our patients was consistent with findings reported by other workers.[16] When evaluating children for cortisol or androgen excess, age, weight, surface area, and pubertal status are needed for reliable testing and interpretation. For example, the dosage for dexamethasone suppression testing must be adjusted to each child's weight. In addition, patients with virilization should be evaluated for other virilizing syndromes. These include congenital adrenal hyperplasia, exogeneous androgen administration, maternal androgen excess (in the case of a newborn), true precocious puberty, premature adrenarche, male pseudohermaphrodism, chromosomal anomalies (XO/XY mosaicism), testicular or HCG producing tumors, ovarian tumors, and Stein-Leventhal syndrome. Patients who present with hypercortisolism should be questioned regarding exogeneous steroid use, including the application of topical steroid preparations. In practice, the major differential in males is central precocious puberty that is suggested by symmetrically enlarged testes secondary to gonadotrophin stimulation. In both sexes, congenital adrenal hyperplasia must be seriously considered and, in girls, Stein-Leventhal syndrome commonly presents with mild virilization. Severe forms of congenital adrenal hyperplasia present in infancy with ambiguous genitalia in genetic females or as an addisonian crisis in either sex. Mild forms are more difficult to diagnose, although the 17-hydroxyprogesterone response to ACTH may be useful. After considering these conditions, appropriate laboratory evaluation for an adrenal tumor and Cushing's disease can proceed. As indicated in our subjects, no single test was uniformly diagnostic of Cushing's disease or adrenal tumor. However, clinical presentation in combination with several appropriate laboratory and radiologic studies should lead to the appropriate diagnosis.

The histologic features that differentiate adrenal adenoma from carcinoma are ambiguous. Nuclear size, anaplasia, and number of mitoses are not considered to be as reliable as capsular or vascular invasion.[7,8] However, in this group of patients, sinusoidal invasion could be demonstrated in all tumors. Although mitoses were more prominent in the patients with carcinoma, their absence did not exclude this diagnosis. Although the most reliable criterion is the presence of metastatic disease, the literature supports the finding that a neoplasm greater than 75 gms is more likely malignant.[7,8] Hayles was first to emphasize the likelihood of metastasis being best correlated with the relation of tumor weight to body weight, for example, >0.7 gm/100 gm of body weight. In his review of 32 children,[19] the incidence of metastasis was 13% in patients with tumors below this weight compared with 50% incidence in tumors above this weight. Utilizing Hayles criteria, the tumors of five patients in this series would be considered malignant, namely, D.P., M.W., D.L., M.T., and H.W. All tumors regardless of size should initially be regarded as potentially malignant. Wide surgical excision is advised, although the value is not well established since recurrence is rarely local except in very large neoplasms. Recurrence is most likely to be manifest by metastatic disease in liver, lung, lymph nodes, and occasionally brain.[17,30] Tumor size appears to be a greater factor in influencing survivorship than the extent of surgical treatment.

The relatively excellent survivorship in these patients with adrenocortical neoplasms is unusual. Of eight patients, only one died of recurrent disease and this was a 17-year-old girl whose original tumor was 19 cm in diameter, weighed 1600 gms, and had numerous mitotic figures. Of the remaining seven patients, six are alive and well from 1 to 20 years after adrenalectomy (Fig. 2). One patient expired 6 years after adrenalectomy from a brain tumor (glioblastoma multiforme) without evidence of recurrent adrenal carcinoma. The neoplasms in the six surviving patients were all of modest size with weights varying from 8 to 440 gms.

Computerized tomography is the single most effective radiologic means of establishing the diagnosis of primary adrenal disease with an estimated accuracy of 90%.[27,31,32] Computerized tomography is also valuable in screening for lung metastasis and recurrence in the adrenal bed. Adrenal disease may also be evaluated *via* adrenal venous sampling (100% accuracy), venography (75%), and arteriography (58%).[31] These latter methods are associated with increased risk but may be required in selected circumstances. Ultrasound may be helpful and is useful for evidence of invasion of the inferior vena cava in malignant tumors. Characteristic findings in adrenocortical carcinoma are a tumor greater than 9 cm in diameter with varying degrees of necrosis.[32]

Current Management

Various modes of treatment have been used for Cushing's disease in children. These include bilateral adrenalectomy, pituitary irradiation, chemotherapy, and more recently transsphenoidal surgery. The greatest experience

in the management of children has been with bilateral adrenalectomy. While this has been effective, the disadvantages are well recognized. These include an operative mortality of 4–10% in adults,[10] occasional recurrence due to ectopic adrenal tissue,[10] the need for lifetime corticosteroid and mineralocorticoid replacement, potential for addisonian crisis and the development of Nelson's syndrome. Nelson's syndrome is comprised of hyperpigmentation and a pituitary tumor following adrenalectomy.[33,34] The hyperpigmentation is presumably secondary to a postoperative rise in ACTH secretion. Development of Nelson's syndrome is associated with enlargement of a corticotroph adenoma that can become invasive, extend beyond the pituitary fossa, and lead to cranial nerve impairment.[35] The incidence of this syndrome in children in two of the larger series is over 50%[24,28] which is higher than that reported for adults (10–20%).[10,36] After adrenalectomy, children usually have normal growth and sexual development unless growth has been severely compromised by long-standing disease prior to surgery. In addition to hyperpigmentation, patients should be monitored for the development of visual field defects and/or an enlarging sella turcica. If Nelson's syndrome develops and is treated with irradiation or extensive pituitary surgery, panhypopituitarism with associated growth failure, hypogonadism, and diabetes insipidus may develop.[28]

Total adrenalectomy at present would appear to have its primary role in: (1) patients in whom there is an undefined ectopic source of ACTH; (2) patients in whom the disease originates in the adrenals, for example, most individuals with micronodular adrenal hyperplasia; and (3) patients with recurrent Cushing's disease after prior pituitary irradiation. Two patients in the current series fell in this category, one with micronodular adrenocortical hyperplasia and one in whom the highest ACTH level was in the region of the hepatic veins and in whom the ACTH level fell after adrenalectomy. Recent studies have demonstrated that the adrenal medulla can produce ACTH.[37,38] This patient may have had her disease on the basis of an adrenal source of ACTH. Adrenalectomy is appropriate in recurrent disease following prior pituitary irradiation since these patients are less likely to develop Nelson's syndrome and the technical problems associated with a transsphenoidal approach may be formidable.

Our data clearly show that while adrenalectomy is indicated for adrenal neoplasms, transsphenoidal hypophysectomy is the current treatment of choice for Cushing's disease. The high incidence of Nelson's syndrome following bilateral adrenalectomy in this condition makes it clear that total adrenalectomy should be abandoned until such time as further research leads to medical means of preventing this development. Successful excision of the pituitary adenoma should leave pituitary hormone production intact and permit normal growth and development without the need for replacement therapy. There are, however, limitations of pituitary surgery. Recurrent disease appears to be more of a problem than in adults undergoing a similar operation. In a recent report, recurrence was reported in four of 13 patients below the age of 20 within a 2-year follow-up.[39] A high incidence of recurrence has also been noted by others.[40] One of the patients in this series treated by transsphenoidal surgery had recurrence at 2 years. The reason for this higher recurrence rate is unknown. This could be due to a more aggressive nature of childhood tumors, multiple adenomas, or to a higher proportion of primary hypothalamic lesions in children. In addition, there is an appropriate effort to preserve a functioning pituitary gland and to avoid total hypophysectomy in this age group. This may result in a more conservative surgical approach. The minute size (mean 5 mm) of some pituitary microadenomas may result in difficulty in their identification at the time of transsphenoidal surgery. Bilateral petrosal sinus sampling for ACTH in patients with occult adenomas—not localized by computerized tomography—may permit hemiresection of the pituitary if the lesion is too small to be recognized at surgery.[41]

Pituitary irradiation has been advocated primarily by Jennings[25] as the preferred treatment in children with a report of 15 patients treated over a 20-year period terminating in 1977. Failure occurred in three who subsequently required adrenalectomy. Sexual development was reported to be normal in all, growth was stated to be "normal" for all adolescent children, and neither Nelson's syndrome nor recurrent disease has developed. In eight patients treated before age 16, stature was short but considered socially acceptable (5 ft, 1.6 in–5ft, 5 in). A major limitation of irradiation is the time lag between the initiation of therapy and resolution of hypercortisolism (6–18 months). It is of extreme importance during childhood to terminate the disease immediately because of the adverse effects of even mild cortisol excess on growth. Unlike some forms of growth failure, "catch-up growth" does not occur after correction of cortisol excess. As a consequence, we favor a form of treatment that produces more immediate results. However, in instances where transsphenoidal hypophysectomy fails to lead to a definitive cure, the treatment of choice at the present time is probably conventional irradiation as advocated by Liddle and the Vanderbilt group.[25]

Experience with drug therapy in children has been limited and in general unsatisfactory.[15] Drugs that inhibit steroidogenesis (mitotane [O,p'DDD], aminoglutethimide, metyrapone, and trilostane) are not uniformly effective

or practical for long-term management.[15] Drugs acting on neurotransmitters believed to regulate corticotropin releasing factor, for example, cyproheptadine and bromocryptine, have been used in a small number of children to suppress ACTH secretion.[15] Major limitations to cyproheptadine therapy include severe appetite stimulation with excessive weight gain and delayed therapeutic effect.[42]

In the future, measurement of corticotropin releasing factor may help define the role of the hypothalamus in the etiology of Cushing's disease. The intravenous administration of corticotropin releasing factor with measurements of ACTH secretion has been shown to facilitate differentiation of ACTH dependent Cushing's disease (hyperresponsiveness) from ectopic ACTH production (no further increase) and hypercortisolism of adrenal origin (ACTH remains suppressed).[43]

There is little or no controversy about the management of adrenal tumor producing Cushing's syndrome. Excision of the adrenal tumor in association with periadrenal fat and lymph nodes is well accepted as treatment of choice. An anterior approach is usually advised becasuse it provides wide exposure in the case of a malignant neoplasm. The prognosis in adrenal tumors is related primarily to tumor size. There is excellent survivorship in patients whose tumor is below 75 gms in weight. Studies on ACTH and other hormone receptor sites (PGE_1, L.H., glucagon, epinephrine, and TSH) in adrenal tumors demonstrate a heterogeneity of responses.[44,45] Additional data may help differentiate benign from malignant tumors. Malignancy may be difficult to define by histologic criteria and metastatic disease is the ultimate criterion of adrenal carcinoma which has a dismal prognosis. It is doubtful that the benefits associated with resection of distant metastases, for example, liver, warrant such an approach except as a palliative measure. The poor results of excision of adenocarinoma reported in earlier years are related to the large size of the tumor at operation and inadequate replacement therapy. The sensitivity of ultrasound and CT in evaluating patients with suspected adrenal neoplasms should permit earlier diagnosis and improved results.

Acknowledgment

The authors recognize and appreciate the advice and criticism of J. J. VanWyk, MD.

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Discussion

DR. JOHN C. FLETCHER (Tampa, Florida): I would like to ask Dr. Thomas about the role of transplantation where bilateral adrenalectomy is indicated.

DR. COLIN G. THOMAS, JR. (Closing discussion): That is a good question. I think Dr. Hardy and his group have had the greatest experience in adrenal transplantation, with some degree of success.

We have had one patient in whom we have undertaken adrenal transplantation, a patient with micronodular hyperplasia in whom we transplanted some of the adrenal to the forearm. That was about 3 years ago and we do not have enough data yet to know whether the transplant is functioning or not. Adrenal transplantation may have a role, but the exact role is undetermined.

I do have one slide that I thought might be of interest to you. In a rather extensive search of the early literature, we identified a patient who appeared to have a virilizing tumor. This patient is gargantua and, as recorded by the physician, Rabelais, 1534, had a rather unique birth and early message:

> The cotyledons of her matrix were all loosened, above through which the child sprung up and leaped, and so entering into the vena cava, did climb by the diaphragm even above her shoulders (where that vein divides itself into two) and from thence taking his way toward the left side, issued forth at her left ear. As soon as he was born, he cried, not as other babes used to do, but with a high, sturdy, and big voice shouted aloud: "DRINK! DRINK! DRINK!" as if inviting all the world to drink with him. The noise hereof was so extremely great that it was heard in both the countries at once.

I think this a very appropriate quote for this Society.