Adrenocortical Tumors in Children

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Abstract

Adrenocortical tumors are very rare in children. The records of seven patients (four boys and three girls) who attended Srinagarind Hospital between January 1986 and September 2000 were retrospectively reviewed. Virilization and hypertension were found in four patients, two of whom had untreated congenital adrenal hyperplasia. Hypertension or virilization was the single manifestation found in two other patients. Only one patient showed clinical symptoms of Cushing's syndrome and another nonfunctioning tumor in Down's syndrome. Abdominal ultrasonography was helpful in locating the tumors. Unilateral tumors were found in all of the patients and surgical exploration was done in six of them. Pathological examination revealed four adrenocortical carcinomas, one adrenal gland hyperplasia and one lipoma. The two patients in which the cancer metastasized to the liver and lungs died 1 and 1 $^{1}/_{2}$ months after diagnosis, respectively. The authors concluded that virilization and hypertension remain the primary diagnostic symptoms of adrenocortical tumors in children. Early detection and adrenalectomies prolonged the survival time in these patients.

Key word : Adrenal Gland Tumor, Adrenocortical Carcinoma, Adrenocortical Tumor, Congenital Adrenal Hyperplasia, Virilization, Hypertension, Cushing's Syndrome

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Primary adrenocortical tumors are rare in children. The true incidence of the condition is unknown, but according to the Third National Cancer Survey completed between 1969 and 1971, the incidence of adrenal adeno- or cortical-carcinoma in children is approximately 0.02 to 0.03 cases per million people per year[1]. Functional tumors were detected and reported more frequently. Clinical manifestations of these functional tumors are virilization, hypertension and the clinical features of Cushing's syndrome. Early diagnosis and surgical resection prolonged survival time of the patients with malignant tumors. Late diagnosis and treatment allowed the tumor to metastasize to the lungs and liver.

The objective of this study was to describe the clinical and hormonal characteristics and methods of management of seven children with adrenocortical tumors who were admitted to Sringarind Hospital and to alert pediatricians of the importance of early diagnosis and treatment.

PATIENTS AND METHOD

Seven pediatric patients below 15 years of age with adrenocortical tumors, admitted between January 1986 and September 2000, were retrospectively reviewed. Data collected comprised: clinical history, findings of the physical examination, serum chemistry, plasma and urinary steroid levels, modes of treatment and outcomes.

Definition

Patients were considered to have functional tumors if they had abnormal hormone levels in the serum, urine or both. A patient was said to have Cushing's syndrome if he/she had clinical features of the syndrome, a high 24-hour, urinary excretion of 17-hydroxycorticosteroids (17-OHCS), and a high serum cortisol level unsuppressed by 20 μg of dexamethasone per kg per day for two days[2]. A girl was said to be virilized if she had a deep voice, male musculature, clitoromegaly, high levels of serum testosterone and/or high urinary excretion of 17-ketosteroids (17-KS). Precocious puberty and virilization in a boy was determined by a high serum testosterone level and high urinary excretion of 17-KS. Patients who had no recognizable clinical endocrine syndrome were said to have "nonfunctional" tumors.

Serum testosterone and cortisol were measured by specific radioimmunoassay, while the urinary excretion of 17-OHCS and 17-KS were measured by the Porter-Silber and the Zimmerman methods, respectively. Abdominal ultrasonography was performed in all cases. CT scan and MRI of the abdomen were carried out in three patients between 1995 and 2000. Pathologic diagnosis was performed in the six patients who underwent surgery.

RESULTS

Seven patients (four boys and three girls) with adrenocortical tumors aged one month to twelve years were identified. Clinical findings included: virilization and hypertension in four patients – of which two had untreated congenital adrenal hyperplasia (CAH) and one had Cushing's syndrome. Virilization or hypertension was the single manifestation in two other patients. Abdominal masses were palpated in two patients. We encountered an adrenal tumor using ultrasonography while checking a patient with Down's syndrome for G-I anomalies. Four patients had both a history and findings of accelerated growth. Age, sex and clinical manifestations of the patients are shown in Table 1.

Table 2 shows the results of hormonal studies in the seven patients. Abnormal findings were found in six patients. Elevated urine 17-KS was found in five patients with virilization. Four patients had high urinary 17-OHCS, and two had CAH with low cortisol response to the ACTH-stimulation test. Only one had clinical signs of Cushing's syndrome (unsuppressive to low- or high-dose dexamethasone). In patient No. 7, there were no clinical signs of Cushing's syndrome but there was an elevated level of urinary 17-OHCS. No abnormal endocrine function was detected in patient No. 6.

Table 3 shows the results of the roengenographic studies of all seven patients. Abdominal ultrasonography was performed in all of the patients, a CT scan in two and MRI in one. Right adrenal masses were found in four of the patients while in three the masses were on the left side. The tumor size ranged from 2 to 15 cm in diameter. Metastasis to the liver was found by ultrasonography in patient No. 2. In patient No. 1, a routine

Table 1. Age, sex, and clinical manifestations of seven patients with adrenocortical tumors.

	Patient number						
	1	2	3	4	5	6	7
Age at diagnosis (yr)	12	10	8	9	12	1/12	6
Sex	male	male	male	female	male	female	female
Virilization	+	+	-	+	+	-	+
Hypertension	+	-	+	+	+	-	+
Cushing's appearance	+	-	-	-	-	-	-
Palpable abdominal mass	+	+	-	-	-	-	-
Accellerated growth	+	-	-	+	+	-	+
Associated abnormalities or diseases	herpes zoster	-	-	congenital adrenal hyperplasia, ambiguous genitalia	congenital adrenal hyperplasia	Down's syndrome with imperforated anus	epilepsy
Duration of onset (yr)	3/4	1/2	1	9	11	-	2

Table 2. Laboratory data for seven patients with adrenal gland tumors.

	Patient number						
	1	2	3	4	5	6	7
Urine							
17-KS (mg/d)	21.1	9.0	1.8	36.8	6.8	0.1	26.4
17-OHCS (mg/m^2/d)	62.2	1.9	3.5	75.6	25.2	0.7	53.6
Serum							
Cortisol (μg/dL) 8 AM	35.7	12.5	11.0	2.9	4.2	15.3	9.5
11 PM	19.8	-	-	-	-	-	-
Testosterone (ng/dL)	12.5	10.2	0.6	10.5	17.7	-	2.8
Short ACTH test							
Cortisol at 60 min. (μg/dL)	-	-	-	4.1	4.3	-	12.9
Dexamethasone suppression test							
-Cortisol (μg/dL) after low-dose	29.5	-	-	-	-	-	-
-Cortisol (μg/dL) after high-dose	31.8	-	-	-	-	-	-

Abbreviations and normal prepubertal values are: 17-ketosteroids (17 KS), < 3.0 mg/d; 17-hydroxycorticosteroids (17-OHCS), 3.0±1.0 mg/m^2/d; Testosterone < 15 ng/dL; cortisol response to ACTH test at 60 min, > 10 μg/dL with max. > 25 μg/dL; cortisol 5-29 μg/dL; cortisol after low dose < 5 μg/dL, in Cushing's disease cortisol after high dose < 50 per cent of baseline.

chest X-ray produced a cotton-ball appearance indicating metastasis to the lungs. Both patients had huge palpable abdominal masses.

Surgical management, pathologic findings and results of treatment are shown in Table 4. Adrenalectomy was performed in four of the patients and biopsy in the two with metastasis. Among the five functional tumors, four were the result of adrenocortical carcinomas and one from an untreated CAH - histopathologic findings of the left adrenal tumor was compatible with hyperplasia.

Patient No. 4 had an untreated CAH - the left adrenal gland tumor was 5 cm in diameter. She refused surgery, cortone acetate was given instead. Three years later, abdominal ultrasonography indicated a total remission.

Mild elevated urinary 17-OHCS with low 17-KS were found in patient No.3 who presented with hypertension. Though the pathological section consisted with carcinoma (Table 4), the tumor might involved some parts of the cortex especially the zona glomerulosa or the low level might be due to inadequate urine collection.

Table 3. Roengenographic findings in seven patients with adrenocortical tumors.

	Patient number						
	1	2	3	4	5	6	7
Abdominal ultrasonography	Right	Right	Right	Left	Left	Left	Right
Diameter of adrenal mass	15 cm	10 cm with liver metastasis	5 cm	5 cm	4 cm	2 cm	5 cm
CT scan abdomen	-	-	Right 4x5 cm	-	Left 3x4 cm	-	-
MRI abdomen	-	-	-	-	-	-	Right 4x5 cm
Chest X-ray with lung metastasis	+	-	-	-	-	-	-

Table 4. Surgical management and pathologic findings in six patients with adrenocortical tumors.

	Patient number						
	1	2	3	4 *	5	6	7
Surgery							
Adrenalectomy	-	-	+	-	+	+	+
Biopsy	+	+	-	-	-	-	-
Pathologic findings							
Carcinoma	+	+	+	-	-	-	+
Hyperplasia	-	-	-	-	+	-	-
Lipoma	-	-	-	-	-	+	-
Results of treatment							
Dead (month, after diagnosis)	1	1 1/2	-	-	-	-	-
Follow-up with tumor Free time (yr)	-	-	8	4	4 1/2	1	3/4

* Patients No. 4 had congenital adrenal hyperplasia with left adrenal gland tumor 5 cm in diameter and refused surgery.

The nonfunctioning tumor in patient No. 6 grew from 2 to 4 cm in diameter in the six month follow-up period : the pathologic finding was lipoma. The two patients who suffered tumor metastasis to the liver and lung died 1 and 1 1/2 months after diagnosis, respectively. Five patients survived and come for follow-up every 3 to 6 months. They have normal levels of urine 17-KS and 17-OHCS. Abdominal ultrasonography was performed twice a year for signs of carcinoma. The follow-up time ranged from nine months to eight years and no evidence of tumor recurrence occurred in any of the patients.

DISCUSSION

Adrenocortical tumors are very rare in children. Should one encounter virilization and/ or hypertension, a functional tumor may be present, especially if accompanied by accelerated growth rates and signs of Cushing's syndrome. Several congenital abnormalities and a family history of other malignancies are associated with adrenocortical tumors[3-5]. In our study, we found two patients with CAH and one Down's syndrome patient with associated adrenal gland tumors.

Virilization should be differentially diagnosed from CAH (especially 21-hydroxylase and 11-hydroxylase deficiencies) and adrenal incidentalomas may complicate findings of untreated CAH[6-10]. High incidences of adrenal mass, nearly 82 per cent in homozygous and 45 per cent in heterozygous patients, were found[8]. Most of the tumors were benign. In our study, the two untreated CAH patients with hypertension had left adrenal gland tumors - only one patient had a pathologic diagnosis compatible with hyperplasia -

and one who had a tumor measuring 5 cm in diameter. This patient refused surgery but the tumor disappeared after three years of treatment with cortone acetate. These findings indicate that adrenal tumors in CAH may be generally resolved without surgical treatment. Though malignant transformation is unlikely, adrenocortical carcinomas have been reported in adults with CAH[9,10]. Jaresch et al recommended that an inactive tumor >6 cm in diameter should be removed[8].

Most cases of adrenal incidentalomas have been found in adults, more than 80 per cent of unilateral tumors showed normal hormonal function, only 17 per cent showed subclinical abnormal function. In bilateral incidentalomas, abnormal function was more frequent accounting for 29 per cent of cases[11]. Among these tumors 9 per cent had a pathologic finding compatible with carcinoma and 3 per cent had metastasized. The potential for malignancy increases as masses exceed 5 cm in diameter[12-14]. except for those which present during CT or MRI with characteristics typical of myelolipomas, cysts or hematomas. In our study, a nonfunctioning tumor was encountered during abdominal ultrasonography of a newborn girl with Down's syndrome. At the 6-month follow-up, the tumor was observed to have grown from 2 to 4 cm in diameter, so surgery was recommended.

Adrenocortical carcinoma was the most common cause of adrenocortical tumors in our study. Metastasis and large tumors have a poor prognosis. Lee et al reported the death of a child who suffered metastasis to the liver and lungs and seven children surviving without chemotherapy from 1 to 6 years after follow-up[5]. In our study, two children with carcinomas (with capsule invasion and no distant metastasis) survived from one half year to eight years after follow-up.

The molecular mechanisms involved in adrenocortical carcinomas are not well understood. Recent studies of these tumors have focused on abnormalities at the 11p 15 regions and alterations by the insulin-like growth factor (IGF) system[15]. A study by Boulle et al showed increased levels of IGF-II and IGF binding protein-2 (IGFBP-2) associated with malignancy in sporadic adrenocortical tumors[16]. Long-term over-expression of IGFBP-2 in adrenocortical tumor cells was also shown to be associated with an enhanced tumorigenic potential[17]. In the imprinted 11p 15 region, the $p57^{KIP2}$ gene is maternally-expressed and encodes a cyclin-dependent kinase (CDK) inhibitor involved in G1/S phase of the cell cycle. Bourcigaux et al demonstrated that maternal loss of heterozygosity with duplication of the paternal allele or pathological functional imprinting of the 11p 15 region were responsible for loss of expression of the $p57^{KIP2}$ gene and increased expression of the IGF-II gene[18]. Additional studies on the cellular mechanism of IGF-independent tumor growth-promoting action of IGFBP-2 may contribute to the development of future diagnosis and new therapeutic approaches in the management of adrenocortical tumors.

SUMMARY

Adrenocortical tumors were reported in seven children. The pathologic findings were compatible with carcinoma in four children, hyperplasia in one and lipoma in one. Two children died with huge, metastasized tumors. Surgical treatment by adrenalectomy was the treatment of choice, except in the case of one child with untreated CAH where the tumor resolved after glucocorticoid treatment.

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เนื้องอกของเปลือกต่อมหมวกไตในเด็ก

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ได้รายงานผู้ป่วยเด็ก 7 รายที่ป่วยด้วยโรคเนื้องอกของเปลือกต่อมหมวกไตในระหว่างเดือนมกราคม 2529 ถึงกันยายน 2543 อาการสำคัญทางคลินิกคือ virilization และความดันโลหิตสูงพบในผู้ป่วยคนเดียวกัน 4 ราย ผู้ป่วย 2 รายในจำนวนนี้เป็นผู้ป่วยโรค congenital adrenal hyperplasia ที่ไม่ได้รับการรักษา อีก 1 รายมีอาการแสดงของ Cushing's syndrome ร่วมด้วย virilization และความดันโลหิตสูงยังเป็นอาการแสดงเพียงอย่างเดียวของผู้ป่วยอีกอย่างละ 1 ราย ผู้ป่วย Down's syndrome 1 รายไม่มีอาการแสดงทางระบบต่อมไร้ท่อ แต่ตรวจพบเนื้องอกโดยบังเอิญ โดยผู้ป่วยทุกรายได้รับการตรวจอัลตราซาวนด์ของช่องท้อง ผู้ป่วย 6 รายได้รับการผ่าตัด ผลการตรวจชิ้นเนื้อทางพยาธิวิทยาพบ carcinoma 4 ราย hyperplasia 1 ราย และ lipoma 1 ราย ผู้ป่วย 2 รายซึ่งมีเนื้องอกขนาดใหญ่ร่วมกับมีการแพร่กระจายไปยังปอดและตับเสียชีวิต หลังได้รับการวินิจฉัย 1 และ 1 $^{1}/_{2}$ เดือน ตามลำดับ ผู้ป่วย congenital adrenal hyperplasia 1 รายซึ่งปฏิเสธที่จะรับการผ่าตัดได้รับการรักษาด้วยยากลูโคคอร์ติคอยด์ และตรวจไม่พบก้อนเนื้องอกอีกหลังได้รับยานาน 3 ปี ขณะนี้ผู้ป่วย 5 คนที่ยังมีชีวิตอยู่ได้รับการติดตามอย่างสม่ำเสมอ และยังไม่พบการกลับเป็นซ้ำของก้อนเนื้องอกอีก

คำสำคัญ : เนื้องอกเปลือกต่อมหมวกไต, คาร์ซิโนมาของเปลือกต่อมหมวกไต, ความดันโลหิตสูงกลุ่มอาการคุชิง

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