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Adrenocortical Tumors

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Epidemiology

Approximately 5%-15% of autopsies conducted in the adult population harbor silent adrenal masses[1] , however, adrenocortical tumors (ACTs) are rare in children and adolescents. In older literature, over half of ACTs in children are diagnosed at > 3 years of age and 80% of cases occur in children < 8 years of age with a female to male ratio of approximately 3:1.[2] A descriptive analysis of 254 pts registered on the International Pediatric Adrenocortical Tumor Registry, spanning a period of 11 years, showed a median age of 3.2 years with a female to male ratio of 1.6:1. 228 (90%) were carcinomas and only 26 (10%) were adenomas.[3] Liou and Kay[4] reviewed the pediatric series of adrenocortical tumors from 1966-1999 and reported a median age of 4 years and female to male ratio of 2:1. Data from the National Cancer Insitute's Surveillance Epidemiology and End Results (SEER)[5] monograph gives an average annual incidence of adrenal carcinoma in children under the age of 9 of 0.25 per million.

Physiology of the Adrenal Glands

The adrenal gland weighs approximately 3-7 grams. Each adrenal gland contains an outer cortex and inner medulla. The adrenal cortex has three distinct zones:the zona glomerulosa, zona fasciculata and zona reticularis. The peripheral zone, or zona glomerulosa secrete mineralocorticoids, a function controlled by the renin-aldosterone system. Glucocorticoids are secreted by the zona fasciculata, and the sex steroids (androgens, progesterones ,estrogens) are secreted by the inner most zone, the zona reticularis. These two zones are regulated by adrenocorticotrophic hormone ACTH which is released by the anterior pituitary gland.

Mineralocorticoids control the volume and ion content of the extracellular and intracellular fluids. The mineralocorticoid aldosterone controls the reabsoprtion of sodium and excretion of potassium in the urine. Aldosterone hypersecretion produces hypertension, hypokalemia and metabolic alkalosis also known as Conn's syndrome.

Glucocorticoids control carbohydrate metabolism and the immune system. Virtually all cells of the body harbor glucocorticoid receptors. The major glucocorticoid is cortisol which acts my increasing and maintaining glucose levels in the blood by several processes. It also has potent anti-inflammatory and immunosuppressive properties. In Cushing's syndrome or hyperadrenocorticism, the symptoms include hypertension, muscle wasting, obesity and disordered glucose metabolism.

The sex steroids are responsible for primary and secondary sex chracteristics. An excess of androgens in females causes virilization and precocious puberty in the male. Hyperestrogenism causes feminization and hypogonadism in boys and precocious pubery in girls.

Tumors of the adrenal cortex can be classified as functional and non-functional tumors depending on the secretion of adrenocortical hormones. The International Pediatric Adrenocortical Tumor Registry showed that virilization is the most common presentation in 84.2% of patients.[3] In 10% of patients, there are no clinical features of hormone hypersecretion. Only 5.5% of patients show overproduction of glucocorticoids alone with Cushing's syndrome. A smaller case series from Canada show similar clinical distribution.[6]

Molecular Basis and Clinical Phenotypes

Chromosomal markers identified in several syndromes have led to the discovery of genes responsible for tumor growth or suppression, production of growth factors, cytokines and the aberrant expression of receptors by adrenal tumor cells. Table 1 summarizes the genes, chromosome loci and the clinical phenotypes associated with certain tumor types. Several molecular markers have been associated with carcinomas notably LOH in chromosomes 2, 4, 11, 17, and 18.[7,8] Loss of heterozygosity on the short arms of chromosome 11 (*p57*, *Menin*), chromosome 17 (*p53*), and chromosome 18 (*MC2R*), involve losses in tumor suppressor gene. Overexpression of insulin growth factor II which maps to 11p15 is seen in Beckwith-Wiedemann syndrome which predisposes

to adrenocortical tumors. Chromosome gains on chromosome 9q34 have also been described adrenal carcinomas. Hybrid genes like *CYP11B1/CYP11B2* on chromosome 8 fuses the promoter of 11-*B*-hydoxylase with aldosterone synthase resulting in familial hyperaldosteronism type 1. Adrenal tumors with somatic mutations on chromosome 20 involving the *Gsá* gene have been described in McCune Albright syndrome.

Table 1. Clinical and Molecular Features of Benign and Malignant Adrenocortical Neoplasms

Tumor Type	Clinical Symptoms	Genes	Chromosome
Benign adenoma			
Non functional	**none**	**none**	**none**
Aldosterone-producing	Hypertension, hypokalemia acidosis	*ATR 1* *CYP1 B1/CYP1 1B2*	3q21-q25 8q24-tel
Cortisol-producing	Cushing syndrome with central obesity, moon facies, hypertension, hyperglycemia	*MC2R* *Gsá* *Giá*	18p11.2 20q13.2 3p21
Virilizing	Hirsuitism, pseudoprecocious puberty	none	none
Malignant			
Adrenocortical carcinoma	Combined hormone excess, Cushing syndrome, and hirsuitism in 50-60% of patients, abdominal mass, weight loss, metastases	*IGF-II* *p57 (KIP2)* *p53* none	11p15.5 11p15 17p13 9q34
Familial			
MEN type 1	Hyperparathyroidism, *Menin* neuroendocrine features, gut tumors, pituitary adnomas	11q13	
Congenital adrenal hyperplasia	Female and male pseudo-hermaphroditism, cortisol deficiency, mineralocorticoid deficiency or excess	*CYP21B* *CYP11B1*	6p21 8q24-tel
Carney complex	Primary pigmented nodular adrenocortical disease (atrial myxomas, swannomas, lentigines, blue nevi of the skin or mucosa)	none	2p16 17q23-24
Li-Fraumeni syndrome	Familial susceptibility to a variety of cancers, including breast and adrenal cancers, gliomas, sarcomas	p53	17p13
Mccune-albright syndrome	Fibrous dysplasia of bone, pigmentation of skin, precocious puberty	*Gsá*	20q13.2
Wiedemann-Beckwith syndrome	Neonatal macrosomia, macroglossia, midline abdominal wall defects, omphalocoele hypoglycaemia	*IGF-II/11q15,others*	11p15

**Adapted from Stratakis CA Molecular genetics of adrenocrotical tumors, pp 761-764. In: Bornstein SR, moderator, Adrenocortical tumors:recent advances in basic concepts and clinical management. Ann Intern Med 1999;130:759-771.*

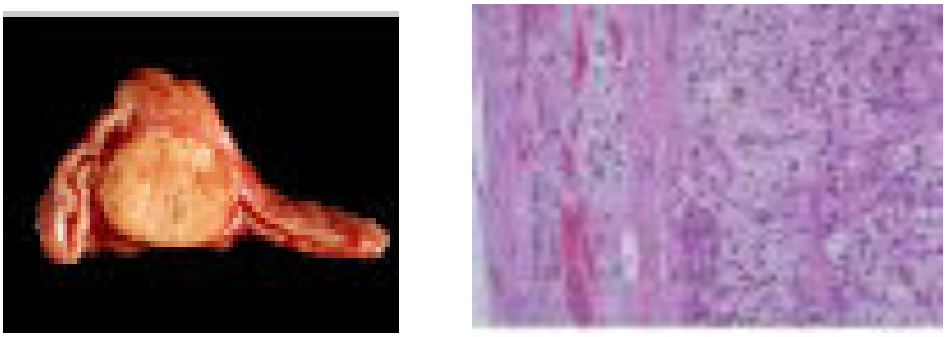
Other mechanisms have been described in tumor formation and one or several mechanisms may be operant in any tumor type. These include inhibition of senescence and/or apoptosis involving telomerase, *BCL*-2 and *BAX* genes, aberrant and ectopic expression of receptors to normal adrenocortical hormones and ligands, and the influence of atypical trophic factors and ligands such as cytokines, growth factors and neurotransmitters.[8,9]

Adrenocortical Adenomas

Approximately 10%-15% of adrenocortical tumors are adenomas. Adrenocortical adenomas may be functional or non-functional. Non-functioning non-malignant adenomas are common in adolescents and young adults and increases with age. Histologically, adenomas have a well-defined capsule with ovoid or polygonal cells with eosinophilic cytoplasm with no evidence of necrosis.[10] The adjacent cortex can be compressed and atrophic. Tumors that cause hyperaldosteronism (Conn's syndrome) are usually small (2-3 cm) and weigh = 6g (Fig. 1). Adenomas in Cushing's syndrome usually weigh = 50 gm, are well-circumscribed and yellow-yellow-brown.

Virilizing and feminizing adenomas are often large, ranging in weight from 175-2000 g and often have small compact cells with prominent eosinophilic cytoplasm.

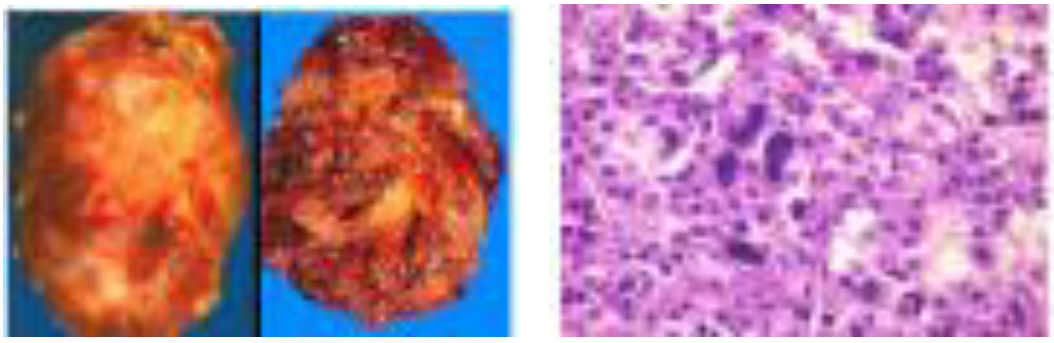
Fig. 1. Adrenal adenoma. (a) 1.3 cm yellow, well-demarcated solitary mass of adrenal cortex. (b) lesion on the right is separated from the normal gland on the left by a distinct capsule



Adrenocortical Carcinomas

It is vitally important for the pathologist to distinguish between a benign or malignant adrenal mass. Adrenal carcinomas are large tumors (Fig 2) and several investigators have shown correlation between tumor size, potential for malignant transformation and prognosis.[3,6,8,12,13] The following microscopic criteria have been unanimously advocated by investigtors: high nuclear grade II or IV, mitotic rate > 5 per 50 high-power fields, diffuse architecture, spindling of tumor cells, necrosis, capsular invasion, and vascular invasion.[11] They typically metastasize to the retropeitoneum, adjacent kidney and blood-borne metastases are found in the liver, lymph nodes, lungs, pleural and peritoneal surfaces, and bone. Tumor weight greater than 100g, tumor size greater than 200 cm^3 , age greater than or equal to 3.5 years at diagnosis, interval of greater than or equal to 6 months between first symptoms and diagnosis, high levels of urinary 17-ketosteroids, and 17-hydroxycorticosteroids have been associated with unfavorable outcome.[12] Clinically, children with Beckwith-Wiedermann syndrome with hemihypertrophy, Li-Fraumeni syndrome, Multiple Endocrine Neoplasia type 1 (MEN-1), Carney Complex and McCune-Albright syndrome have an increased risk of developing carcinoma of the adrenal cortex. Children who present with virilizing as well as feminizing tumors must always be suspected of having a malignant tumor.

Fig. 2. Adrenal carcinoma. (a) surface of a large 14 x 7 cm adrenal carcinoma, yellow-pink-tan color, hemorrhagic with some cystic changes. (b) bizarre cells with large hyperchromatic nuclei



Diagnostic Evaluation

The child who presents with virilization or Cushing's syndrome must be evaluated for the presence of a hormone-secreting adrenal tumor. This diagnosis usually begins with imaging procedures to define extent of disease, stage, invasion of adjacent organs and major vessels for surgical planning and treatment. The first modality of choice for children is usually ultrasonography followed by CT scanning or MRI. Adrenal masses as small as 10 mm can be reliably detected by CT although the relative lack of retroperitoneal fat in children might decrease the sensitivity of the test. More recently, whole body positron-emission tomographic (PET) imaging

has shown utility in detecting distant metastases not picked up on CT or MR scans or when biochemical studies for tumor are negative.[14,15]

An endocrine work-up is mandatory for all children suspected to have an adrenal tumor Plasma hormone levels are useful tumor markers after complete surgical resection to monitor disease recurrence or progression. Laboratory studies include serum glucose, plasma androgens and estrogens, 24-hour urinary free cortisol, urinary aldosterone,and urinary 17-ketosteroids.[7] Levels of 18-hydroxycorticosterone are elevated in aldosterone-producing adenomas and lower in patients with idiopathic hyperaldosteronism. A screening test for cortisol-producing adenoma is the single dose (1 mg) overnight dexamethasone suppression test. Virilization and hypercortisolism usually resolve in weeks or months after surgical resection. A modified staging classification has been proposed by the Children's Oncology Group which takes into account size, surgical resection and hormone activity of the tumor.[18]

Treatment and Prognosis

The mainstay for all ACTs is surgical resection. The transabdominal approach allows for en bloc resection of the kidney and other adjacent structures in locally invasive tumors. Even in large tumors, it is possible to effect a complete excision with tumors weighing more than 250 g (4-750 g).[6] Other surgical techniques have been developed including retroperitoneal laparoscopic adrenalectomy, needlescopic surgery using laparoscopic instruments no larger than 3 mm in diameter, interstitial adrenal cryoablation and robotic telepresent adrenalectomy.[15,16] In the case of unresectable, metastatic, or recurrent disease, chemotherapy has been tried with some success in adults using mitotane. It has not been systematically studied in children. Mitotane (o,p'DDD) is an adrenocytolytic agent that dramatically decreases the production of adrenocortical hormone and induces cortical necrosis. It is used to treat metastatic disease prior to surgery at high doses of 6-10 g daily, as adjuvant chemotherapy in high-risk patients and to control symptoms associated with hormone excess.[17] At high doses, side effects may be severe which include include nausea, vomiting, anorexia, diarrhea, somnolence, mental confusion, ataxia, blurred vision, headaches, renal and hepatic dysfunction. Lower dose between 2-3 g/day for longer periods up to 40 months have been tried with manageable side effects.[18] Mayer[6] and collegues have used combination chemotherapy using 5-flurouracil, folic acid, interferon and o,p'DDD for metastatic disease. Another patient was treated with cyclophosphamide, actinomycin-D and vincristine. Currently, patients histologically proven adrenocortical carcinomas are eligible to enroll in the Children's Oncology Group (COG) phase III trial using mitotane administered in conjunction with cisplatinum, etoposide and doxorubicin. (Table 4)

Analysis of data from the International Pediatric Tumor Registry has given us valuable information on clinical as well as biologic factors influencing prognosis. The median follow-up was 2 years and 5 months with 157 of 254 patients (61.8%) surviving with no evidence of disease. Overall survival at 5 years is 54%. Small completely resected tumors measuring less than 5-10 cm, or weighing less than 100-200g have an excellent prognosis. No treatment other than surgery is required and the 5-year event free survival (EFS) for this group of patients is 91%. The other factors associated with good prognosis are age less than 4 years, virilization alone, and absence of tumor spillage at the time of surgery. Patients with Cushing's syndrome with or without other endocrine syndromes as well as nonfunctional tumors fared worse. Completely resected large tumors confer an intermediate prognosis. Patients with microscopic or metastatic disease fared worst with a 20% 5-yr EFS. In other series, with aggressive surgery, it is possible to extend survival (range 9 months to 15 years).[6]

Summary

Adrenocortical tumors are rare in children. Its true incidence may be underestimated but the annual incidence in the United States has been estimated at 0.2 cases per million. Several constitutional chromosomal aberrations have been described that explain the pathogenesis of these tumors. Constitutional p53 mutation is the most common reported finding in young children. The majority of children have functioning tumors and the most common symptoms are virilization and excess secretion of cortisol resulting in Cushing syndrome.

50%-60% of patients present with large tumors and with regional or metastatic involvement. Currently, the prognosis is grim for children with unresectable or metastatic tumors, hence, the mainstay of therapy has been complete surgical resection with care to avoid tumor spillage. Multi-agent chemotherapy is currently reserved for this subset of patients. Children with ACTs and other rare tumors must be encouraged to enroll in cooperative international trials to gain better insight into the biology of this tumor, determine the best treatment options and pave the way for the development of novel agents against oncogenic targets.

Table 4. Phase III Study of Neoadjuvant and Adjuvant Cisplatin-Based Chemotherapy and/or Surgical Resection in Young Patients with Stage I-IV Adrenocortical Tumor

Stage I: Pts undergo primary tumore resection, retroperitoneal lymph node sampling followed by observation.

Stage II: Pts undergo primary tumor resection and extended regional lymph node dissection followed by observation. Pts who have undergone prior surgery with simple resection of the primary tumor should undergo exploratory surgery with extended regional lymph node dissection followed by observation.

Stage III or IV Disease:
Induction chemotherapy (2-4 courses every 21 days in the absence of disease progression)

Mitotane	Days 1-21
Cisplatinum	Days 1-2
VP 16	Days 1-3
Doxorubicin	Days 4-5
GCSF	Day 6

Pts with stable disease or partial response proceeds. Pts with complete response proceed directly to continuation chemotherapy.

Surgery: Pts with stage III disease undergo extended surgery and regional lymph node dissection . Pts with Stage IV disease undergo primary tumor resection (if feasible) with regional lymph node dissection and resection of metastases. Pts then go to continuation chemotherapy

Continuation chemotherapy: Chemotherapy as in induction for 4-6 courses followed by mitotane alone for 2 months. Pts with stage IV disease proceed to additional surgery when feasible.

Additional surgery: Pts with Stage IV disease can undergo additional primary tumor resection with regional lymph node dissection and re-resection of metastasis.

After completion of chemotherapy, pts are followed periodically for at least 5 years.

Table 3. Staging of Adrenocortical Tumors

Stage I	Completely resected tumor (< 100 g and < 200 cm^3) with normal postoperative hormone level
Stage II	Completely resected large tumors (= 100 g or = 200 cm^3) with normal postoperative hormone level
Stage III	Unresectable gross or microscopic residual disease Tumor spillage Patients with Stage I and II tumors who fail to normalize hormone levels after surgery Patients with retroperitoneal lymph node involvement
Stage IV	Presence of distant metastasis

**Adapted from the Children's Oncology Group[19]*

Table 2. Comparison of Pediatric Adrenocortical Tumor Series

Study	Number of Patients	Median Age ©	F:M Years
Hayles *et al* USA, 1966	12	3	11:1
Kenney *et al* USA, 1968	8	3.5	6:2
Burrington and Stephens Canada, 1969	8	2.3	7:1
Zaitoon and Mackie Canada, 1978	7	3	6:1
Lee *et al* USA,1985	8	3.8	5:3
Cagle *et al* USA,1986	23	5.5	19:4
Cacciari *et al* Italy, 1986	9	5	3:6
Hartley *et al* England, 1987	14	3.8	12:2
Ribeiro *et al* Brazil, 1990	40	3.9	28:12
Lack *et al* USA,1992	30	5	18:12
Sabbaga *et al* Brazil, 1993	55	5	42:13
Federici *et al* Italy, 1994	12	5	7:5
Mendoca *et al* Brazil, 1995	18	2.4	13:5
Bergada *et al* Argentina, 1996	20	7	15:5
Mayer *et al* Canada, 1997	11	7	8:3
Sandrini *et al* Brazil, 1997	58	4.3	41:17
Driver *et al* England, 1998	18	5.6	15:3
Teinturier *et al* France, 1999	54	4	27:27

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