Original Articles

A CLINICOPATHOLOGIC PROFILE OF ADRENOCORTICAL TUMORS

P.S. Upadhye, M.P. Desai, M.P. Colaco, P.B. Desai*, R.K. Deshpande* and R.A. Mokal**

*From the Bai Jerbai Wadia Hospital for Children and Institute of Child Health & Research Center, Parel, Mumbai 400 012; *Tata Memorial Center, Dr. E. Borges Marg, Parel, Mumbai 400 012; and **Sir H.N. Medical Research Society, Raja Rammohan Roy Road, Mumbai 400 004.*

Reprint requests: Dr. (Mrs) Meena P. Desai, Honorary Consultant, B.J. Wadia Hospital for Children and Institute of Child Health and Research Center, Parel, Mumbai 400 012.

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Objective: *To study the clinical, biochemical, hormonal, radiological and histopathological profile of adrenocortical tumors in children; to assess the clinicopathological correlations and note the future outcome.* ***Design****: Retrospective and prospective study.* ***Setting****: Hospital based; Endocrine Service of our institution and other institution based services.* ***Subjects****: 14 children (Females = 11, Males = 3) with adrenocortical tumor, aged 8 months to 13 years (mean age 5.1 ± 3.42 years), seen over a period of 9 years.* ***Results:*** *Females predominated (F:M = 3.7:1). Majority (64%) had a mixed picture with cushingoid features and virilization, whereas 36% presented only for virilization. Elevated serum cortisol levels with loss of diurnal variation was noted only in those with mixed clinical presentation. Adrenal androgen elevation was noted in majority of cases as virilization was common to all. CT confirmed the diagnosis of tumor, 7 on either side. Thirteen cases were operated. Histopathologic diagnosis was carcinoma in 7 and adenoma in 6 cases. Three of the seven with carcinoma died within 3 months to 2 years but two of these with small tumours (weight 60-65 g and diameter < 6 cm) were well at 2 and 5 years, while as one of the six with a large adenoma had recurrence and metastasis after three years.* ***Conclusion:*** *Female preponderance was marked (4 times), 43% of tumors had occurred by 3 years of age and 64% by 6 years. Neither the hormonal parameters nor the histopathology correlated well with the biological behavior and outcome. Prolonged and vigilant follow up is essential.*

Keywords: *Adenoma, Adrenocortical tumor, Carcinoma, Clinicopathologic correlation, Prognosis.*

A DRENOCORTICAL tumors are rare in childhood constituting less than 1% of all pediatric neoplasms(l), with adrenocortical carcinoma comprising only 0.002% of all childhood malignancies(2). Majority of these tumors occur in the first decade with a higher prevalence below five years of age(3,4)- Congenital tumors are also described(5).

In contrast to adrenocortical tumors in adults, majority of tumors (95%) in children are hormonally active(3,6) and secrete varying amounts of glucocorticoids, mineralocorticoids and sex steroids or an excess of any one of these. Depending upon the nature and amount of the steroid secreted, these children may present with a clinical picture predominantly of Cushing's syn-

drome which is rare, or an adrenogenital syndrome (virilization), or more commonly a mixed picture(6-8). Tumors producing primary hyperaldosteronism (Conn's syndrome) or feminizing syndrome, are rare(9). Less than 5% of these tumors are hormonally nonfunctional, occur more often in males and have a grave prognosis(6,8). Asymptomatic adrenal masses detected accidentally on imaging studies are termed 'incidentaloma'; the incidence in pediatric age group is not known. In some of these cases, underlying congenital adrenal hyperplasia should be excluded(l0).

The present communication, based on our personal experience, evaluates the clinical, biochemical, hormonal, radiological, and histopathological profile of adrenocortical tumors in children.

Subjects and Methods

This study included 14 cases (F = 11, M = 3) of adrenocortical tumors between 8 months to 13 years of age who presented to our endocrine service in the past 9 years and were managed by a collaborative undertaking. Complete clinical, biochemical, hormonal, radiological evaluation and histopathological examination of the resected tumors were carried out.

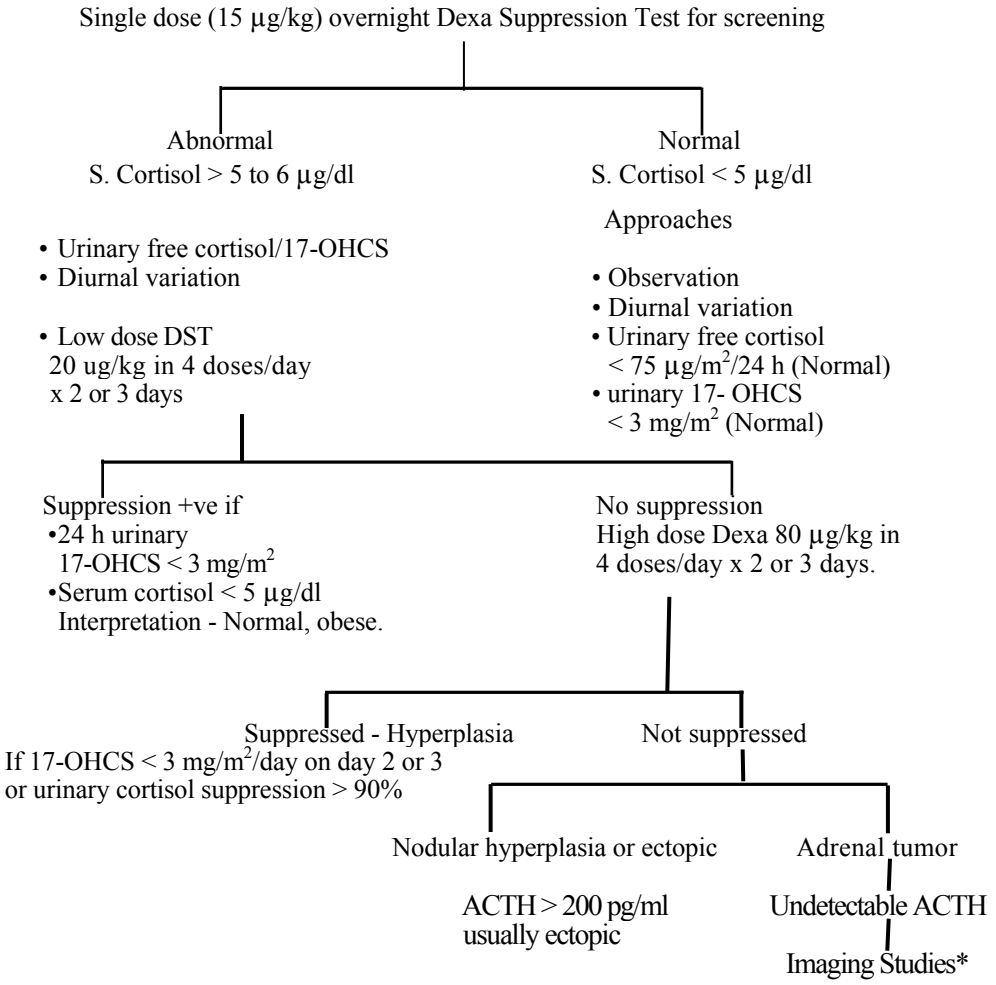
Detailed history regarding the age al onset, the nature of presenting symptoms like obesity, virilization, growth retardation, abdominal pain or distension, general weakness, recurrent infections, past medications, *etc.* was obtained. Family history of similar illness or other malignancies was noted. Clinical examination included anthropometry and evaluation for cushingoid features, hypertension, presence of congenital malformations like hemihypertrophy and signs of virilization-pseudosexual precocity in boys, and masculinization in girls. Presence or absence of abdominal mass was noted, and detailed systemic examination was carried out.

Laboratory investigations included routine blood count and biochemical parameters including blood sugar, serum electrolytes, liver and renal profiles. Standard radio-immuno-assay (RIA) kits were utilized for hormonal estimations. Hormonal parameters included the study of serum cortisol levels (8 A.M. and 10 P.M.) to demonstrate hypercortisolism and note the diurnal rhythm and estimation of adrenal androgens-dehydroepiandrosterone sulphate (DHEA-S) and androstenedione (AD). Low dose dexamethasone (20 µg/kg/day divided in four doses for 3 days) suppression test (DST) was done in 5/9 cases with a mixed picture. High dose (80 µg/kg/day divided into 4 doses for 3 days) DST was done in 3 cases as part of a routine work up, but not done in all, as clinical examination showed palpable mass in five, and imaging studies showed the presence of an adrenal tumor in all in the presence of marked elevation of serum cortisol and/or adrenal androgens. Serum aldosterone could be estimated in 5 of the 10 cases having hypertension. Serum testosterone (T) in 8 children and serum 17-hydroxyprogesterone (17-OHP) in 6 cases presenting with adrenogenital syndrome. Twenty four hours urinary 17-ketosteroids (17-KS) and 17-hydroxy-corticosteroids (17-OHCS) were estimated in 5 older children because of practical difficulties in young female patients. Urinary free cortisol could be done in only one patient.

Radiological evaluation included plain X-rays of abdomen for calcification, of the chest for metastasis, of the spine for evidence of osteoporosis, and of the hands for bone age (Greulich and Pyle Atlas). Abdominal ultrasonography (USG) and CT scan for adrenals helped in detection and localization of tumor. The usual diagnostic protocol followed is summarized in *Fig. 1.*

Thirteen of these 14 cases underwent

Fig. 1. Diagnostic protocol for hypercorticolism to establish diagnosis and differentiate the causes.



• Early CT Scan of adrenals after hypercortisolism is confirmed, abdominal mass is felt and in young children more so in females, will obviate the need for long series of tests including high dose DST. (In Cushing's disease-CRF test and inferior petrosal sinus sampling is employed in older age group)

excision of tumor with adrenalectomy while surgery was refused in one patient. Cortisol was administered both preoperatively and postoperatively as the unaffected contralateral gland is often suppressed by the large amounts of cortisol produced by the tumor. Gross as well as histopathological examination of the resected tumors was carried out.

Twelve of the fourteen cases were followed up postoperatively at one month and later at 3 to 6 monthly intervals. The follow up period ranged from 1 month to 5 years. Follow up examination involved clinical and biochemical/hormonal evaluation and repeat radiological and imaging studies as indicated. Steroid replacement therapy was administered postoperatively

for a period of 3 to 6 months or more in tapering doses and discontinued after assessing respone of the contralateral adrenal gland to ACTH stimulation.

Results

The present study involved 14 cases; 11 females and 3 male children (F:M = 3.7:1) with adrenocortical tumors. The mean age at onset of symptoms was 4.4 ± 3.44 years (range 8 months to 13 years) and at diagnosis was 5.1 ± 3.42 years, six of the 14 cases occurred by 3 years and nine by 6 years of age. The time lapse between the onset of symptoms and diagnosis was (mean ± SD) 10.7±10.3 months. Specific clinical, laboratory and histopathological data of the 14 cases reported here are summarized in *Tables I and II.* The symptoms included progressive obesity, hypertrichosis and variable degree of virilization in nine children (64%) and virilization with hypertrichosis in five (36%). Thus virilization and hypertrichosis were noted in all 14 children, while cushingoid features and hypertension (range 130-220/90-140 mm of Hg) were noted in 9 children (64%). Hypertension (BP 150/110 mm of Hg) was also noted in one female child (No. 3) presenting only for virilization. Five patients (3 carcinomas and 2 adenomas) had palpable abdominal mass. Associated congenital malformations were not seen. Virilization manifested as pseudosexual precocity in boys and as masculinization in girls. Signs of hypercorticolism included centripetal obesity, buffalo hump and moon facies in 9 children, muscle wasting, weakness and easy fatigability in 3, and increased pigmentation in 6. Growth retardation and purplish skin striae were not seen in any probably due to associated hyperandrogenism.

Serum cortisol levels were high (8 A.M., 30 to 625 µg/dl-normal 6.5 to 26µg/dl and 10 PM, 30 to 828 µg/dl (normal 2 to 8 µg/dl) with loss of diurnal variation in the 9 cases with a mixed picture of hypercortisolism with virilization. In two patients (Nos. 1 and 13), where the morning serum cortisol levels were only marginally high (30 µg/dl), the 10 PM levels were markedly elevated (35 µg/dl and 27 µ*g/dl)* respectively; 3 to 4 times more *(Table IT),* showing the importance of late evening levels in the diagnosis of hypercortisolism. In all the 5 cases presenting only for virilization, serum cortisol levels were normal (Nos. 2, 3,6,10 and 11). Demonstration of significantly high serum cortisol and/or adrenal androgen levels in presence of adrenal tumor on CT scan in all the cases favored the diagnosis of tumor related adrenocortical hyperfunction. In 5/9 cases with mixed clinical picture where low dose DST was done, there was no suppression of serum or urinary 17-OHCS. In three patients where the high dose DST was done, serum cortisol and urinary 17 OHCS remained unsuppressed.

Adrenal androgens (DHEA-S) estimated in 10 cases, were markedly elevated and ranged from 140 to 1000 µg/dl (mean ± SD - 533.3 ± 329.38 µg/dl). Androstenedione (AD) in 6 cases ranged from 1.45 to 12 µg/nl (mean ± SD - 6.87 ± 3.99 µg/ml) and serum testosterone (T) values in 8 subjects ranged between 0.95 to 14 µg/ml (mean ± SD-4.85 ± 4.48) [normal prepubertal range— DHEA-S-25 to 50 µg/dl, AD - 0.57 to 2.8 µg/ml, and T - < 1 ng/ml]. In all the children presenting only for virilization, 17-hydroxyprogesterone (17-OHP) values were normal *(Table II).* Serum aldosterone estimated in 5/10 children with hypertension ranged between 80 to 1572 pg/ml (normal 50 to 194 pg/ml) being high in 3 (609 to 1572 pg/ml). Urinary 17-ketosteroid was elevated for age (5.5 to 164.7 mg/ 24h and 17-OHCS was high (12.5 to 22 mg/ 24 h) in the five children where it was estimated.

Abdominal USG and CT scans localized unilateral adrenal tumor in all 14 cases, 7 on the right side and 7 on the left side. Calcification in the tumor was noted in 3 cases and hepatic metastasis in one.

Thirteen of the 14 patients underwent excision of the adrenal tumor while 1 patient refused operation. Histopathologic diagnosis was adrenocortical adenoma in 6 cases and carcinoma in 7 children. The adenomas were well encapsulated, firm with homogeneous consistency, without adhesions or increased vascularity with weights ranging from 30 to 75 g and the longest diameter between 2 to 6 cm in 5/6, but in one patient (No. 13) the tumor weighed 94 g and the diameter was 7 cm. The significance of this large size and weight became apparent on follow up as discussed later. There was no histopathological evidence of capsular involvement or vascular embolization; however, pleomorphism was observed in 3/6 cases (Nos. 11,12 and 13).

The adrenocortical carcinomas in 7 children were well encapsulated and appeared greyish, yellowish-brownish, of varying consistency with areas of hemorrhage and increased vascularity. In five of them, the largest diameter varied between 5 to 12 cm with weights ranging between 250 to 800 g but in two patients (Nos. 1 and 6) the tumors were smaller, weighing 60 and 65 g with diameters of 6 cm and 5 cm. The significance of this small size is discussed later. Histopathology showed areas of necrosis, hemorrhage, few mitotic figures, pleomorphism and invasion of fibrous capsule and vascular embolization. The hormonal levels of corticosteroids or adrenal androgens showed no correlation with the size and nature (adenoma/carcinoma) of the tumor *(Table II)*.

Of the 7 children with histopathologic diagnosis of adrenocortical carcinoma, 3 died, one during surgery and 2 had recurrence and metastasis in the liver, lungs and lymph nodes within 3 months to 2 years of surgical resection. All these 3 patients had palpable abdominal mass on presentation. Two patients were lost to follow up, while 2 cases (Nos. 1 and 6) with small size tumors but histopathologic diagnosis of carcinoma showed no clinical or laboratory evidence of recurrence on subsequent follow up at 2 years and 5 years, respectively.

Of the 6 children with adenoma, one was lost to follow up while 3 could be followed up for 1 year (one upto five years) and were doing well. However, one 13 years old girl (No. 13) with a mixed clinical picture, and a well encapsulated large tumor (7 cm and 94 g) did very well clinically and biochemically for 3 years but had a recurrence of tumor and later lung metastasis. These three patients (2 small size adrenocortical carcinomas and 1 large size adrenal adenoma) illustrate the relatively poor correlation of histopathology to prognosis and a probable better predictability of tumor weight and size with clinical outcome.

Discussion

Adrenocortical tumors are infrequent in the general population (about 0.2/100,000 per year) and rare in children(11). One of the first cases of adrenocortical tumor in childhood was reported in 1865(4). In a recent review of 209 children(8), the reported mean age at presentation was 4.63 years which is similar to 5.14 years in the present series. Forty three per cent presented by 3 years age and the remaining 64% by 6 years. Females clearly predominate (2.3:1) accounting for 65 to 90% of the reported cases(3,7,8,12) as also in this series (F:M = 3.7:1).

The etiology of adrenocortical tumors/ carcinoma is unknown. There are several

TABLE I- *Clinical Data of Children with Adrenocortical Tumor.*

St. No.	Sex	Age-Years		Clinical features			
		Onset	CA	Cushing	Hypertrichosis Virilization	BP	Abdominal mass
1	M	1.0	2.83	+	+	150/90	--
2*	F	4.5	5.16	--	+++	N	+
3*	F	5.0	7.50	--	+++	150/100	--
4	M	2.5	2.83	++	+	140/80	+
5	F	6.0	6.41	+	++	140/100	+
6*	F	4.6	5.00	--	++	N	--
7	F	9.5	9.66	+	++	140/100	--
8	F	4.3	4.75	++	++	160/114	--
9	M	7.0	10.00	+	+	150/100	--
10*	F	1.5	2.25	--	+++	N	--
11*	F	0.83	1.08	--	++	N	+
12	F	0.66	1.16	++	++	130/100	+
13	F	12.83	13.3	+	++	150/100	--
14	F	1.3	2.16	+	+	220/140	--

* Cases presenting for adrenogenital syndrome; remaining had a mixed picture.

TABLE II- *Laboratory and Follow Up Data of Children with Adrenocortical Tumor.*

	Hormonal profile							Tumor		Histopatho-logical diagnosis	Follow up remarks
Sr. No.	Cortisol 8 am (µg/-dl)	Cortisol 10 pm (µg/-dl)	DHEA-S (µg/-dl)	AD (ng/-ml)	T (ng/-ml)	17-OHP (ng/-ml)	Aldo-sterone (pg/ml)	Wei-ght (g)	Longest diameter (cm)		
1.	30	35	-	-	-	-	-	60	6	Carcinoma	5 yrs-Living well.
2.	13.6	-	>1000	6.2	3.8	3.6	-	800	11.5	Carcinoma	Recurrence & Meta-stasis 2 yrs-Died.
3.	12.5	-	800	12.0	2.7	0.3	1572	250	12	Carcinoma	Lost to follow up
4.	56	32	-	-	-	-	609	250	10	Carcinoma	Recurrence & Meta-statis-Died 6 mo.
5.	44	35	600	8.2	2.7	-	-	Large		Carcinoma	Died during operation.
6.	20.5	5.9	270	-	4.6	0.88		65	5	Carcinoma	2 years-Living well
7.	70.0	75	400	1.45	-	-	-	-	-	-	Refused surgery
8.	625	828	800	-	-	-	-	350	10	Carcinoma	1 mo-Lost to follow up.
9.	37	-	-	-	-	-	-	75	4.5	Adenoma	1 mo-Lost ot follow up.
10.	6.5	7	-	-	-	0.2	-	30	2	Adenoma	9 mo-Living well
11.	15	6	165		10.6	0.56		60	5	Adenoma	5 yrs-Living well.
12.	53	25	920	3.4	14	-	836.9	65	6	Adenoma	1 yr-Living well.
13.	30	27	240	>10	0.95	-	102.3	94	7	Adenoma	Normal-3 yrs, Recurre-nce & metastasis
14.	37	-	140	-	1.05	2.5	80	56	5.5	Adneoma	1 yr-Living well.

Normal levels: Serum Cortisol (8 am = 6.5 - 26 µg/dl, 10pm = 2-8 µg/dl); DHEA-S (Prepubertal range = 25-50 µg/dl); AD (Androstenedione) - (0.57-2.8 ng/ml); T (Testosterone) - (Prepubertal < 1 ng/ml); 17-OHP - (0.5 - 2.5 ng/ml); S.aldosterone - (50 -194 pg/ml in supine position)

reports of adrenocortical tumors arising 3 to 36 years after an initial diagnosis of congenital adrenal hyperplasia (CAH)(3,13,14) which may predispose to this condition. However, adrenal carcinoma is more likely to arise *de novo* rather than from a pre-existing adenoma(15). Heredity probably plays a part as adrenal tumors occur in siblings(16), and a high familial incidence of other malignancies is also known(12). A high frequency of associated congenital anomalies like hemihypertrophy, Beckwith-Wiedemann syndrome, hamartomas, cerebral gigantism and other tumors are described in association with adrenocortical carcinoma(16,17). These abnormalities or antecedent CAH were not seen in the present series. Adrenal adenoma in a 5 years old patient with CAH has been recently reported from India(18).

In the present study, 9 children (64%) presented with signs of hypergluco-corticolism and virilization, while 5 children (36%) presented as adrenogenital syndrome. Thus virilization and hypertrichosis were noted in all. Hypertension was noted in 71.4% of the cases. Isolated Cushing's syndrome was not encountered in this series. As in other series, a mixed picture predominated. In a review of 222 cases in childhood, two thirds had virilization as a preponderant sign and one third had hypercortisolism(7). In childhood, retarded growth rate, muscle wasting and skin striae characteristic of excess glucocorticoid secretion are often masked by concomitant effects of androgen secretion(4). Truncal obesity may be seen in older children but infants tend to exhibit generalized obesity(3). Five of these 14 cases had palpable abdominal mass at presentation which is often indicative of a poorer outcome. Approximately 50% of the malignant adrenocortical tumors secrete biosynthetic precursors with diminished bioactivity, hence diagnosis is often delayed -till these assume a large size(11).

The diagnosis of Cushing's syndrome is usually confirmed by the demonstration of serum and urinary hypercortisolism, the loss of diurnal variation and the lack of suppression of serum cortisol and 24 hours urinary 17-OHCS or free cortisol with low dose dexamethasone suppression test (DST). The high dose DST test demonstrating lack of suppression of plasma and urinary cortisol and 17-OHCS, favor the possibility of adrenal tumor as the source of hypercortisolism. Marked elevation of serum androgens (DHEA-S and AD) with excess of 24 hours urinary 17 ketosteroids which are similarly non-suppressible favor the presence of a virilizing tumor. More often a mixed pattern of cortisol and androgen elevation is noted. Serum testosterone elevation often results from peripheral conversion of adrenal androgens, rather than adrenal over-production. Autonomous ACTH independent steroidogenesis is a characteristic feature of adrenal tumors. Hormonal studies do not differentiate adrenocortical adenoma from carcinoma(3) though the later may secrete more of precursor steroids(11).

The serum cortisol levels were significantly elevated with loss of diurnal variation in all the 9 cases presenting with a mixed picture of cushingoid features and virilization, but were normal in 5 children with adrenogenital syndrome. Adrenal androgens-DHEA-S, AD and testosterone were markedly elevated for age in presence of virilizing features. Normal 17-OHP values in children with predominant virilizing features excluded antecedent 21-hydroxylase deficiency. Serum aldosterone was elevated in 3/10 children with hypertension. Hypertension in cushing's syndrome may be due to glucocorticoid excess with or without any excess of aldosterone secretion.

In general, virilizing tumors without hypercortisolism tend to have a low degree of malignancy. In the present series no specific correlation of the hormonal profile with tumor size or tumor type (adenoma or carcinoma) was evident. Very high levels of adrenal androgens or urinary 17 KS are described with malignant tumors. However, these do not necessarily distinguish between benign and malignant adrenal neoplasms(3).

Imaging studies help in confirming the presence and locating the site, size and the spread of the adrenal tumor. In the younger age group, particularly in presence of a mixed clinical picture which is the commonest, once a state of hypercortisolism is confirmed by initial testing and hyperandrogenism due to CAH is excluded in those with adrenogenital syndrome by appropriate tests (*e.g.,* 17-OHP or 11-deoxycortisol, if possible) imaging studies can take a precedence over the high dose DST so that diagnostic delays can be avoided. With improved technology, CT has demonstrated unequivocal diagnostic superiority over USG in imaging the adrenal gland(19). Tumors as small as 0.5 cm have been detected(19) and CT can reliably delineate lesions larger than 1 cm, although the lack of retroperitoneal fat in children may make detection of smaller tumors difficult(3). MRI holds considerable promise and in future may help in distinguishing benign from malignant lesions(3). Both left as well as right sided prevalence of adrenal tumors is reported(12) though the present series showed equal distribution. Bilaterality has been reported in 2 to 10% of cases(5).

Surgery is the cornerstone and remains the mainstay of successful treatment of adrenocortical carcinomas(17). Radical excision with enbloc resection of any local invasion offers the best chance for cure and long term survival(17). Adjuvant therapy, both radiation as well as chemotherapy, have been disappointing. In the present series, the tumor could be resected successfully in all except one with intraoperative death. One refused surgery. Histopathologically 7 had carcinoma and 6 had adenomas.

Adrenocortical adenomas tend to be less than 100 g(3), while as carcinomas are variously stated to weigh more than 200 to 500 g or greater than 0.7 g/100 g of body weight in infants and small children(3,7). Many authors have noted a strong correlation between adrenal tumor size and malignancy, stating that 92% of symptomatic adrenal carcinomas are larger than 6 cm in diameter whereas only 0.025% of adrenal adenomas exceed 6 cm in diameter(20). The histopathologic correlation with the prognosis is relatively poor.

Inspite of all the criteria laid down, years of experience and observations have shown that distinction between benign and malignant tumors of the adrenal cortex remains difficult. As there are no absolute clinical, biological, anatomical, hormonal or even histopathological criteria, the benign or malignant nature of a localized tumor cannot always be strictly asserted nor the future malignant potential can be predicted(11). Some patients where tumors exhibited histologically benign features have had late metastases or local recurrence(15), whereas others whose tumor had a microscopic appearance typical of malignancy have survived for years(15,21). Despite these apparent contradictions some generalizations have been made(3,15). Earlier, as well as recent studies, have concluded that tumor size seems to remain the only consistently reliable morphologic predictor of malignant behavior(15). All fatal tumors have had a large size(3). This was well exemplified in one of our cases with a well

circumscribed encapsulated, resectable tumor (7 cm in diameter and weighing 94 g) o labelled as adenoma histopathologically, who finally had a local recurrence and lung metastasis. The two patients with tumor size and tumour weight not exceeding 6 cm and 65 g, respectively but with histopathologic diagnosis of adrenocortical carcinoma, behaved like adenoma, showing no clinical or laboratory evidence of recurrence over the period of follow up. Thus pediatricians and parents need to know about the guarded prognosis, and the need for continued diligent surveillance and prolonged follow up, as apparent early remission may be complicated by delayed recurrence.

Adrenal carcinomas have a very poor prognosis, with a mean survival in 50% at 2 years and 20% at 5 years(11). In a review of 222 children with functional adrenocortical tumors, there were only 23 survivors at 2 years(7). Although OP'DDD and chemotherapy have been reported to have some effect on tumor reduction, no therapeutic agent or regimen has been really successful(11). In addition to the tumor's inherently aggressive nature, poor survival has been attributed to delay in diagnosis. The rarity of the disease further compromises attempts to establish accurate survival figures in children.

Beyond a few case reports, there is a distinct paucity of reported data on adrenal tumors in Indian children(18,22-25). Awareness about the occurrence of this uncommon tumor often with a dramatic onset, early diagnosis, and prompt surgical intervention are the only means to salvage these patients with a probable malignant potential, while adjuvant therapy continues to evolve to ensure better outcome in future.

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REFERENCES

1. Morales L, Rovira J, Rotterman M, Julia V. Adrenocortical tumors in childhood: A report of four cases. J Pediatr Surg 1989; 24: 276-281.
2. Young JL, Miller RW. Incidence of malignant tumors in U.S. children J Pediatr 1975; 86: 254-258.
3. Randy M, Chudler MD, Robert Kay MD Adrenocortical carcinoma in children. Urol Clin North Am 1989; 16: 469-479.
4. Lee PDK, Winter RJ, Green OC. Virilizing adrenocortical tumors in childhood: Eight cases and a review of the literature. Pediatrics 1985; 76: 437-444.
5. Artigas JR, Niclewicz ED, Silva APG, Ribas DB, Athayde SL. Congential adrenal cortical carcinoma. J Pediatr Surg 1976; 11: 247-252.
6. Weatherby RP, Carney JA. Pathologic features of childhood adrenocortical tumors. *In:* Adrenal and Endocrine Tumors in Children. Eds Humpherey GB, Grindey GB, Dehner LP, Mosby C Bostan, Martinus, Nijhoff, 1983; pp 53-72.
7. Hayles AB, Hahn HB, Sprague RG, Bahn RC, Priestly JT. Hormone-secreting tumors of the adrenal cortex in children. Pediatrics 1966; 37:19-25.
8. Neblett WW, Frexes-Steed M, Scott HW. Experience with adrenocortical neoplasms in childhood. Am Surg 1987; 53: 117-125.
9. Me Kenna TJ, O'Connel Y, Cunningham S, McCabe M, Culliton M. Steroidogenesjs

in an estrogen producing adrenal tumor 16 in a young woman: Comparison with steroid profiles associated with cortisol and androgen-producing tumors. J Clin Endocrinol Metab 1990; 70: 28-34.

10. Lighter ES. The adrenal incidentaloma-A pediatric perspective. Am J Dis child 1993; 147:1274-1276.

11. Gicquel C, Bertagna X, Le Bouc Y. Recent advances in the pathogenesis of adrenocortical tumors. Europ J Endocrinol 1995;133: 133-144.

12. Stewart DR, Jones PH, Jolleys A. Carcinoma of the adrenal gland in children. J Pediatr Surg 1974; 9: 59-67.

13. Pang S, Becker D, Cotelingham J, Foley TP, Drash AL. Adrenocortical tumor in a 21 patient with congential adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics 1981; 68: 242-246.

14. Bauman A, Bauman CG. Virilizing 22 adrenocortical carcinoma: Development in a patient with salt losing congenital adrenal hyperplasia. JAMA 1982; 248: 3140-3141.

15. Tang CK, Gray GF. Adrenocortical neo plasms: Prognosis and morphology. Urology 1975; 5: 691-695.

16. Fraumeni JF, Miller RW. Adrenocortical neoplasms with hemihypertrophy, brain tumors and other disorders. J Pediatr 1967; 70:129-138.

17. Kay R, Schumacher OP, Tank ES. Adrenocortical carcinoma in children. J Urol 1983; 130: 1130-1132.

18. Bhatia V, Shukla R, Mishra SK, Gupta RK. Adrenal tumor complicating untreated 21-hydroxylase deficiency in a $5^{1/2}$ year-old boy. Am J Dis Child 1993; 147: 1321-1323.

19. Abrams HL, Siegelman SS, Adams DF, Sanders R, Finberg HJ, Hessel SJ. Computed tomography versus ultrasound of the adrenal gland: A prospective study. Radiology 1982; 143:121-128.

20. Gussain S, Belldegrun A, Seltzer S, Richie JP, Gittes RF, Abrams HL. Differentiation of malignant from benign adrenal massess: Predictive indices on computed tomography. Am J Roentgenol 1985; 144: 61-65.

21. Van Slooten H, Schaberg A, Smeenk D, Moolenar AJ. Morphologic characteristics of benign and malignant adrenocortical tumors. Cancer 1985; 55: 766-773.

22. Desai MP, Colaco MP, Merchant SM. Cushing's syndrome in childhood. Indian J Pediatr 1982; 49: 457-460.

23. Garg S, Marwaha RK, Pathak IC, Dash RJ. Virilizing adrenocortical carcinoma with Cushing's syndrome in a 14 months old child. Indian J Pediatr 1984; 51: 497-500.

24. Sarda AK, Bal S, Kapur MM. Virilizing adrenocortical tumor. Indian Pediatr 1988; 25: 793-795.

25. Sanyal KS. Bajaj P, Thaper M, Hari MK, Ayyar RD, Vaishnava S, Cushing's syndrome due to adrenocortical carcinoma. Indian Pediatr 1968; 5:164-169.