

Adrenocortical carcinoma¹

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Abstract

ACC is a cancer that arises from the adrenal cortex, the outer layer of the adrenal gland. It comprises 0.2% of childhood malignancies with an international incidence of 0.5/1 million and occurs far more commonly in girls than boys (ratio 1.5:1). There is an increased incidence of ACC in patients with isolated hemihypertrophy, Wiedemann-Beckwith syndrom , congenital adrenal hyperplasia (CAH) and Li-Fraumeni syndrome (LFS). Most ACC in children and adolescents are hormone secreting and the clinical presentation reflects the pattern of adrenocortical hormones secreted by that tumor. Signs and symptoms of virilisation are present in over 90% of cases. Hirsutism, acne and deepening of the voice may be apparent in both sexes. Girls may also present with cliteromegaly and facial hair while boys present with phallomegaly and virilisation. Cushing's syndrome occurs in a third of cases with moon facies, centripetal fat distribution and plethora being the most common sign. Diagnosis is based on urine and blood tests, dexamethasone suppression test, abdominal ultrasound, CT and MRI scans. Complete, radical surgical resection is the treatment of choice and may be curative, especially in small tumors. In patients with incomplete resection or metastatic spread, treatment options include chemotherapy and/or Mitotane.

Key-words

Childhood malignancies, adrenal gland, adrenocortical hormones, chemotherapy, Mitotane

Disease name and synonyms

- Adrenocortical carcinoma (ACC)
- Adrenocortical tumors (ACT)

Definition

ACC is a cancer, which originates in the adrenal cortex. The adrenal cortex arises from

mesenchyme and at term the 'fetal' cortex represents about 80% of the adrenal gland. Within a few days there is rapid involution by apoptosis with little cortex remaining by 6 months of age.

Clinical Presentation

Most ACC in children and adolescents are hormone secreting and the clinical presentation reflects the pattern of adrenocortical hormones secreted by that tumor. Less than 10% of adrenocortical tumors are non-secreting [1]. Signs and symptoms of virilisation are present in over 90% of cases [Table 1]. Hirsutism, acne and deepening of the voice may be apparent in both sexes. The development of acne in a child under 6 years should make the exclusion of ACC a priority. Girls may also present with cliteromegaly and facial hair while boys present with phallomegaly and virilisation. Cushing's syndrome occurs in a third of cases with moon facies, centripetal fat distribution and plethora being the most common sign. Hypertension is often present and children may present in hypertensive crisis [Table 1]. Generally, ACT are inefficient in producing active hormones such as cortisol and about half will be large enough to palpate at diagnosis. In a recent retrospective study of 54 children with an ACT referred to a regional center, 60% had endocrine symptoms, virilisation, and 40% with an abdominal mass [1]. Careful examination of this cohort revealed endocrine signs and symptoms in 81% [1]. There is often a considerable delay between presentation with endocrine dysfunction and diagnosis [1, 2, 3]. In one large series only 11% of the patients were diagnosed within 6 months of their initial presentation [1].

Table 1: Clinical manifestations of ACT in children [1, 2, 4]

Premature/ Secondary Sexual Hair	90%
Cliteromegaly	92%
Phallomegaly	81%
Hirsutism	62.5%
Palpable Abdominal Mass	61%
Hypertension	54%
Acne	47%
Plethora	42%
Deep Voice	42%
Moon Face	35%
Seizure (Hypertensive crisis)	17%
Headache	12%

Incidence

ACC comprises 0.2% of childhood malignancies with an international incidence of 0.5/1 million

and occurs far more commonly in girls than boys (ratio 1.5:1) [5]. A bi-modal age distribution curve with a peak incidence at 3.5 and 57 years of age is seen.

Staging

Stage I	Total excision of tumor, tumor volume < 200cm ³ Absence of metastases and normal hormone levels after surgery
Stage II	Microscopic residual tumor, tumor volume >200cm ³ , persistently elevated adrenocortical hormone levels after surgery
Stage III	Gross residual or inoperable tumor
Stage IV	Distant metastases

Prognosis

The histopathological distinction between adrenal adenomas and carcinomas is difficult. A modification of the Weiss criteria based on mitotic index, atypical mitoses, confluent necrosis and nuclear grade is reported to predict clinical outcome [6]. Where tumors fulfil the histological criteria for adenoma, prognosis is excellent with no recorded deaths [6]. It is, however, widely accepted that tumor size is the best available predictor of biological behavior; tumors greater than 100grams/ 200cm³ are associated with a worse prognosis [2]. Other adverse prognostic factors include older age at presentation, increased urinary steroid levels and delay in diagnosis [2]. Capsular and vascular invasion has been associated with a high frequency of recurrence [1]. A recent publication from the International Pediatric Adrenocortical Tumor Registry confirms these prognostic findings but with larger numbers -254 patients [37].

Treatment

Detailed clinical guidelines are available on the UKCCG site: <http://www.ukccsg.org>
Joint patient management between a pediatric surgeon, an oncologist and an endocrinologist is recommended.

Surgery

Complete, radical surgical resection is the treatment of choice and may be curative, especially in small tumors. Patients achieving complete resection (stage I) survive significantly longer than those with residual disease [7]. In one recent series, survival rate reached 70% if resection was complete, but was a dismal 7% if complete resection was not achieved [1]. Surgical resection of isolated recurrence and metastatic disease is also indicated where possible. Because of tumor friability, rupture of the capsule and tumor spillage can be frequent,

up to 20% of cases, in Sandrini's series [8]. Infiltration of the vena cava makes radical surgery difficult but resection in this clinical scenario has been reported in patients undergoing cardiopulmonary bypass [7]. Follow up should involve regular surveillance with clinical examination, ultrasound examination of the adrenal bed and estimations of urinary steroid profiles which were raised preoperatively.

Mitotane/Chemotherapy

In patients with incomplete resection or metastatic spread (Stage II-IV), treatment options include chemotherapy and/or Mitotane. Due to the rarity of this condition no randomised or controlled studies have been performed. It is not even completely clear whether chemotherapy or Mitotane should be the initial treatment of choice. Mitotane, the ortho-prime derivative of an insecticide, dichlorodiphenyl-dichloroethane (DDD) was serendipitously noted to cause adrenal necrosis, leading to its use in ACC [9]. Mitotane is usually effective in controlling the endocrine symptoms and may cause tumor regression but is not an anti-neoplastic agent and a recent large retrospective study in adults concluded that Mitotane did not have a significant effect on survival [10]. There is, however, some evidence that Mitotane is more effective in children than adults [11-13], particularly if the neoplasm is hormonally active [14]. There is no clear evidence base for a treatment dose. Most series give Mitotane within the range of 5 to 10 grams/m² per day but dose levels will depend on symptoms [1, 15, 16]. A role for low dose Mitotane 0.5-1 grams/m² per day has been suggested due to unacceptable side effects, but the evidence base for this is weak [17, 18]. Recent studies have shown that Mitotane exhibits a clear dose response curve, being most effective when the serum level is > 14mg/L [19]. Unpleasant side effects, include gastrointestinal, neurological, dermal and miscellaneous, are common and very careful monitoring is essential ([appendix 1](#)). More serious side effects have been reported. Side effects can be minimised by keeping the serum Mitotane level between 14 - 20mg/L and measured monthly [19]. It is possible that the equivocal results achieved with Mitotane reflect the administration of sub-therapeutic levels of this drug, particularly as it has a narrow therapeutic window [4, 20]. UKCCG guidelines recommend a starting dose of Mitotane at 1- 2 grams/m² per day, increasing at a rate of 1-2 gm/m²/day every 3-5 days, aiming to reach 8 grams/m² per day or until therapeutic levels are achieved. It is also important to recognise that higher than normal doses of mineralocorticoid and glucocorticoid therapy are required due to an increased serum steroid-binding capacity

during mitotane therapy [21]. Functional recovery of the zona glomerulosa and fasciculata has been reported following Mitotane therapy [11].

Effective chemotherapeutic agents include cisplatin, etoposide, doxorubicin, 5-Fluoruracil and cyclophosphamide [1, 15, 20, 22-26].

It is recommended that patients are treated with cisplatin and etoposide with mitotane concurrently (as above). The suggested regimen is that used by Kushner (UKCCSG protocol NB 1999 02 – [appendix 2](#)) for neuroblastoma. The combination of Cisplatin/ etoposide and Mitotane whilst tolerable may confer a survival advantage over chemotherapy alone in one adult study. However, no randomised trials have been performed [15].

Radiotherapy

Radiotherapy has been used, however, the use of this modality in the presence of a high risk of genetic predisposition to cancer is not advised, indeed secondary tumors have been reported within the radiation field [27].

Etiology

Although a rare component of Li-Fraumeni syndrome (LFS), a familial cancer syndrome [28], ACC occurs 100 times more frequently than would be expected. Germline mutations of the *TP53* gene have been identified in most but not all of the families with classic LFS [29,30]. Molecular analysis has shown that 50% of children with ACC carried germline *TP53*, suggesting that presentation with ACC in childhood may be the first manifestation of LFS within a family [31].

There is also an increased incidence of ACC in patients with isolated hemihypertrophy and the Wiedemann-Beckwith syndrome [1, 32]. A number of children with congenital adrenal hyperplasia (CAH) who have subsequently developed ACC have also been reported [33].

Mutations in the *CYP21* gene are responsible for most cases of CAH [34]. Molecular analysis of *CYP21* in 27 cases of sporadic ACT revealed no mutations, excluding this gene in the etiology of ACT and of mild undiagnosed CAH as a predisposing factor [35]. The gene for multiple endocrine neoplasia type 1, *MEN1*, has been localised to 11q13; although deletions in this chromosomal region are frequently found in ACT, no mutations in the *MEN1* gene have been detected. Loss of heterozygosity studies have also implicated region 2p16, particularly in malignant tumors. Whether this region contains a tumor suppressor gene important in adrenocortical carcinoma remains to be evaluated.

The incidence of ACC in Brazil is 1.5/million, more than 3 times the international rate for

reasons that are currently unclear [5, 2]. A retrospective study noted that 7 fathers and 4 mothers of the 14 children with ACT in the Manchester Children's tumor registry were exposed to potentially toxic substances during the pregnancy [36]. This finding raises the possibility that environmental as well as genetic factors are important in the etiology of some ACT.

Diagnostic methods

- 24 hour urinary collection to measure: free cortisol, 17-hydroxycorticosteroids (17-OH) and androgens;
- plasma samples for: cortisol, dehydroepiandrosterone sulfate (DHEA-S), testosterone, androstenedione, deoxycorticosterone, and 17-hydroxyprogesterone;
- Dexamethasone suppression test;
- Abdominal ultrasound;
- CT/MRI scan of abdomen;
- CT chest;
- Bone scintigraphy by ⁹⁹Tc-diphosphonate.

Unresolved questions

There is still much to be learnt concerning the biology of ACC, in particular the relationship between genetic predisposition and environmental factors.

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