Childhood Adrenocortical Tumors: A Single-Center Experience

Çocukluk Çağı Adrenokortikal Tümörleri: Tek Merkez Deneyimi

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ABSTRACT

Objective: Childhood adrenocortical tumors (ACTs) are rare neoplasms, about which etiopathogenesis and disease management are not yet clearly understood. We aimed to review the management of ACTs in our single medical center.
Methods: We retrospectively reviewed findings in seven children, who were 15 years old or younger, and were diagnosed with ACTs in our institution over the past 10 years. Information recorded for each patient included age, sex, presenting symptoms, hormonal status, pathological findings, stage of disease, treatment and outcome.
Results: Four girls and three boys were treated for ACTs. Five had adrenocortical carcinoma (ACC) and two had adrenocortical adenoma (ACA). All patients underwent laparotomy and complete excision. Two of ACCs had a stage I disease, one had a stage III, and the latter two ACCs had a stage IV disease. ACAs were treated successfully by total excision without any concomitant therapy. Adjuvant chemotherapy and mitotane were commenced postoperatively in ACC patients. Six patients are alive and doing well at a mean follow-up of 5 years and 8 months.
Conclusion: The small number of ACTs and the short follow-up period limit the assessments of prognosis and management. As a result, patients with ACTs should be studied in multi-institutional trials to address the role of prognostic factors and cytotoxic drugs in the disease management.

Key Words: Adrenocortical tumors, children

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ÖZET

Amaç: Çocukluk çağı adrenokortikal tümörleri, etyopatogenezi tam olarak bilinmeyen ve standart bir tedavi yaklaşımı olmayan oldukça nadir tümörlerdir. Bu yazımızda bölümümüzde adrenokortikal tümör tanısı almış çocukların tedavi, takip ve sonuçlarını yayınlamayı amaçladık.
Yöntemler: Bölümümüzde son 10 yılda tanı alan 15 yaş ve altı 7 tane adrenokortikal tümörlü hastanın kayıtları geriye dönük olarak incelendi. Hastaların yaş, cinsiyet, başvuru belirtileri, hormonal durumu, patolojik bulguları, tümörün evresi, tedavisi ve sonuçları değerlendirildi.
Bulgular: Son 10 yılda 4 kız ve 3 erkek hasta adrenokortikal tümör tanısı alarak tedavi edildi. Hastaların beşi adrenokortikal karsinom, ikisi adrenokortikal adenom tanısı aldı. Bütün hastalarda laparotomi yapılarak komplet tümör eksizyonu gerçekleştirildi. Adrenokortikal karsinomlu hastaların ikisi evre I, biri evre III ve kalan ikisi evre IV olarak değerlendirildi. Adrenokortikal adenomlu hastalar sadece cerrahi ile başarılı şekilde tedavi edilirken, adrenokortikal karsinomlu hastalara mitotan ve adjuvan kemoterapi uygulandı. Ortalama takip süresi 5 yıl, 8 ay olan hastalardan altısı halen remisyonda izlenmektedir. Bir hastamız cerrahiden 20 ay sonra, remisyonda iken takipten çıkmıştır.
Sonuç: Literatürde adrenokortikal tümörlü hasta sayısının sınırlı ve takip sürelerinin kısa olması, prognozu ve tedavi yaklaşımını belirlemeyi güçleştirmektedir. Sonuç olarak bu hastalar çok merkezli çalışmalara dahil edilerek prognostik faktörler ve tedavide sitotoksik ilaçların rolü incelenmelidir.

Anahtar Sözcükler: Adrenokortikal tümörler, çocuk

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INTRODUCTION

Adrenocortical tumors are rare pediatric neoplasms and constitute less than 0.2% of all pediatric cancers (1). They account for 6% of all adrenal tumors in children with an estimated incidence of 0.3-0.5 per million in children younger than 15 (2). The title of adrenocortical tumors comprises adrenocortical adenoma and adrenocortical carcinoma, which are different entities. They may occur in all age groups with two peaks occurring before the age of 5 and between the fourth and the fifth decade (3). Adrenocortical tumors are usually sporadic but can sometimes be associated with tumor syndromes such as the Beckwith-Wiedemann and Li-Fraumeni syndromes (4,5). Most of these tumors are functional. As a result, the patients usually present with symptoms and signs of androgen excess, hypercortisolism, and rarely with hyperaldosteronism. However, they may also present with general symptoms such as abdominal pain, swelling and discomfort. Because of the rarity of pediatric ACTs, no single pediatric oncology center has acquired extensive experience with this tumor (6). Consequently the rarity of these tumors has not allowed for a clear definition of a clinical presentation and prognostic factors.

We reviewed findings in seven children, who were 15 years old or younger, and were diagnosed with ACTs in our institution over the past 10 years.

METHODS

The records of seven children treated for ACTs in our unit between 2003 and 2013 were reviewed retrospectively. Information recorded for each patient included age, sex, presenting symptoms, hormonal status, pathological findings, stage of disease, treatment and outcome.

The extent of disease was defined as localized or advanced on the basis of a modified staging system proposed by Sandrini et al. (7). Assignment to the localized disease (stage I: tumor weight ≤ 200 gram or stage II: tumor weight > 200 gram) category required complete tumor resection and no evidence of disease elsewhere. Assignment to the advanced disease (stage III or IV) category required the presence of local residual or metastatic disease. When tumor weight was not provided, it was estimated from tumor measurements obtained from computed tomography scans, ultrasound examinations, or pathology reports by using the following formula: weight = $1.342x(volume)^{0.8563}$ (8).

RESULTS

There were seven children treated for ACTs in the study period. Of these five had ACC and two had ACA. Clinical characteristics and laboratory findings of these patients are shown in Tables 1 and 2. The mean age of the patients at presentation was 4.5 years (range, 7 months to 15 years) with a female to male ratio of 4:3. The tumors were right-sided in three patients, left-sided in three, and bilateral in one patient. Six patients had clinical evidence of an endocrine syndrome. Virilization, alone or in combination with signs of over production of adrenal hormones, was the most common clinical presentation. Five patients had virilizing symptoms, including a variable combination of precocious development of pubic hair, accelerated height, acne, increased body hair and enlargement of genitals. Two of these patients also had cushingoid features such as hypertension, central obesity and buffalo hump (patient 3 and 5).

Table 1. Clinical Characteristics of Patients.

No	Sex	Age	Feature	Tumor Size (mm)	Tumor Site	Stage	Pathol Dx
1	F	2 yr 6mo	Virilization	150x128x65	Left	IV	ACC
2	F	3 yr	Virilization	22x16x10	Right	III	ACC
3	M	9 mo	Virilization + Cushings' syndrome	Enlargement of bilateral adrenal glands	Bilateral	IV	ACC
4	M	8 yr	Virilization	40x32x26	Left	I	ACC
5	F	1 yr 6mo	Virilization+ Cushings' syndrome	53x45x34	Right	I	ACC
6	F	15 yr	Hyperaldesteronism	12x12x10	Left	_	ACA
7	M	7 mo	Nonfunctional tumor	33x28x23	Right	_	ACA

ACA, adrenocortical adenoma; ACC, adrenocortical carcinoma; F, female; M, male; Yr, year; Mo, month.

Table 2. Laboratory Findings of Patients at Presentation.

No	ACTH pg/ml	Cortisol µg/dl	DHEA-S µg/dl	17OHPG ng/ml	Testosterone ng/dl	Aldosterone pg/ml
1	<10	>50	515	5.3	225	ND
2	26.69	11.3	52.06	50.16	ND	166
3	<10	>50	>1000	>20	>1600	ND
4	14.8	9.18	1000	1.78	646.7	288
5	28	40	996.3	9.19	869	145
6	13.3	19.2	317.5	5.26	37.8	1007
7	34.7	8.39	3.1	0.3	<10	17.13

ACTH, adrenocorticotrophic hormone (normal, 0 to 46 pg/ml); Cortisol plasma (normal, 5 to 25 µg/dl); DHEA-S, dehydroepiandrosterone-sulfate (normal, 25 to 219 µg/dl); 17OHPG, 17-hydroxyprogesterone (normal 0.07 to 1.53 ng/ml); Testosterone (normal 0 to 40 ng/dl); Aldosterone (normal 40 to 480 pg/ml); ND (not done).

All of these five patients had increased levels of androgens, glucocorticoids, and/or mineralocorticoids. One patient presented with the symptoms of hyperaldosteronism including hypertension and hypokalemia (patient 6). This patient had an increased secretion of aldosterone alone (9). One patient had nonspecific symptoms such as discomfort, and the tumor did not cause clinical manifestations of any hormone excess and it was identified as a nonfunctional tumor (patient 7).

The tumor could be seen with ultrasonography (US) in five of seven patients, whereas computed tomography (CT) scan demonstrated the lesion in all cases. All of the patients underwent laparotomy and the complete excision of their tumors. Mean tumor weight was 120 g (range, 5 g to 600 g). All patients showed macroscopically negative margins. Bilateral adrenalectomy was performed on Patient 3. Two of ACCs had a stage I disease (Patient 4 and 5).

Patient 5 had a relapse with hepatic metastasis 20 months after the operation and had a stage IV disease. This patient underwent a second surgery and a right lobectomy was performed. The pathology supported the diagnosis of an ACC metastasis. One patient had a stage III (Patient 2 who had a local spread to lymph nodes) and the latter two ACCs had a stage IV disease (Patient 1 and 3). These two patients had a hepatic metastasis and a hepatic metastasectomy was performed only on Patient 3.

Patients with ACA (Patient 6 and 7) were treated successfully by total excision without any concomitant therapy. Adjuvant chemotherapy consisting of mitotane (Patient 2, 3), mitotane plus cisplatin, etoposide and doxorubicin (Patient 1 and Patient 5 at relaps) was commenced postoperatively in ACC patients. All of the patients were treated with mitotane and had glucocorticoid and mineralocorticoid replacement to avoid adrenal insufficiency. Serum levels of mitotane were monitored regularly and any significant adverse effects were noted. None of our patients received radiotherapy.

At a mean follow-up of 5 years and 8 months (range, 20 months to 10 years) six patients are alive and doing well. Five of these patients had no evidence of disease recurrence. Patient 5 who relapsed with a hepatic metastasis had been in remission for 18 months after the hepatic metastasectomy combined with a chemotherapy and a mitotane therapy. The remaining one patient (Patient 1) was lost to follow up 20 months after the operation. She had been in remission at the last visit. Treatment methods and outcomes of patients are shown in Table 3.

Table 3. Treatment Methods and Outcomes of Patients.

No	Treatment	Result	Follow-up (months)
1	TE + Chemotherapy + Mitotane	Cured	20, (Lost)
2	TE + Mitotane	Cured	96, NED
3	TE (Bilateral adrenalectomy) + Hepatic lobectomy + Mitotane	Cured	120, NED
4	TE	Cured	66, NED
5	TE	Relaps	38
	*Hepatic lobectomy+Chemotherapy+Mitotane	Cured	NED, for 18 months
6	TE	Cured	48, NED
7	TE	Cured	84, NED

TE, total excision; NED, no evidence of disease.

DISCUSSION

Adrenocortical tumors arise from one of three adrenal cortex layers: glomerulosa, fasciculata and reticularis. It has classically been considered an epithelial tumor and therefore is classified as carcinoma and adenoma. The diagnosis of an ACT is made on the basis of the gross and histologic appearance of tissues obtained at surgery. The pathologic classification of pediatric ACTs is troublesome. Even an experienced pathologist can find it difficult to differentiate carcinoma from adenoma (10). International Pediatric Adrenocortical Tumor Registry (IPACTR) reported 254 patients younger than 20 years of age with diagnosis of ACT (8). Two-hundred twenty-eight tumors (89.7%) were histologically classified as carcinoma, and the remaining 26 were classified as adenoma. Approximately one third of all ACTs reported in the literature were ACAs. Our group is similar to the cases reported in the literature, with two (28.6%) of our seven patients being ACAs.

Epidemiologic data has suggested that ACTs are more frequent among girls with an approximate female:male ratio of 2 to 3:1. The same ratio was 4:3 in our group. Some authors suggest that tumors occur more frequently in the left than in the right adrenal gland (2, 3). But Ribeiro et al. reviewed information on 520 published and unpublished cases from institutions worldwide, and found no tumor laterality predominance (10), as it was the case in our group. Bilateral tumors were observed in one of our cases. In the literature bilaterality has been reported in 2% to 10% of the cases (11). ACTs may occur in all age groups with two peaks occurring before the age of 10 and between the fourth and the fifth decade (12). Childhood ACT has peculiar clinical and biological features that contrast with those observed in other pediatric carcinomas (10).

The incidence of most childhood carcinomas increase with age, whereas 65% of ACTs occur in children younger than 5 years of age (3). Five (71.4%) of our seven patients were younger than 4. Also the mean age was 4.5 years as was the case in other larger series reported in the literature.

ACT usually presents with a clinical picture of hormone overproduction, virilization, Cushing's syndrome, or a combination of the two (13, 14). Virilization alone (42.8%) was the most common presentation in our group followed by the combination of virilization and Cushing's syndrome (28.6%). Also, we emphasize that virilization was present in all of the ACC patients (100%). Moreover plasma DHEA-S, 17OHPG and testosterone levels were abnormal in most of our cases. Only one patient with ACA had a nonfunctioning tumor in our group. Thus, most of our cases presented with endocrine symptoms in contrast to adults, who usually present with nonfunctional tumors. Aldosterone producing ACT is extremely rare in children. However in our group, a 15-year-old girl presenting with the signs and symptoms of hyperaldosteronism (headache, weakness of muscles, hypertension and hypokalemia) was found to have an adrenal adenoma. She had a medical history of nearly 1.5 years. Although the mass was excised surgically, and aldosterone levels were decreased to normal, hypertension persisted, and she received an antihypertensive treatment for 10 months. Since the ambulatory blood pressure monitorization was normal at the 10^{th} postoperative month, anti-hypertensive treatment was ceased (9).

All patients underwent US scan and CT scan evolution. The tumor could not be seen with US in two of seven patients, so that CT scan was more sensitive than US in identifying the tumor mass in our group. This finding was similar to what was previously reported in the literature (10). Daneman et al. reported that CT is the singly most important modality in assessing primary and metastatic diseases at diagnosis and during the follow-up in ACTs (15).

Complete resection of tumor and local lymph nodes is the singly most important procedure in the successful treatment of ACT (16). All seven patients who underwent surgery had macroscopically complete excision of their tumors. Complete resection of the tumor totally cures ACA patients as observed in our group; however, 30% to 50% of patients with ACC have local or distant recurrences in spite of an apparently curative surgery (17). So, surgery for suspected ACC should be limited to specialized centers to yield better results. Only one patient in our group had a distant recurrence. Surgical resection is also indicated for recurrent local disease or metastases. Our patient is in remission after second surgery and systemic therapy.

The role of chemotherapy is still unclear in the management of childhood ACTs. It has been frequently used to treat metastatic tumors and for those cases of large inoperable or partially excised tumors and for recurrences. Despite the use of different protocols of chemotherapeutic agents, none has emerged that has been shown to be sufficiently effective to be widely adopted (16). Mitotane [1, 1 –dichloro-2-(0-chloro-phenyl)-2-(p-chlorophenyl)-ethane, or o,p'-DDD] an insecticide derivative has been used since 1960s, initially for adult patients (18). Mitotane causes cytotoxic atrophy of the adrenal cells (both normal and neoplastic) by acting on the mitochondria, leads to adrenal insufficiency in most patients, and increases the metabolic clearance of corticoids (19). The use of mitotane is controversial as adjuvant therapy in stage I and II ACC, due to the lack of convincing data showing that the drug can prevent tumor recurrence. However, it has been indicated in stage III and IV ACC in association with cisplatin, etoposide, and doxorubicin (CED) as it was previously recommended for adult patients. Berruti et al. reported CED plus mitotane is an active and manageable combination scheme for ACC patients as a result of large prospective phase II trial in adults (20). Only one of the ACC in our group did not have an adjuvant therapy (patient 4, stage I). We used a mitotane monotherapy for two of the ACCs [Patient 2 (stage III) and Patient 3 (stage IV)]. The latter two ACCs had received a combination chemotherapy of etoposide, doxorubicine and cisplatin plus mitotane [Patient 1 (stage IV) and Patient 5 (relapsed with a hepatic metastasis)]. All four patients used mitotane longer than six months within the therapeutic plasma levels. Despite the fact that all the patients had a good response to different treatment modalities in our group, further studies are necessary to optimize mitotane use in children.

Because of the heterogeneity and the rarity of ACTs, prognostic factors have been difficult to establish. Both of ACAs are treated successfully by total excision without any complication as it was the case in the previous reports of ACAs in the literature. However the prognostic factors are more complicated in ACCs. A multivariate analysis showed that only tumor size was significantly associated with survival (7). Furthermore, McAteer et al. analyzed 85 pediatric ACCs and found only the age of ≤ 4 years to be associated with better outcomes (16).

Additionally Michalkiewicz et al. reported in a multivariate analysis that disease stage I, virilization alone and the age between 0 and 3 were independently associated with a greater probability of event-free survival in ACTs. (8). Prognostic factor analysis was not performed in our group because of its small size, but four of five ACCs were younger than 4 years of ageand virilization was present in all of the ACC patients. Despite the fact that three of five ACCs had an advanced disease, their age and presenting signs of endocrine dysfunction may explain the favorable outcomes associated with their case. Conversely one of our stage I patients had distant metastases 20 months after the operation. We can not explain this conflicting result with the current staging systems and prognostic factors. This may be associated with adrenocortical tumorigenesis, which is not well understood at the present time. We also need further studies to answer why some tumors are confined to certain dimensions and secrete exclusively one type of steroid, while others display more aggressive growth and metastasize and co-secrete various types of hormones. Answers of these questions will let us identify additional prognostic factors and probably new staging systems.

CONCLUSION

Although ACT is a heterogeneous and a rare tumor group associated with considerably varying prognosis, in our group we observed that complete response is possible with a resection followed by mitotane, administered either alone or in combination with a chemotherapy. Nevertheless more prospective trials are needed to address the role of prognostic factors and cytotoxic drugs in the management of ACT.

Conflict of Interest

No conflict of interest was declared by the authors.

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