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FUNCTIONING ADRENAL TUMORS IN CHILDREN: A REPORT OF 17 CASES

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Background / Purpose : *Tumors of the adrenal gland are extremely rare in children, those of the adrenal cortex account only for 0.3-0.4 % of all childhood neoplasms. This study aimed to evaluate the various clinical syndromes of these lesions, the different methods for their diagnosis, their pathologic findings, the different surgical approaches for their excision, and their clinical outcomes in correlation to their pathological features.*

Methods : *All patients with functioning adrenal tumors presenting to the Pediatric Surgical Division over a period of 14 years, between 1986 and 2000 were clinically analyzed. Radiological studies primarily included bone age determination, IV urography, ultrasonography and scintigraphy scan .Magnetic resonance imaging was performed for only one patient. Hormonal evaluation included urinary levels of 17-ketosteroids and 17-hydroxycorticoids together with serum levels of testosterone and its precursors and cortisol. Dexamethasone suppression test was performed for all patients with suspected adrenocortical lesions. Estradiol, FSH and LH levels were done in a female presenting with isosexual precocious puberty. Estimation of catecholamines was performed for three patients with sustained hypertension. All patients were treated by surgery using different surgical approaches. The tumor's size and weight were recorded and its histological grading was performed according to Weiss criteria. Followup of the patients was achieved through clinical, radiological and hormonal assessments.*

Results : *The study included seventeen patients 9 females and 8 males with their ages ranging between 1.8 and 9 years (mean = 4.9 years). Two sisters were affected with left-sided virilizing adrenocortical carcinoma. Ten patients presented with features of virilism, three cases had signs of Cushing's syndrome, one girl with feminization and three cases with sustained hypertension. Palpable abdominal masses were present in four patients: three with signs of virilization and one with Cushing's syndrome. The left adrenal gland was involved in ten cases, the right in seven with no bilateral lesions. Fourteen lesions were operated upon through an anterior transabdominal approach; in two cases the tumor was removed through a posterior incision and in one case a small lesion was excised through a lumbar approach. Seven lesions were less than 5 cm in diameter, one of them was malignant, while 10 tumors were less than 100 gm in weight, two of them were malignant. Medullary lesions included two cases of benign pheochromocytoma and a case of ganglioneuroblastoma. Among 14 patients with adrenocortical tumors, seven had four or less positive Weiss histological criteria ,all of them had favorable outcome while two of the other seven cases remained disease-free with a follow-up which ranged between 6 months and 7 years. One case developed local recurrence after surgery and four patients died postoperatively after partial response to chemotherapy, three of them had distant metastases.*

Conclusion: *Functional adrenal tumors are extremely rare in children specially pheochromocytoma. Virilization is the commonest presentation, which is commonly due to carcinoma in females or adenoma in males. On the contrary, Cushing' s syndrome is commonly due to carcinoma in males and adenoma in females. Palpable abdominal mass is rather uncommon and considered a late manifestation with poor prognosis. CT scan remains the standard accurate modality for their localization and during follow-up.Complete removal of the tumor is the only effective treatment, the role of adjuvant chemotherapy or radiotherapy can not be confirmed. The anterior transabdominal approach provides the best exposure especially for large tumors, although very small lesions can be removed safely through a lumbar extra-abdominal approach. Laparoscopic adrenalectomy needs to be tried and evaluated in small lesions. The determination of the neoplasm's behavior by morphologic and histological criteria can often be unpredictable, even small lesions can be malignant and potentially lethal.Careful clinical follow-up may remain the final indicator for the diagnosis in some of these tumors. Early diagnosis*

and management are important with special care for postoperative adequate steroid replacement. A more advanced study to analyze the familial occurrence of adrenal tumors in children is needed for the possible role of exposure to toxic substances in its occurrence.

INTRODUCTION

Tumors of the adrenal gland are extremely rare in children. Those of the adrenal cortex account for only 0.3 0.4 % of all childhood neoplasms [1].Its rarity has hindered the identification of meaningful prognostic factors. Because so few children have been treated for adrenal tumor, even at major cancer centers, clinical experience is relatively limited; therefore optimal therapy has not been established[2].

Although non-secreting tumors have been reported, the majority of pediatric patients have been initially seen with clinical signs of hormonal activity. In most childhood cases, the increased secretion of adrenocortical hormones, especially androgens causes precocious puberty or virilism. In some cases, excessive glucocorticoid production is accompanied by Cushing's syndrome and in rare cases; symptoms of feminization or hyperaldoseronism may be present [3].

Clinically-functional medullary tumors of the adrenal gland in children are rare. Pheochromocytomas produce symptoms by secreting large amounts of catecholamines and are responsible for approximately 1% of cases of childhood hypertension, typically occurring between the ages of 8 and 9 years [4].

Surgery remains the treatment of choice for these tumors. Most of the published reports indicate that their complete removal is the best treatment approach with little or no apparent effect of adjuvant chemotherapy or radiotherapy on the outcome [5].

Roux in Lausane and Mayo in Rochester performed the first anterior adrenalectomies in 1927. Although Young described the posterior approach for the adrenals in 1936, it was only in the late 1970's that surgeons gradually accepted the technique [6].

The explosion of laparoscopic surgery witnessed the last few years has reached the retroperitoneal region of the adrenal glands. So the dilemma facing surgeons for many years " anterior or posterior approach? " has become a trilemma "anterior, posterior or laparoscopic approach?"[6].

Reports in the literature have been controversial regarding the prognosis and survival rate in patients with adrenal cortical tumors. Poor prognosis has been reported in studies that include adults and children [7].

Assessment of malignancy through histologic criteria has been controversial. Several investigators reported high degree of accuracy in the evaluation of malignancy by microscopic examination [8, 9]. Furthermore, Bugg et al reported that histological type and tumor weight were the most reliable predictors of tumor behavior in the pediatric age group [10].

PATIENTS AND METHODS

During a 14-year period, from 1986 to 2000, seventeen patients with clinically functioning adrenal tumors were studied in the Pediatric Surgical Division, the New Children's Hospital of Cairo University. The analyzed clinical data included symptoms at presentation and their duration prior to diagnosis, age, sex and the clinical features including abdominal examination for palpable masses with blood pressure measurement.

Patients were considered to have functional tumors when they manifest with a clinical syndrome due to excessive production of adrenergic hormones, namely adrenocortical steroids and catecholamines.

Hormonal evaluation of the adrenocortical functions was primarily done under basal conditions including blood cortisol, testosterone with its precursors: delta-4 androstenedione, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), estradiol, FSH, LH and their ratio, urinary free cortisol, 17-hydroxycorticoids (17-OHCS) and 17-ketosteroids (17-KS).

A Dexamethasone inhibition test (0.5 mg every 6 hours for 3 days) was performed in all patients with suspected adrenocortical tumors. Urinary catecholamine levels and their metabolites were estimated for those patients presenting with sustained hypertension.

A diagnosis of Cushing's syndrome was made if the patients presented with a moon face, buffalo hump, weight gain, centripetal fat distribution, and / or hypertension with high concentrations of plasma and urinary cortisol and unaffected excretion of urinary 17- OHCS after dexamethasone administration. They were reported to have virilization if they presented with clitoromegaly or macrogenitosomia, hirsutism, deep voice, precocious pubarche, acne, and / or increased muscle mass with elevated concentrations of plasma androgens and unaffected levels of urinary 17- KS after dexamethasone administration. On the other hand, feminization was

considered if the patient has precocious pubarche, enlargement of the breasts (thelarche), pubertal distribution of fat and enlargement of both labia majora and minora with elevated levels of estradiol and decreased FSH. Other laboratory investigations in the form of serum electrolytes and blood sugar levels, full blood indices, liver and kidney functions, etc… were also done.

Radiological evaluation included an intravenous pyelogram, adrenal ultrasound and abdominal computerized (CT) tomography scan. Magnetic resonance imaging (MRI) was done in only one patient. The radiological bone age was determined according to Greulich and Pyle criteria [11] with its comparison to the chronological age. Radiologic scanning for distant metastases was also performed when suspected.

The reported cases were staged radiologically according to SEER classification (Summary Staging Guide for Cancer Surveillance, Epidemiology and End Result Reporting Program) into localized, regional or distant disease[12].

In adrenocortical tumors, steroid replacement using hydrocortisone injection was started 24 hours before surgery and continued 48 hours postoperatively. The dose was then gradually decreased and replaced by oral hydrocortisone until an adequate maintenance dose was reached within one week after surgery. This oral steroid replacement therapy was gradually tapered off over a period of six months.

Patients with high blood pressure due to medullary tumors were controlled preoperatively by using sympathetic blockade (phenoxybenzamine) in a dose increasing from 0.25 to 0.75 mg / kg. Propranolol was also added to the regimen in two cases. To avoid arrhythmia, halothane was avoided together with the use of propranolol and lidocain. Arfonad and nitroprosside were prepared for intraoperative hypertensive crises.

All patients underwent complete surgical resection of the neoplasm. Nephrectomy was performed enbloc with tumor resection in four children so as to achieve complete excision whereas one patient underwent splenectomy and transverse colectomy due to infiltration of their mesentery with the tumor.

Adrenalectomy was performed through the anterior transabdominal approach using extended transverse subcostal incisions in all patients except in three cases where a posterolateral approach was done through the bed of the eleventh rib in two lesions. The pleura was opened which necessitated the application of underwater-seal drainage. In one case, the tumor was approached through a lumbar incision, which provided an extraperitoneal access. No cases of laparoscopic adrenalectomy were performed.

The tumor's size and weight were recorded in all patients. Histological analysis was reviewed by one pathologist, using Weiss histological criteria in adrenocortical lesions [8,13]. Each tumor was graded from 0 to 9 according to the presence of the following features: 1-nuclear size or grading III or IV, 2- mitotic rate greater than 5/50 cells per high power field (HPF), 3 atypical mitosis, 4 clear cells comprising 25% or less of the tumor, 5- diffuse architecture, 6 microscopic necrosis, 7- invasion of venous or sinusoidal structures, 8 invasion of tumor capsule, 9 spindling of tumor cells.Tumors that met more than four of the 9 criteria were defined as malignant.

Lung metastasis was detected in one case and hepatic involvement in two. Postoperative local recurrences that were excised resulted after 8months and 1.5 years in two cases respectively, one of them died 6 months later. In one case of pheochromocytoma, the regional lymph nodes were enlarged and excised.

Both adjuvant radiotherapy and chemotherapy – O, P1– DDD or Mitotane , [1,1-dichloro-2- (O-chlorophenyl) –2-(P-chlorophenyl) – ethane] –were given in five malignant lesions which showed persistent symptoms and hormonal elevations after tumor resection or with evidence of recurrence or metastases.

RESULTS

Of the seventeen cases included in the study, there were 9 females and 8 males with a ratio of 1.1: 1. Their ages at presentation ranged between 1.8 and 9 years (mean=4.9); (Table1). Fourteen lesions were adrenocortical in origin, while three were medullary. A total of 10 neoplasms was affecting the left adrenal gland, all of them were adrenocortical with equal results of adenoma and carcinoma. Seven tumors were right-sided; three of these were medullary. None of the patients had bilateral tumors.

Ten cases presented essentially with virilization: all the females were carcinomas (n=5/5), (Fig. 1,2), while the majority of the males (n=4 /5) were adenomas; (Fig.3).Three patients presented with Cushing's syndrome: two females were adenomas and a male was a carcinoma (Fig 4,5). One female patient showed signs of feminization due to an adenoma, (Fig. 6). Three medullary lesions presenting with sustained hypertension, irritability and headache were reported: two males aged 8.5 and 9 years had pheochromocytoma, (Fig. 7) and a female 3.5 year-old had ganglioneuroblastoma. Four patients, beside their endocrinological clinical picture, presented with a palpable abdominal mass, all of them proved histopathologically to be adrenocortical carcinomas (ACC). Three of these patients had signs of virilization.

Two of the patients who presented with signs of virilization were female siblings, aged five and six years.

Both of them proved to be ACC and both have developed postoperative recurrence and received adjuvant chemotherapy. The younger child died six months after surgery.

The hormonal data of the patients were then analyzed. All children with adrenocortical tumors had high levels of DHEAS except a single female patient who had signs of feminization. Testosterone, DHEA and androstenedione were elevated in 12 cases. Urinary 17-KS were elevated in 13 patients. High levels of serum cortisol and urinary 17-OHCS with altered suppression after dexamethasone administration were reported in five cases, three of them showed signs of Cushing's syndrome and two cases had virilization.The 11-deoxycortisol was elevated in seven patients; four of them presented with virilization (all were carcinomas) and three cases showed signs of Cushing's syndrome (two of them were adenomas). Elevated estrogen levels with suppressed FSH and LH and normal levels of serum cortisol and 17-OHCS were detected in a single case with feminizing adenoma.

In the three reported cases of medullary tumors, both levels of serum epinephrine and urinary vanillylmandelic acid were minimally elevated while levels of nor-epinephrine were markedly raised.

Generally, all the patients who came for follow-up had their hormonal profiles repeated every three months after surgery;those who developed recurrence showed elevated levels.

Radiologic assessment of bone age proved to be exceeding the chronological age in 12 cases. It was normal in two cases of virilizing adrenocortical carcinoma and in the three cases of medullary lesions. Chest x-ray revealed lung metastases in one case .

Abdominal sonography was helpful in detecting the adrenal mass in all cases although it has underestimated its size in 6 patients.According to SEER grading, eight cases were stage I : six were adrenocortical adenomas, a benign pheochromocytoma and a ganglioneuroblastoma. Stage II included six cases; four were adrenocortical carcinoma, an adenoma and a case of benign pheochromocytoma with enlarged regional lymph nodes. In stage III , three cases were cortical carcinomas.

CT scan was more accurate in detecting the size of the tumor (n=14), areas of necrosis (n=8), calcification (n= 2), invasion to surrounding tissues (n=4), enlarged lymph nodes (n=5) and liver metastases (n=2). It has detected a thin capsulated rim surrounding the tumor in six cases, two of these proved histopathologically to be carcinomas. MRI was performed in a single case and was not considered to add any data superior to CT scan.

Fourteen patients were operated upon through an anterior transabdominal incision; the sides were equally affected, (7 cases each). In ten cases, the tumor's size was exceeding 5 cm: nine lesions were adrenocortical (six were carcinomas) and one case of medullary ganglioneuroblastoma.In seven cases, the tumor's weight was exceeding 100 gm, six were carcinomas; (Table 2).

Besides tumor resection, nephrectomy was performed in five adrenocortical carcinomas, in one of these additional splenectomy and transverse colectomy were performed. Excision of enlarged regional lymph nodes was performed in a single case of right-sided pheochromocytoma, but this proved to be reactive hyperplasia with no evidence of malignancy on histological examination. Small billiary fistula has resulted in one case which closed spontaneously in 3 weeks. Reactionary hemorrhage occurred in another case that necessitated re-exploration and haemostasis.

A posterior incision with resection of the eleventh rib was performed in two left-sided adrenocortical adenomas presenting with Cushing's syndrome of 6.5 and 9 cm respectively.Extra-peritoneal lumbar excision was performed in a single case of left-sided adenoma, 2.5 cm in size. This case had the fastest convalescence with the shortest hospital stay.

Interpretations of the results regarding the tumors's size &weight, the radiological SEER grading and the Weiss criteria (only for adrenocortical lesions) with their relation to the pathologic results and outcome are summarized in (Table 2 , 3).

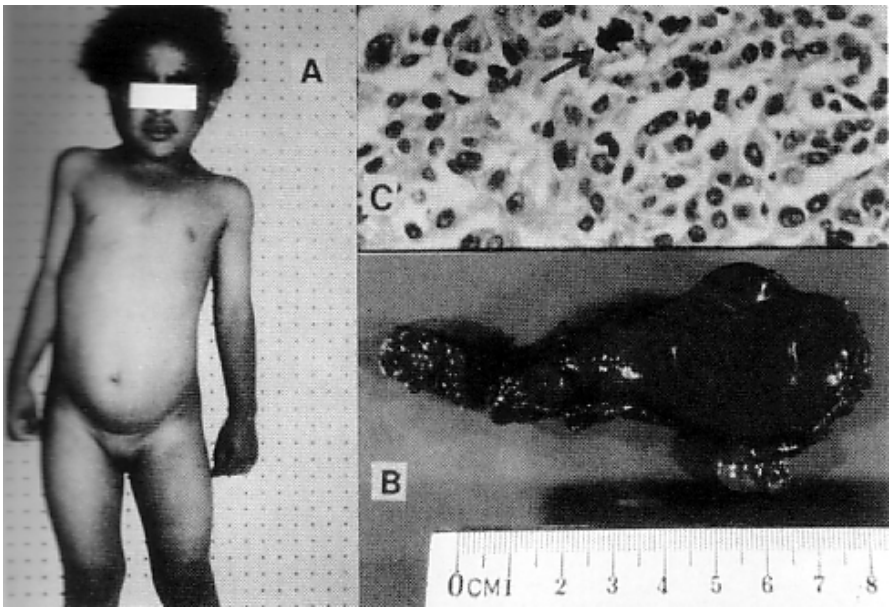

Fig (1) :

A- *Virilization in a female aged 6 years due to a left-sided adrenocortical carcinoma.*
B- *The tumor after resection.*
C- *High power photomicrograph of the lesion showing marked pleomorphism and atypical mitosis[arrow](H & E stain X200).*

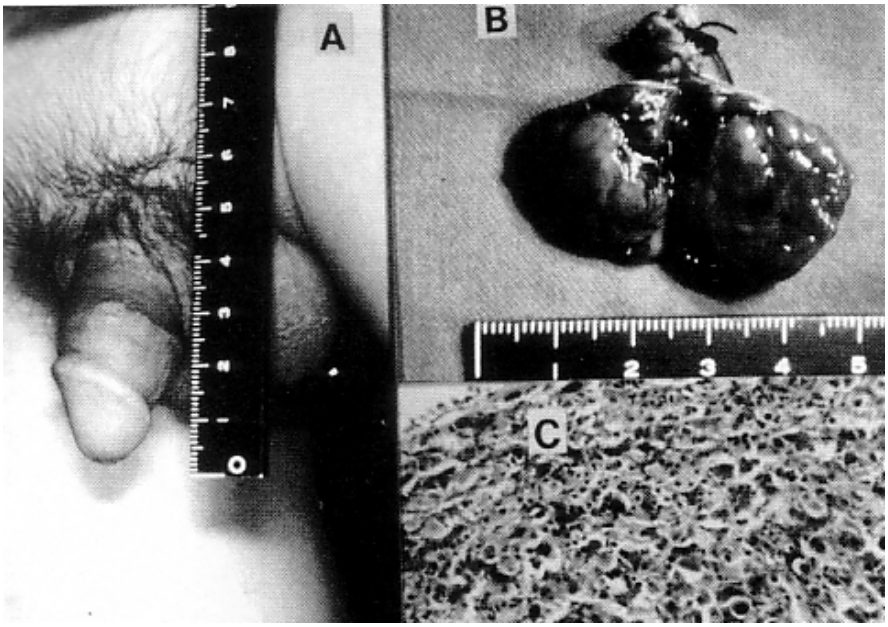

Fig (2) :

A- *Severe virilization with clitoromegaly and hirsutism in a female aged 4 years due to left-sided adrenocortical carcinoma .*
B- *The tumor excised-en- lock with the kidney.*
C- *High power photomicrograph of the lesion showing marked pleomorphism and atypical mitosis (H & E stain X100).*

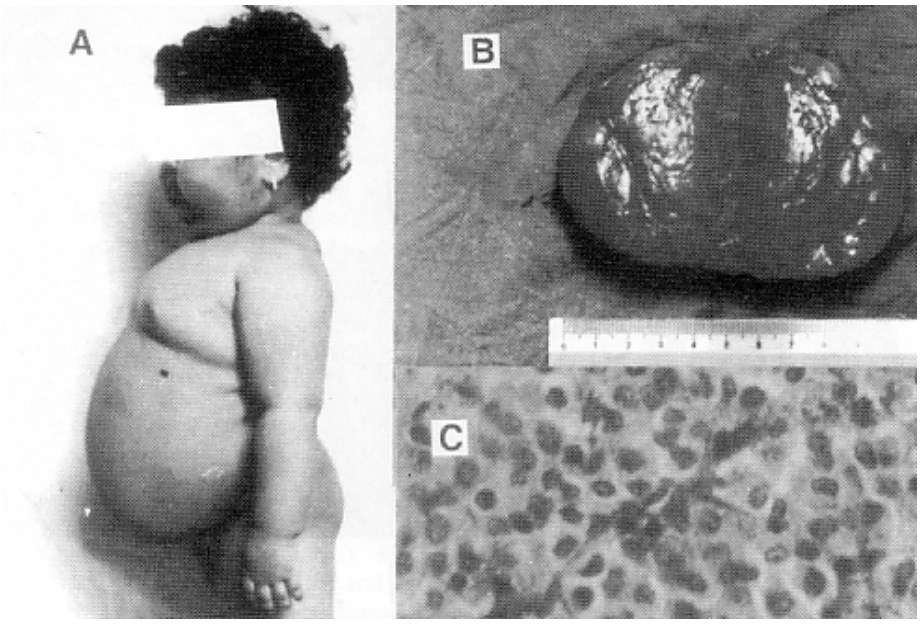

Fig (3) :

A- ***Virilization with premature pubarche in a male aged 2.4 years having a left-sided adrenocortical adenoma.***

B- ***Cut section of the tumor showing no areas of gross necrosis.***

C- ***Histopathology of the adenoma showing marked pleomorphism with no atypical mitosis (H &E stain X100).***

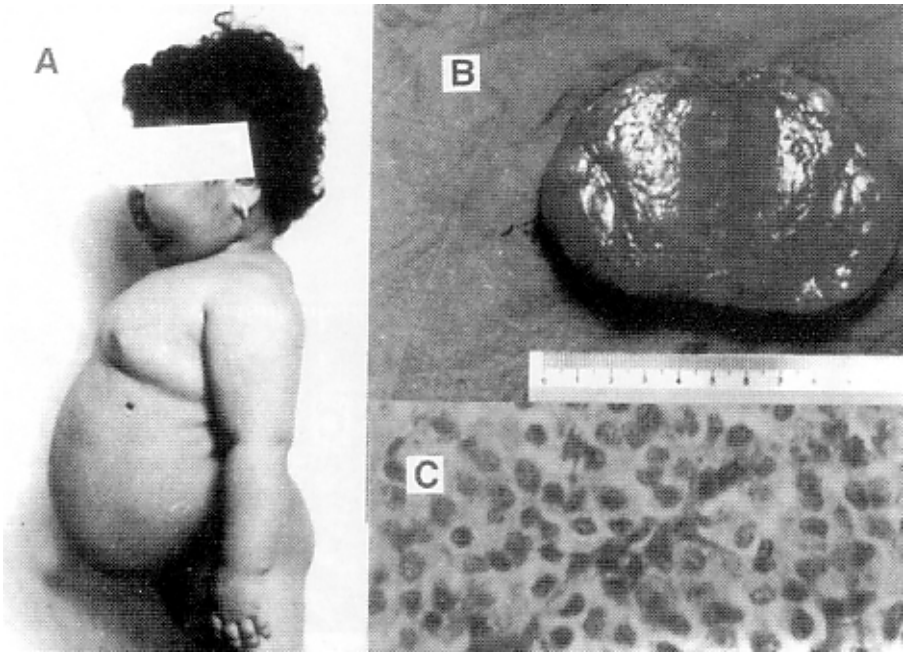

Fig (4) :

A- ***4-year-old female presenting with Cushing's syndrome due to left-sided adrenocortical adenoma.***

B- ***Cut section of the tumor.***

C- ***Histopathology of the adenoma showing no pleomorphism or atypical mitosis (H & E stain X100).***

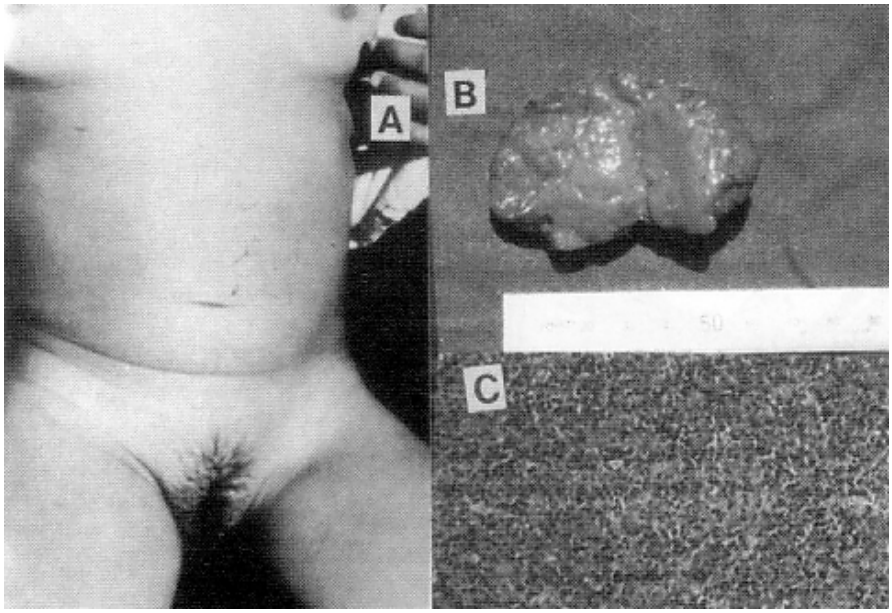

Fig (5) :

A- *An 8-year-old male presenting with Cushing's syndrome due to right-sided adrenocortical carcinoma.*

B- *Tomographic scan showing areas of .necrosis.*

C- ***The tumor after its***

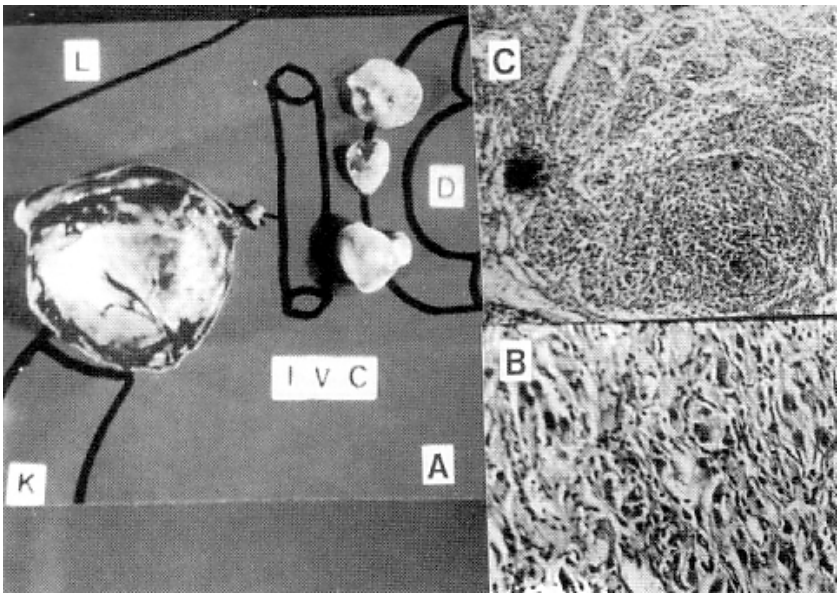

Fig (6) :

A- *Feminization in a 4-year-old female with premature thelarche and pubarche due to a left-sided adrenocortical adenoma.*

B- *Cut section of the tumor .*

C- *Histopathology of the adenoma showing no pleomorphism or atypical mitosis (H & E stain X40).*

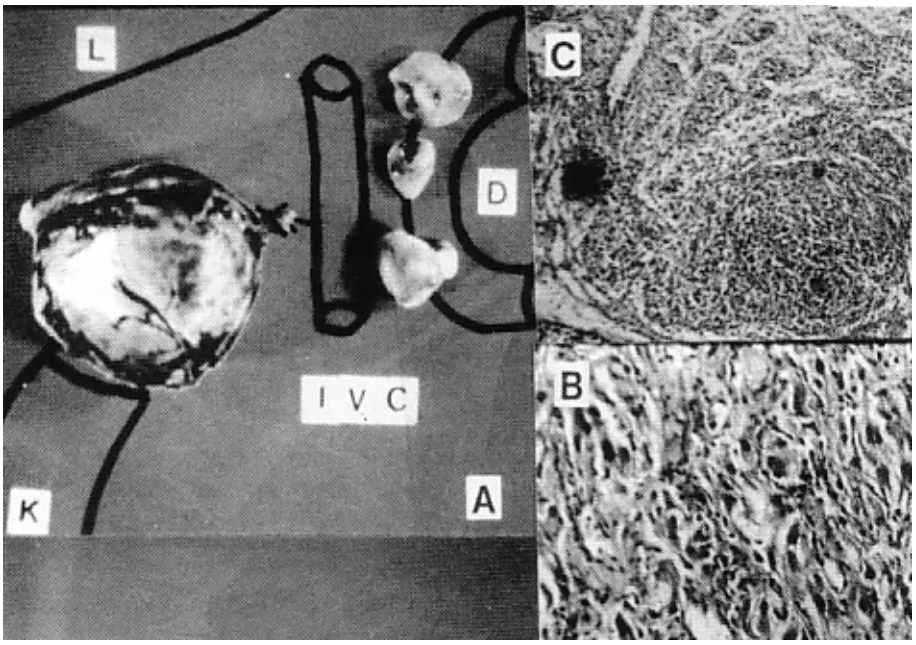

Fig (7) :

A- *Pheochromocytoma of the right adrenal gland in a male 8 ½ -year old with enlarged regional lymph nodes, (L=liver, K=kidney, IVC=inferior vena cava, D=duodenum).*

B- *Histopathology of the tumor showing clusters of polygonal cells separated by vascularized stroma (H & E stainX40).*

C- *Histopathology of the enlarged lymph nodes showing reactive hyperplasia with no malignancy. (H & E stain X100).*

PRESENTATION	*SEX*		*AGE*			*SIDE*		*PATHOLOGY*		*OUTCOME*		
	M	*F*	*0-3 Y*	*3-5Y*	*5-9 Y*	*Rt*	*Lt*	*Bening*	*Malignant*	*NED*	*Recur*	*Died*
Virilization	5	5	4	5	1	3	7	4***	6	5	1	4
Cushing's S.	1	2	1	1	1	1	2	2	1***	3	0	0
Feminization	0	1	0	1	0	0	1	1	0	1	0	0
Hypertension	2	1	0	1**	2*	3	0	2*	1**	3	0	0
Total	8	9	5	8	4	7	10	9	8	12	1	4

Table (1) *: Relation between the clinical presentations, side,sex and age distributions to the pathology and outcome.*

** Pheochromocytoma ** Ganglioneuroblastoma *** male patients*

FACTOR		*PATHOLOGY*		*OUTCOME*		
Type	Grade	Benign	Malignant	NED	Recur.	Died
Tumor's size	0 - 5 cm	6	1	6	1	0
	6 - 10 cm	3	3	5	0	1
	11 - 20 cm	0	1	0	0	1
	> 20 cm	0	3	1	0	2
Tumor's weight	0 - 100 gm	8	2	9	1	0
	100 - 250 gm	1	3	3	0	1
	250 - 1000 gm	0	2	0	0	2
	> 1000 gm	0	1	0	0	1
SEER grading	I	7	1	8	0	0
	II	2	4	4	1	1
	III	0	3	0	0	3

Table (2) : ***Relation between the tumor's size & weight and the SEER grading to the pathology and outcome.***

ITEM		*N*	*PATHOLOGY*		*OUTCOME*		
Type	Grade		Benign	Malignant	NED	Recc	Died
Nuclear grade	I	4	4	0	4	0	0
	II	5	3	2	4	0	1
	III	3	0	3	1	0	2
	IV	2	0	2	0	0	2
Mitotic rate	0 - 5	6	5	1	5	0	1
	6 - 20	7	2	5	3	1	3
	21 - 50	0	0	0	0	0	0
	> 50	1	0	1	1	0	0
Atypical mitosis	Absent	12	7	5	9	1	2
	Present	2	1	2	0	0	2
Cytoplasm	0 -25 %	12	8	6	7	1	4
	26 - 50 %	1	1	1	1	0	0
	51 - 75 %	1	0	0	1	0	0
	76 - 100 %	0	0	0	0	0	0
Tumor architecture	Diffuse	7	5	4	2	1	4
	non-diffuse	7	3	3	7	0	0
Necrosis	Absent	5	3	1	5	0	0
	Present	9	5	6	4	1	4
Capsular invasion	Absent	7	3	1	6	0	1
	Present	7	5	6	3	1	3
Invasion of venous structures	Absent	11	6	5	8	0	3
	Present	3	2	2	1	1	1
Spindling of tumor cells	Absent	10	5	5	5	1	4
	Present	4	3	2	3	0	1
Weiss grading	1	4	4	0	4	0	0
	2	0	0	0	0	0	0
	3	1	1	0	1	0	0
	4	2	2	0	2	0	0
	5	3	0	3	1	1	1
	6	1	0	1	1	0	0
	7	3	0	3	0	0	3
	8	0	0	0	0	0	0
	9	0	0	0	0	0	0

Table (3) : ***Relation between data of the Weiss Grading to the pathology and outcome.***

DISCUSSION

The first childhood case of adrenal tumor was reported in 1865. Since that time, till 1978, approximately 300 cases have been described [14]. In a 48-year review of cases at the Roswell Park Memorial Institute, USA, it was found that adrenal tumors made up only 0.04% of all cancer cases and only one case occurred in a patient younger than 20 years[15]. In a review of 141 cases of adrenal neoplasms in the pediatric population in Manchester, England over 20 years, three were pheochromocytoma and only eight were cortical tumors [16]. From May 1988 to December 1994, 67 children with adrenocortical tumors were registered on the International Registry of Childhood Adrenocortical Tumors (IRCAT), a voluntary registry including but not confined to the United States, Brazil, Canada, Uruguay, Norway, Iceland, and Chile [17]. Mendoca et al from Brazil studied 38 patients with adrenocortical neoplasms, from 1980 to 1992, 18 were children [18]. Lobo-Sanahuja et al from Costa Rica treated 11 children with adrenocortical functional tumors in a period of 20 years [19]. Londe reviewed the etiology of secondary hypertension in a series of 563 children, only 0.5% had a pheochromocytoma [20].

In accordance with previous series, the majority of the adrenocortical lesions included in the current study were younger than 5 years (n = 12/14), females were more common than males (7/12). On the other hand, medullary pheochromocytomas were affecting older males, 8.5 and 9 years [4,10,16,21,22].

The study has also confirmed the previous reports that among adrenocortical lesions in most pediatric patients, contrary to adults, there was predominance of virilization over Cushing's syndrome, 71% and 21% respectively [2,18,23]. It was observed that virilization was exclusively due to carcinoma in females and to adenoma in the majority of males. Contrary to what has been stated by many authors that Cushing's syndrome is highly indicative of malignancy in children with adrenal tumors [16,24,25,26], two of the three reported cases in this study were females having adenomas with favorable outcome.

A perceptible abdominal mass is usually noted late in the course of the disease [2]. Hassan et al reported 10 children with functional adrenal tumors, 6 had signs of virilization and 4 had signs of Cushing's syndrome, none of them presented with palpable abdominal mass [27]. In the present study, 4 patients presented with a clinically palpable mass - 3 had signs of virilization and one had signs of Cushing's syndrome, fatal outcome resulted in three.

Removal of the adrenocortical tumors was followed by rapid regression of most of the clinical signs of the disease. Acne, plethora, abnormal body hair, hypertension, and obesity usually disappeared within few weeks to few months. Phallomegally was arrested in part and the palpable acinar tissue in the breast of the feminizing tumor decreased but did not completely disappear.

Similar to the previously published series [20,22], both cases of pheochromocytoma reported in the study presented with sustained hypertension, irritability and headache that were controlled after excision of the tumors.

Although bilaterality has been recorded in pheochromocytoma of children with an incidence of 30%, up to 70% in some series [28], cortical lesions usually affect both glands equally [29]. All cortical tumors in the study were unilateral and showed no preference for side of location. Both cases of pheochromocytoma were arising from the right adrenal gland. This predominance has been reported in some series [29].

ACC is known to be a part of a familial syndrome that includes sarcomas, brain tumors, breast cancer and leukemia (30). Tsukamoto et al reported a 5 year-old boy with functioning ACC whose young family members died of cancer: osteosarcoma, hepatoblastoma and malignant lymphoma [31].

The current study has reported two female siblings, aged 5 and 6 years, presenting with severe aggressive virilizing adrenocortical carcinoma, both were affecting the left adrenal gland. One child died of progressive disease shortly after surgery while the other developed local recurrence that was re-excised and received adjuvant chemotherapy. Steiner was the first to note a sibship occurrence ,only two subsequent cases have been described with a clinical presentation similar to those reported in our study [32,33].

One intriguing observation by Hartley et al is that 4 mothers and 7 fathers of the 14 patients with ACC registered in Manchester Children's Tumor Registry had been exposed to potentially toxic substances before or during the index pregnancy [34]. Southern Brazil is a predominantly agricultural region where fertilizers, insecticides and herbicides are used indiscriminately [2]. The two sibs with ACC reported in our study were living in Fayoum, a province well known to be highly agricultural raising the possibility that the parents might have been exposed to toxic materials.

There have been few published studies regarding the steroidogenic hormonal pathways of adrenal neoplasms [12,23,35]. Testosterone and / or its precursors were elevated in all adrenocortical tumors except the single case with signs of feminization. This explains the mild signs of virilization as hirsutism seen in patients with Cushing's syndrome. Some authors described these lesions as "mixed " types [2,17].

The elevated cortisol levels in two virilizing tumors could suggest an autonomous cortisol secretion not expressed by clinical features and probably due to precocious diagnosis based on clear virilization signs and / or low cortisol secretion. The possible explanation for the increased 11-deoxycortisol secretion in 7 cases may be autonomous adrenal hormonal overproduction or in virilized tumors it may be related to testosterone induced inhibition of 11 B-hydroxylase.

Although the bone age was advanced in most of the cases associated with excessive secretion of glucocorticoid and sex hormones, yet it was normal in two cases of aggressive ACC, this may be explained by the rapid progression of the tumor in a short period of time.

Both ultrasonography and CT scan were effective in identifying the adrenal tumors, although CT scan was more accurate in estimating its size and its relation to the surrounding tissues. This is contrary to the results of Cerfolio et al who reported that CT underestimated adrenal tumors greater than 6 cm in 32% of cases and by 47% in those less than 6 cm [36]. Against to what have been stated by Adams et al that CT allows the differentiation between benign and malignant lesions [37], this study showed that CT has visualized large areas of necrosis in a tumor that proved histopathologically and with follow-up to be an adenoma and in a case of pheochromocytoma where it visualized enlarged lymph nodes labeled as sign of malignancy with metastases which proved histopathologically to be benign with favorable outcome after 4 years of follow-up.

This study also supported the conclusion of Fishman et al[38] at ACC may present as a smooth homogenous functioning mass 6 cm or less as proved in one case of ganglioneuroblastoma. Although MRI was performed only in one case, but it did not prove to be superior to CT and ultrasonography.

All patients underwent complete resection of the tumor. In most of the cases (n=14), this was achieved via the anterior transabdominal surgical approach which was mandatory in large tumors over 5 cm (n=10) for the possibility of malignancy and in a case of pheochromocytoma 3.5 cm in size for the presence of enlarged regional lymph nodes. Also in 5 cases, additional concomitant intraabdominal procedures (nephrectomy, splenectomy, colectomy…) were performed. This technique was also preferred as it allows palpation of the other adrenal gland and also due to the pneumothorax resulting with the posterior approach; a criteria supported by Newsome [39].

The posterior approach with resection of the 11 the rib was performed in two cases presenting with Cushing's syndrome as recommended by some authors due to the higher incidence of pancreatitis, wound infection and dehiscence in these cases [39,40].

The lumbar incision was performed in only one case of adenoma 2.5 cm in size. Although this technique had a short hospital stay and a very smooth convalescence, yet it had a somewhat deep exposure with some difficulty in dissection and haemostasis of the tumor.

Linos et al in a comparative study between the anterior, posterior and laparoscopic adrenalectomy concluded that the perioperative complications, the postoperative in-hospital stay and the requirements for postoperative analgesia were significantly better in the later approach. They also stated that when the adrenal tumor is larger than 5-6 cm and especially when the radiological appearance is suspicious for carcinoma, it is best to proceed immediately with the open anterior approach [6]. None of the cases in the study were operated upon laparoscopically. It was considered – as stated by most authors- that this technique needs more experience in this field and it should be reserved for small lesions [41,42].

Reports in the literature have been controversial regarding the prognosis and survival rate in patients with adrenal tumors. Because no large series of children with such lesions has been described, the clinical and biologic characteristics associated with prognosis have not been firmly established [2]. Many authors have stressed the influence of tumor size and weight over prognosis. Hassan et al stated that tumors less than 6 cm in diameter and 150 gms in weight behaved in a benign fashion while tumors more than 7 cm in size and 500 gm in weight acted in a malignant fashion [27]. Humphrey et al reported that of patients with tumors smaller than 170 gm, 74% had a 5-year survival rate compared to 36% with larger tumors [43]. In another study, all tumors weighing more than 500 gm were malignant and all but one less than 100 gm were benign [8]. Cagle et al stated that a case with a tumor size of 7.5 cm and weight of 350 gm which proved to be adrenocortical carcinoma, died one year later from recurrence [7]. Ribeiro et al have shown that the event free survival proportion decreases dramatically in patients with tumor weight more than 200 gm [2].

In the present study, although patients with small tumors had the best outcome, yet the tumor's size and weight could not have been considered as single criteria for assessment of malignancy in these lesions. Among tumors less than 5 cm (n=7), one case showed criteria of malignancy on histopathology and developed recurrence1.5 years following its excision. Lesions of less than 100 gm (n=10) included two cases that behaved as malignant. This incidence increased in tumors of less than 10 cm in diameter and 250 gm in weight. On the other hand, all tumors above these criteria had poor prognosis: out of the four patients who died after excision of the tumor, three of them had

tumor sizes more than 10 cm and weight more than 250 gm. All of them proved to be adrenocortical carcinoma.

Assessment of malignancy through histological criteria has been controversial. Several investigators reported a high degree of accuracy in the evaluation of malignancy by microscopic examination [8,9,44]. Bugg et al reported that the histological type and tumor weight were the most reliable predictors of tumor behavior in the pediatric age group [10]. Hough et al found that no single parameter separated benign from malignant adrenal tumor, but the summation of 12 histologic and non- histologic criteria enabled total separation between metastasizing and non-metastasizing tumors [45].

In a study by Weiss on 43 adrenocortical neoplasms and their analysis using nine histological criteria he found that the patient who had less than 4 criteria did not have any recurrences nor metastases whereas in those patients who had more than four criteria, there was only one tumor without metastases nor recurrence [8].In another study by Weiss et al on 53 adrenal neoplasms, they concluded that the most important of the nine histological criteria were the mitotic rates more than 20/50 HPFs, presence of atypical mitosis, capsular invasion in junction with the two non-histological criteria which were tumor more than 10 cm in diameter and weight more than 250 gm.

Mendoca et al in their comparative study of adrenocortical neoplasms in childhood and adulthood mentioned that histological analysis in the children suggested malignant evolution in 14/18 (77.7 %) but only 2 had signs of recurrence followed by death. In adults, they found that Weiss criteria were more precise than in children.They concluded that tumor size in both groups and histological features according to Weiss criteria in the pediatric group were not reliable indications of benign or malignant behavior and that the careful clinical follow-up may remain the final indicator for the diagnosis in some of these tumors [18]. This opinion was also supported by Zin-ul-Miraj et al who stated that no single test could differentiate an adrenal adenoma from carcinoma. Interestingly, tumor appearing histologically benign has been shown to recur locally, and those appearing malignant may never recur if completely excised [46].

In accordance with the previous reports, the present study showed that the tumor behavior after its total excision can not be correlated to the criteria suggestive of malignancy in its histopathologic examination. Among 7 cases that showed more than 4 criteria of Weiss, two showed favorable outcomes with no recurrence on follow-up. Although capsular invasion was present in 3 cases, they showed no recurrence after total excision of the tumor.Again,favorable outcome was noticed in 4 lesions with tissue necrosis. On the contrary, unfavorable results occurred in one case with nuclear grade I and in another case with mitotic rate less than 5 cells per 50 HPFs. In addition two patients died and another developed local recurrence without evidence of atypical mitosis on histopathologic examination of their lesions.

Analysis of DNA by flow cytometry has been suggested as promising in predicting outcome [47]. However, Cibas et al reported that ploidy alone is not a reliable discriminator of the biologic potential of adrenal tumors [48].

Radiotherapy and chemotherapy has been both condemned and advocated with, thus far, no convincing data to support either viewpoint [1].Humphrey et al reported 72 children with adrenocortical neoplasms and noted that up to the age of 7 years, there was a 5-year survival rate of 53% compared to 17% for those older than 9 years [43]. On the other hand Mendoga et al reported better prognosis for their patients – both adults and children- probably due to earlier diagnosis and the fact that their patients had smaller tumors [18]. Lee et al advocated the high incidence of deaths in the older literature might have been due to postoperative complications and inadequate steroid replacement [1]. Unfavorable outcomes in the current study resulted in 5/17 cases, four of these died after resection of the tumor and a single case developed local recurrence.

From this study, it was concluded that functional adrenal tumors are extremely rare in children specially pheochromocytoma. Virilization is the commonest presentation, which is commonly due to carcinoma in females or adenoma in males. On the contrary, Cushing' s syndrome is commonly due to carcinoma in males and adenoma in females. Palpable abdominal mass was rather uncommon and considered a late manifestation with poor prognosis. CT scan remains the standard accurate modality for their localization and during follow-up.Complete removal of the tumor is the only effective treatment, the role of adjuvant chemotherapy or radiotherapy can not be confirmed. The anterior transabdominal approach provides the best exposure especially for large tumors, although very small lesions can be removed safely through a lumbar extra abdominal approach. Laparoscopic adrenalectomy needs to be tried and evaluated in small lesions. The determination of the neoplasm's behavior by morphologic and histological criteria can often be unpredictable, even small lesions can be malignant and potentially lethal.Careful clinical follow-up may remain the final indicator for the diagnosis in some of these tumors. Early diagnosis and management are important with special care for postoperative adequate steroid replacement. A more advanced study to analyze the familial occurrence of adrenal tumors in children is needed for the possible role of exposure to toxic substances in its occurrence.

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