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ORIGINAL ARTICLE

Adrenocortical tumors in children 18 years old and younger

Min Jeng Cho, Dae Yeon Kim, Seong Chul Kim, Tae Hoon Kim, In Koo Kim

Division of Pediatric Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Purpose: Pediatric adrenocortical tumors (ACTs) are rare. We reviewed findings in 8 children, 18 years of age or younger, diagnosed with ACT in our institution over the past 15 years. **Methods:** We retrospectively reviewed 8 children with ACTs treated between 1996 and 2010. **Results:** Three girls and 5 boys were treated for ACTs; their median age at presentation was 144 months (range, 28 months to 18 years). Seven patients showed signs of endocrine dysfunction, 4 with Cushing syndrome, 2 with virilization, and 1 with hyperaldosteronism. One patient, with symptoms of hematuria, underwent a computed tomography scan, which showed an adrenal mass. The median duration of symptoms prior to resection was 6 months (range, 1 to 24 months). Five patients had adenomas and 3 had carcinomas. All underwent complete resection of the tumor, with laparoscopic adrenalectomy performed on 3 patients with adenoma and 1 with carcinoma. The median tumor weight was 12.5 g (range, 1 to 130 g) and the median tumor volume was 18.3 cm^3 (range, 2.2 to 299.2 cm^3). At a median follow-up of 5.1 years (range, 4 months to 15 years), all 8 patients remain alive with no recurrence of disease. **Conclusion:** The characteristics of pediatric ACTs vary considerably. Laboratory findings, clinical hormonal features, and tumor size could not distinguish adenomas from carcinomas before surgery. Complete tumor resection was successful, with no tumor recurrence. However, the small number of patients and short follow-up period limit assessments of prognosis.

Key Words: Adrenocortical adenoma, Carcinoma, Child

INTRODUCTION

Adrenocortical tumors (ACTs) are rare in children, comprising less than 0.2% of all pediatric neoplasms and 6% of all pediatric adrenal tumors [1]. ACTs usually present with symptoms and signs of androgen excess and hypercortisolism, and rarely, hyperaldosteronism. To date, the rarity of these tumors has not allowed a clear definition of clinical presentation and prognostic factors. We reviewed findings in 8 children, 18 years of age or younger, diagnosed with ACTs in our institution over the past 15 years.

METHODS

The records of all children with ACTs treated between 1996 and 2010 were reviewed retrospectively. Information

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Correspondence to: Dae Yeon Kim
Division of Pediatric Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-3961, Fax: +82-2-474-9027, E-mail: kimdy@amc.seoul.kr

recorded for each patient included age, sex, presenting symptoms, diagnostic features, hormonal status, pathological findings, stage of disease, treatment, and outcome.

Tumor stage was determined by the modified MacFarlane staging system [2]. Localized disease was defined as tumor confined to one of the adrenal glands; regional disease as tumor extending beyond the limits of the adrenal gland to the surrounding organs and tissues, including the regional lymph nodes; and metastatic disease as disease accompanied by distant metastases, in the presence or absence of regional disease. Patients with neuroblastoma, pheochromocytoma, and other tumors metastatic to the adrenal gland were excluded.

RESULTS

Three girls and 5 boys were treated for ACTs during the 15-year study period. Their median age at presentation was 144 months (range, 28 months to 18 years). All neoplasms were unilateral, with 6 presenting on the left side and 2 on the right side. Clinical characteristics of these patients are shown in Tables 1, 2.

Seven patients showed signs of endocrine dysfunction, the most frequent being Cushing syndrome, consisting of hypertension, central obesity, buffalo hump, and moon face, observed in 4 patients. Two patients showed virilization, including growth of pubic hair and clitoromegaly, and one presented with symptoms of hyperaldosteronism including hypertension and hypokalemia. The remaining patient, who was diagnosed with congenital adrenal hyperplasia at age 2 months, has been continuously monitored as an outpatient and has shown symptoms of hematuria for 1 month. To assess this patient, we performed a computed tomography (CT) scan, which revealed an adrenal mass. The hematuria in this patient was a temporary,

Table 1. Clinical presentation and treatment outcomes in patients with adrenocortical adenoma

No.	Sex/age	Sx (duration)[a]	Lab finding				Tumor		Tx	Follow-up (mo)
			Cortisol	DHEA	17-KS	17-OHCS	Site	Size (cm)		
1	M/14 yr	Cu (24)	ND	238.3	3.9	12.6	Lt	2.7	A	180, NED
2	F/18 yr	HTN (24)	9	ND	ND	ND	Lt	2.1	Lap-A	156, NED
3	M/12 yr	Cu (6)	22.6	104	12.4	16.8	Lt	2.5	A	51, NED
4	F/2 yr 4 mo	V (16)	9.5	87.2	1.2	3	Rt	1.9	Lap-A	8, NED
5	M/7 yr	Cu (1)	22.6	1,280	50.8	ND	Lt	4.8	Lap-A	4, NED

Sx, symptom; Cortisol, plasma (normal, 5 to 25 ug/dL); DHEA, dehydroepiandrosterone-sulfate (normal, 35 to 430 ug/dL); 17-KS, urine 17-ketosteroid (normal, 3 to 12 mg/day); 17-OHCS, urine 17-hydroxycorticosteroid (normal, 5 to 23 mL/day); Tx, treatment; Cu, Cushing; ND, not done; NED, no evidence of disease; HTN, hypertension; Lt, left; A, adrenalectomy; V, virilization; Rt, right; Lap-A, laparoscopic adrenalectomy.
[a]Symptom duration before diagnosis (mo).

Table 2. Clinical presentation and treatment outcomes of patients with adrenocortical carcinoma

No.	Sex/age	Sx (duration)[a]	Lab finding				Tumor			Tx	Follow-up (mo)
			Cortisol	DHEA	17-KS	17-OHCS	Site	Stage	Size (cm)		
1	M/7 yr	Cu (6 mo)	ND	1,080	34.7	ND	Rt	M	9.5/6[b]	A + RL + CTx	116, NED
2	F/2 yr 7 mo	V (1 mo)	5.1	213	8.7	ND	Lt	Lo	5	Lap-A	72, NED
3	M/15 yr[c]	Hu (1 mo)	5.2	31.2	ND	ND	Lt	Lo	6.5	A	18, NED

Sx, symptom; Cortisol, plasma (normal, 5 to 25 ug/dL); DHEA, dehydroepiandrosterone-sulfate (normal, 35 to 430 ug/dL); 17-KS, urine 17-ketosteroid (normal, 3 to 12 mg/day); 17-OHCS, urine 17-hydroxycorticosteroid (normal, 5 to 23 mL/day); Tx, treatment; Cu, Cushing; ND, not done; Rt, right; M, metastasis; A, adrenalectomy; RL, right lobectomy; CTx, chemotherapy; NED, no evidence of disease; V, virilization; Lt, left; Lo, local; Lap-A, laparoscopic adrenalectomy; Hu, hematuria.
[a]Symptom duration before diagnosis (mo). [b]Liver metastasis size. [c]This patient and his sister were both diagnosed with congenital adrenal hyperplasia.

non-specific symptom and later improved without treatment. The median duration of symptoms was 6 months (range, 1 to 24 months). ACTs were diagnosed using ultrasound imaging and CT scan.

Elevated concentrations of plasma cortisol and several plasma and urinary steroids were found in some patients. However, no positive correlation was observed between clinical stage and urinary concentrations of steroid metabolites. All patients received preoperative steroid replacement.

All patients underwent complete tumor resection via a transabdominal approach. The median tumor weight was 12.5 g (range, 1 to 130 g), and the median tumor volume was 18.3 cm^3 (range, 2.2 to 299.2 cm^3). Five patients had an adrenocortical adenoma and three had an adrenocortical carcinoma. One of the patients with carcinoma who had liver metastasis on presentation underwent an adrenalectomy and a right lobectomy simultaneously. Laparoscopic adrenalectomy was performed on four patients, 3 with adenoma and 1 with carcinoma. All patients showed macroscopically negative margins. There was no perioperative mortality.

Of the 3 carcinoma patients, only patients who showed liver metastasis received chemotherapy with cisplatin, 5-fluorouracil and doxorubicin for a total of 6 cycles. At a median follow-up of 5.1 years (range, 4 months to 15 years), all eight patients remain alive with no evidence of disease recurrence.

DISCUSSION

Epidemiologic data has suggested that ACTs are more common in girls than in boys, with a 2.5:1 ratio [3-5], and that tumors occur more frequently in the left than in the right adrenal gland. We found, however, that, although tumors showed left side predominance, five of our eight patients were boys. Li Fraumeni and Beckwith-Wiedemann syndromes are common anomalies associated with ACTs. Congenital anomalies of the kidney and congenital adrenal hyperplasia also increase the risk of ACTs [6,7]. The steadily increasing incidence of precancerous genetic syndromes of the adrenal glands and the poor prognosis of patients with adrenocortical carcinomas force children with endocrine disorders to go through a detailed diagnostic evaluation and appropriate treatment, as given to adults.

ACTs have shown a bimodal age distribution, with peaks occurring in the first and fourth to fifth decades of life, although these tumors have also been reported to peak at age <5 years [3,8]. Although younger age at diagnosis has been associated with improved survival rate [9], other studies have found that age was not prognostic [10,11]. We did not observe a correlation between age and prognosis, due to the small numbers of patients and their ages, with only 2 patients <5 years old. Functional tumors produce symptoms due to the overproduction of cortical hormones, and most children with ACTs show endocrine symptoms, in contrast to adults who usually present with nonfunctional tumors [12,13]. Of our 8 patients, 7 presented with evidence of a hormonally active tumor. In general, virilization is the most frequent symptom of ACTs, followed by Cushing syndrome, with hyperaldosteronism being extremely rare. Of our 8 patients, four displayed the characteristics of Cushing syndrome and only the 2 youngest patients developed virilization. The patient with hypertension showed a decrease in renin concentration and an increase in aldosterone concentration. Although functional tumors are diagnosed earlier than nonfunctional tumors, the latter are frequently associated with distant metastases, inoperable abdominal masses, and pain [14,15]. Another study, however, reported no correlation between tumor type, functional vs. nonfunctional, or the time of symptom appearance and tumor stage [5]. Rather, the rapid growth rate of cancer cells in carcinomas results in nonspecific symptoms before the symptoms caused by hormones [16]. Of our 3 carcinoma patients, one exhibited no symptoms and the other two showed rapid development of symptoms, over 1 and 6 months, respectively. The patient with the largest adenoma also showed rapid development of hormonal symptoms. Thus, despite the small number of our patients, our findings suggest that tumor type, functional or nonfunctional, cannot aid in distinguishing adenomas from carcinomas.

Increased concentrations of cortisol, dehydroepian-

drosterone-sulfate, urine 17-ketosteroid, and urine 17- hydroxycorticosteroid before surgery may indicate carcinoma rather than adenoma [17], with a positive correlation between tumor stage and hormone concentration level [5]. We found, however, that many of our patients with functional tumors showed normal hormone levels, and that only one patient with adenoma and one with carcinoma had increased hormone concentrations. Since only 3 of our patients had carcinomas, larger studies are needed to determine correlations between laboratory data and clinical stage.

Surgical treatment has long been the cornerstone of therapy for ACTs, being the only form of treatment that unquestionably cures the tumors or prolongs survival significantly [3]. For small tumors, complete resection without radical lymph node dissection (RLND) may be sufficient [18], although the effect of RLND on recurrence rate or long-term prognosis in patients with advanced cancer has not been determined. At our institution, surgical resection of an ACTs includes macroscopically negative margins and no tumor spillage, with node dissection only if lymph nodes are grossly enlarged.

Laparoscopic adrenalectomy has recently been performed in pediatric patients as well as in adults [19-22]. Although most of these patients have benign diseases, laparoscopic adrenalectomy has shown the same oncologic results as open surgery in children with neuroblastoma and other adrenal cancers. Using this technique, we observed macroscopically negative margins, without tumor spillage, after complete resection of 3 adenomas and 1 carcinoma. Although the first operation took a long time, later operations were finished within 2 hours, with no significant differences from open surgery. Spillage should be avoided during complete resection since adenomas and carcinomas cannot be completely distinguished before surgery.

Due to the relatively small number of patients with ACTs, the role of chemotherapy is still unclear. Mitotane, an insecticide derivative that causes adrenocortical necrosis, has been used in adults, but its efficacy in children has not been well studied [23,24]. Chemotherapy generally is reserved for patients with recurrent or metastatic disease or those at high risk of relapse [25]. Therefore, also in our study, chemotherapy was conducted only for patients with liver metastasis after surgery and not carried out on the other two carcinoma patients. Radiotherapy also has not been found to improve survival rate, although patients have shown complete remission [26,27].

Statistically significantly prolonged survival rates has been reported in girls, localized tumors, patients who underwent extirpative procedure, and patients with a disease-free interval of >12 months [28]. Michalkiewicz et al. [29] found that patients with tumors <200 cm^3 in volume and <100 g in weight that were completely resected had an excellent prognosis, and the long-term survival rate of children with adrenocortical carcinoma has been reported to be between 10% and 46% [30]. All of our 8 patients showed positive results from complete resection, with no evidence of recurrence. However, the small number of patients and the short follow-up period limit assessments of prognosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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