Rare Tumors of the Peripheral Nervous System

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42.1 Intra-adrenal (Pheochromocytoma) and Extra-adrenal Paraganglioma

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42.1.1 Introduction and UK Registry Childhood Cancer Registry Data

The WHO in 2004 reclassified endocrine tumors and redefined pheochromocytoma as intra-adrenal paraganglioma and those tumors of extra-adrenal sympathetic or parasympathetic paraganglia as extra-adrenal paragangliomas (Pacak et al. 2007). Although rare in children, they are the commonest pediatric endocrine tumor with an instance of 1–2 per million (Stringel

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D.T. Schneider et al. (eds.), *Rare Tumors In Children and Adolescents*, Pediatric Oncology,
DOI 10.1007/978-3-642-04197-6_42,

Table 42.1.1 Numbers of registrations by calendar period and tumor behavior

	Benign and unspecified	Malignant	Total
1971–1980	6	2	8
1981–1990	11	4	15
1991–2002	20	1	21

Unspecified are regarded as benign in ICD-O

Table 42.1.2 Numbers of registrations by age and sex, 1981–2002

	0–4 years	5–9 years	10–14 years	Male	Female	Total
Benign and unspecified	1	13	17	19	12	31
Malignant	0	2	3	3	2	5

et al. 1980). The majority of paragangliomas arise in the adrenal medulla (Lenders et al. 2005), but when they arise in extra-adrenal sites, they occur in decreasing order of frequency in the abdomen – in the organ of Zuckerkandl, pelvis, mediastinum, and the head and neck (Pacak et al. 2001). In the head and neck, they are mainly parasympathetic and nonsecreting with a specific entity arising in the carotid body – carotid body tumor – which is extremely rare in childhood (Deal et al. 1990). In childhood, they are often multiple or bilateral with 40% probably associated with an underlying genetic condition and very rarely are malignant (Krijger et al. 2006).

42.1.1.1 Pheochromocytomas in the United Kingdom National Registry of Childhood Tumors, 1971–2002

The registration of nonmalignant tumors has clearly been incomplete, especially before 1981. Detailed data therefore only covers the period 1981–2000 (Spoudeas and Harrison 2005) (Tables 42.1.1 and 42.1.2).

Pheochromocytoma was more common in older children, with boys more frequently affected (1.5:1).

Incidence of malignant pheochromocytoma was 0.02 per million children.

For benign and unspecified, a minimum estimate of incidence is 0.11 per million.

Among 31 children with benign or unspecified tumors, three were diagnosed at postmortem; no other deaths have been recorded.

Of five children registered with malignant pheochromocytoma, two died at intervals of 2 days and 14 months after diagnosis; the other three are alive with survival times between 3 and 22 years.

42.1.2 Clinical Presentation

In children the presentation can be very variable, but symptoms are mainly due to the excess catecholamine secretion (Caty et al. 1990; Criftci et al. 2001; Ein et al. 1997). Twice as many cases occur in boys than girls with a mean age of about 11 years at presentation, the majority presenting with hypertension which may be intermittent and not present in all cases (Barontini et al. 2006; Beltsevich et al. 2004; Ludwig et al. 2007). Other symptoms of catecholamine excess include headache, palpitations, excess sweatiness, weight loss, vomiting, anxiety, and behavioral problems (Haws et al. 2007).

Probably in nearly half of paragangliomas in childhood there will be a hereditary basis (Barontini et al. 2006; Krijger et al. 2006; Ludwig et al. 2007), so where there is a clinical suspicion of pheochromocytoma, a detailed family history and clinical examination for the physical characteristics of the following familial/genetic syndromes should be undertaken.

Neurofibromatosis type 1 (NF-1) – Café au lait patches, axillary freckling, neurofibromas, macrocephaly, and Lisch nodules of iris

Multiple endocrine neoplasia type 2B (MEN2B) – Marfanoid habitus, ganglioneuromatosis of bowel, neuromas of tongue and lips, hyperplasia of nerves of conjunctiva

Multiple endocrine neoplasia type 2A (MEN 2A) – Thyroid mass, Hirschsprung's disease, cutaneous lichen amyloidosis

Von Hippel–Lindau (VHL) – Retinal hemangiomas, CNS hemangioblastoma (mainly cerebellar), renal carcinoma (usually in adult life)

Paraganglioma syndrome (SDH) – Head and neck paragangliomas, intra-adrenal paragangliomas, extra-adrenal paragangliomas

42.1.3 Diagnostic Investigations

42.1.3.1 Biochemical

The diagnosis of pheochromocytoma should be confirmed by the measurement of at least two 24-h

urine samples for metanephrines (normetanephrine or metanephrine) and catecholamines, and the degradation product urinary vanillylmandelic acid (VMA) (Lenders et al. 2002; Pacak et al. 2007). If the diagnosis of pheochromocytoma is in doubt, for superior diagnostic accuracy, measurement of plasma-free metanephrine and normetanephrine are considered more accurate biochemical tests both in adults and probably in children (Sawka et al. 2003; Weise et al. 2002).

42.1.3.2 Imaging/Localizing Investigations

Tumor localizing investigations should not be performed until a biochemical diagnosis has been made. However, where there is a hereditary or genetic predisposition, imaging investigations may be used for screening. Magnetic resonance imaging (MRI) of the abdomen and pelvis should be performed avoiding the radiation exposure of computed tomography (CT) scan. The MRI scan clearly helps to localize site of the tumor, assess its size, and look at its relationships to major vessels (Pacak et al. 2001). Functional imaging is required, however, using I^{123} metaiodobenzylguanidine (MIBG) scintigraphy to confirm the diagnosis and detect multiple synchronous primaries and possible malignant disease (Ilias and Pacak 2004; Velchik et al. 1989). This may necessitate further cross-sectional imaging. It should be noted that malignant paragangliomas lose the ability to accumulate MIBG and hence may not detect all sites of metastatic disease. Further imaging that may be useful in this situation include [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) (Timmers et al. 2007a).

42.1.3.3 Other Investigations

Echocardiography and ECG for long-standing evidence of hypertension.

42.1.4 Preoperative Medical Management

Definitive treatment for pheochromocytoma is surgical resection but only after there has been effective blockade of catecholamines for at least 10–14 days prior to surgery. If there is adequate preoperative α-adrenergic blockade with phenoxybenzamine, as the usual agent, the risk of intraoperative complications is significantly reduced (Goldstein et al. 1999). Doxazosin could be considered if phenoxybenzamine is poorly tolerated. β blockers for tachycardia should only be used after adequate α-adrenergic blockade has been achieved. Adequate hydration is necessary to support the relatively reduced circulating blood volume resulting from the α-blockade (Hack 2000).

42.1.5 Operative Management

The preferred approach to resection is laparoscopic, but open resection is acceptable, particularly with invasive or metastatic disease (Brunt et al. 2002). If there are multiple tumors, there should be an attempt to remove all tumors at the same time, and in children with bilateral adrenal involvement, cortical-sparing adrenalectomies should be considered to avoid the difficulties of cortical steroid replacement during adolescence (Table 42.1.3).

42.1.6 Malignant Paragangliomas

The incidence of malignancy is probably low at less than 6% in childhood paragangliomas (Barontini et al. 2006; Chrisoulidou et al. 2007; Criftci et al. 2001). Malignancy cannot be diagnosed by histology alone but by the presence of local invasion and/or metastatic disease usually in bone, lung, or liver. Although generally incurable, some patients can survive for many years (Havekes et al. 2007). There is little or no literature on children with malignant paragangliomas, but individual cases are included in adult series (Gonias et al. 2009; Havekes et al. 2007). Unresectable tumors can be managed symptomatically in order to improve the quality of life of the child with either phenoxybenzamine or doxazosin. Following debulking surgery, MIBG therapy maybe effective either alone or in association with chemotherapy (Sisson et al. 1999) (Loh et al 1997) usually a combination of vincristine, cyclophosphamide, and dacarbazine (Auerbach et al. 1988). In a recent study, including small numbers of children, high-dose MIBG therapy was used with stem cell support producing an improved 5 year survival rate of 64% but with significant toxicities (Gonias et al. 2009).

Temozolamide may have a role presurgery in reducing metastatic disease, although this is based only on a single case report (Bravo et al. 2009).

Table 42.1.3 Guidelines for diagnosis and management of pheocromocytoma and paraganglioma

Physical examination	Hypertension, mass in abdomen or in neck, signs of familial/genetic syndromes such as neurofibromatosis type 1, MEN 2A, or B
Laboratory assessment	24-h urine samples for metanephrines (normetanephrine or metanephrine) and catecholamines
Radiological assessment	
– First assessment	Ultrasound if abdominal mass
– Local staging	Magnetic resonance imaging (MRI) of the primary site is mandatory for local extension assessment before any treatment. MRI avoids exposure to radiation in patients predisposed to further malignancies
– Diagnostic work	I^{123} metaiodobenzylguanidine (MIBG) scintigraphy to confirm the diagnosis and to detect multiple synchronous primaries and possible malignant disease
Pathological assessment	BIOPSY SHOULD NOT BE ATTEMPTED The tumor should be completely resected providing enough diagnostic material for immunochemistry, cytogenetics, biological studies, and central pathology review
General treatment guidelines	Need for multidisciplinary approach
– Surgery	Keystone of treatment Goal: Complete resection and should be referred to specialist centers The preferred approach to resection is laparoscopic, but open resection is acceptable, particularly with invasive or metastatic disease. If there are multiple tumors, there should be an attempt to remove all tumors at the same time, and in children with bilateral adrenal involvement, cortical-sparing adrenalectomies should be considered to avoid the difficulties of cortical steroid replacement during adolescence
– Radiotherapy	No role in the management of paragangliomas. MIBG therapy may be useful in malignant disease with metastases for palliation of symptoms
– Chemotherapy	No role for chemotherapy except in malignant disease with metastases usually following MIBG therapy with a combination of vincristine, cyclophosphamide, and dacarbazine

42.1.7 Carotid Body Tumors

Carotid body tumors (CBT) are a distinct clinical group of extra-adrenal paragangliomas which arise in the chemoreceptive tissue located in the carotid bifurcation or glomus body and hence also described as glomus body tumors. Certainly, in adults, CBT is the most frequent paranganglioma in the head and neck (Dardik et al. 2002; Pellitteri et al. 2004); however, data in children is lacking with only individual cases reported (Gounot et al. 1990; Ophir 1991) either in adults series, (Dickinson et al. 1986; Shamblin et al. 1971) or in pediatric paraganglioma series (Takautz et al. 2003). Carotid body tumors are often bilateral (Dardik et al. 2002; Dickinson et al. 1986), can be multicentric, the most common association between an intravagal paraganglioma and CBTs (Borba and Al-Mefty 1996). Carotid body tumors are usually sporadic but rarely can have a familial inheritance associated with paraganglioma syndromes due to mutations in the succinate dehydrogenase (SDH) genes (Benn et al. 2006). Presentation is usually as a slowly enlarging pulsatile mass in the upper neck, often misdiagnosed as cervical lymphadenopathy, neurofibromas, or brachial cysts. Later, cranial nerve or adjacent pharynx may be involved (Gujrathi and Donald 2005; Takautz et al. 2003).

Malignancy is rare in CBTs (Shamblin et al. 1971), and as with paragangliomas arising at other sites, it is defined by metastatic spread, usually to cervical lymph nodes but infrequently to distant organs. The risk of malignancy is probably greatest in younger patients with heritable tumors associated with SDH mutations (Timmers et al. 2007b). There is only one report, however, of a child with distant metastatic disease from a CBT (Hajnzic et al. 1999).

Once CBTs are suspected, ultrasound studies can help exclude other causes of neck masses such as lymph nodes, thyroid, or brachial cysts with Doppler studies evaluating the hypervascularity of the tumor. MRI scanning, however, usually reveals a well-defined carotid space lesion (Mey et al. 2001). ^{111}In octreotide scintigraphy can detect metastases in patients with malignant tumors with a role for possible PET scanning (Gujrathi and Donald 2005). Complete surgical resection is usually curative for the majority of patients with prior tumor embolization only being reported in one child (Zaupa and Höllwarth 2007),

although there is still a risk of stroke or cranial nerve palsies. Larger and more invasive CBTs in children may require carotid shunting and vascular reconstruction (Thompson and Cohen 1989). The treatment of malignant CBTs remains, as for other paragangliomas, surgical, though as nonsecreting tumors, they do not respond to α-adrenergic blockade with phenoxybenzamine.

42.1.8 Genetic Management

Following the diagnosis of paranganglioma in childhood, referral for genetic testing should be done in all cases as approximately nearly half of paranganglioma in children will have an underlying genetic or hereditary basis (Krijger et al. 2006). The absence of a family history does not preclude the patient having a mutation; indeed childhood paragangliomas can be considered a probable genetic disease requiring lifelong follow-up (Ein et al. 1990). It is important when taking a history and examining patients with paragangliomas to consider a diagnosis of the following hereditary syndromes.

42.1.8.1 Multiple Endocrine Neoplasia Type 2 (MEN 2)

This autosomal dominant tumor syndrome is a result of a mutation in the *RET* (rearranged during transfection) proto-oncogene in an autosomal dominant pattern. There is a high percentage of bilateral paranganglioma in more than 50% of cases, but malignant paragangliomas are rare (Eisenhofer et al. 2001).

42.1.8.2 Von Hippel–Lindau (VHL) Disease

This autosomal dominant disease is due to a mutation in the *VHL* gene on chromosome 3p25-26 with paragangliomas developing in 10–20% of patients (Ong et al. 2007). Though the paragangliomas mainly develop in adulthood, they have been reported in children with VHL and are often bilateral, but malignant disease is rare (Criftci et al. 2001; Krijger et al. 2006; Ludwig et al. 2007).

42.1.8.3 Neurofibromatosis Type 1 (NF 1)

This distinctive clinical syndrome occurs from a mutation in the *NF1* gene on chromosome 17q11.2. Paragangliomas only occur in a small percentage of patients.

42.1.8.4 Paraganglioma Syndrome (SDH)

Mutations in subunits of the succinic dehydrogenase enzyme complex gene in the mitochondrial respiratory chain are associated with familial paragangliomas. Two particular subunits, SDH and SDHB, are most likely to be associated with childhood with paragangliomas (Pham et al. 2006). Patients with SDHD mutation are more likely to have head and neck paranganglioma, multifocal disease, and a small chance of developing malignant tumors (Benn et al. 2006; Havekes et al. 2007). Patients with SDHB mutations are more likely to present at a younger age with paragangliomas in extra-adrenal sites with a higher chance of metastatic disease (Benn et al. 2006; Ludwig et al. 2007; Timmers et al. 2007b).

42.1.9 Conclusions

The management and diagnosis of paragangliomas in childhood has improved over time with better preparation prior to surgery, increasing use of laparoscopic techniques, and potentially newer imaging studies to detect metastatic disease. The outcome is generally excellent for children, but genetic testing is paramount to determine the lifelong risk for further disease and malignancy.

42.2 Adrenocortical Tumors in Children

Carlos Rodriguez-Galindo

42.2.1 Introduction

Adrenocortical tumors (ACT) encompass a spectrum of diseases with often seamless transition from benign (adenoma) to malignant (carcinoma) behavior. Their incidence in children is extremely low (only 0.2% of pediatric cancers) (Bernstein and Gurney 1999), and most pediatric oncologists see few cases or none. Little is known about these tumors, and most available information has been learned from their more frequent adult counterpart. In recent years, an international registry has provided insight into the clinical characteristics and relevant management issues regarding pediatric ACT and tumor tissue for biological studies. These studies have resulted in the discovery of a novel mechanism of tumorigenesis (Ribeiro et al. 2001).

42.2.2 Epidemiology of Adrenocortical Cancer

ACT appear to follow a bimodal distribution, with peaks during the first and fourth decades (Wooten and King 1993). In children, 25 new cases are expected to occur annually in the United States, for an estimated annual incidence of 0.2–0.3 cases/million. Internationally, however, the incidence of ACT appears to vary substantially. The incidence of ACT is particularly high in southern Brazil, where it is approximately 10–15 times of that observed in the United States. Most cases occur in the contiguous states of Sao Paulo, Paraná, and Santa Catarina (Figueiredo et al. 2006; Pianovski et al. 2006; Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005).

Predisposing genetic factors have been implicated in >50% of the cases in North America and Europe and in 95% of the Brazilian cases. Germline *TP53* mutations are almost always the predisposing factors. In the non-Brazilian cases, relatives of children with ACT often, though not invariably, have a high incidence of other nonadrenal cancers (Li–Fraumeni syndrome), and germline mutations usually occur within the region coding for the *TP53* DNA-binding domain (exons 5–8, primarily at highly conserved amino acid residues). In the Brazilian cases, in contrast, the patients' families do not exhibit a high incidence of cancer, and a single, unique mutation at codon 337 in exon 10 of the *TP53* gene is consistently observed (see below).

Patients with Beckwith–Wiedemann and hemihypertrophy syndromes have a predisposition to cancer, and as many as 16% of their neoplasms are ACT (Hoyme et al. 1998). However, less than 1% of children with ACT have these syndromes (Steenman et al. 2000). ACT have also been reported in association with other genetic diseases such as congenital adrenal hyperplasia (Varan et al. 2000).

The differential diagnosis of ACT includes other diseases characterized by adrenal hormone hyperproduction. ACTH-independent macronodular adrenal hyperplasia (AIMAH) is a benign proliferative disorder of the adrenal cortex that presents with ACTH-independent Cushing's syndrome. The majority of patients with AIMAH present in the fifth decade of life with sporadic isolated disease; however, in children, AIMAH can be associated with McCune–Albright syndrome (Sutter and Grimberg 2006). A similar macronodular adrenocortical hyperplasia is seen in up to one third of patients with multiple endocrine neoplasia syndrome type 1 (MEN1) and although rare, adrenocortical carcinomas have been described in this population, usually in adult age (Langer et al. 2002). Primary pigmented nodular adrenocortical disease (PPNAD) is a benign bilateral proliferative disorder characterized by small hyperpigmented nodules, usually associated with the Carney complex. This is an autosomal dominant syndrome that includes lentiginosis (perioral, ocular, or genital), cardiac and peripheral myxomas, melanotic schwannomas, and endocrine overactivity. Clinically evident PPNAD is seen in up to 30% of patients with Carney complex and usually presents in childhood, late adolescence, or early adulthood (Sutter and Grimberg 2006).

42.2.3 Biology of ACT

The molecular mechanisms of tumorigenesis of the adrenal cortex are not well understood (Kirschner 2002; Barlaskar and Hammer 2007). Carcinogenesis is a multistep process, and the pathogenesis of ACT may combine dedifferentiation and unchecked proliferation

induced through the activation of hormonal or growth factor signaling receptors. The insulin-like growth factor (IGF) system is well characterized for its contribution to normal and pathological adrenocortical growth. Clues to the role of this pathway in the development of ACT also came through the recognition of the increased incidence of ACT in children with Beckwith–Wiedemann syndrome (BWS) (Steenman et al. 2000). Genetic alterations associated with BWS are mapped to regions of chromosome band 11p15 designated BWS chromosomal regions (*BWSCR*) 1, 2, and 3 (Steenman et al. 2000). *IGF2* is mapped to *BWSCR1*. The strong association of BWS, *IGF2*, and ACC suggests that IGF2 participates in tumorigenesis, and studies have shown increased IGF2 protein and mRNA in ACC (Ilvesmaki et al. 1993; Boulle et al. 1998). Sporadic adrenocortical carcinomas (ACC) also show striking overexpression of *IGF2*, and studies in adults have documented >100-fold higher expression levels in carcinomas in comparison to adenomas and normal adrenal tissue (Gicquel et al. 2001). This differential *IGF2* expression between adenomas and carcinomas doesn't seem to be observed in pediatric tumors (see below) (Almeida et al. 2008; West et al. 2007). Interestingly, the antiproliferative effect of ACTH is blunted in ACT cell lines overexpressing *IGF1R* (Weber et al. 2000). Further, transgenic mice expressing *IGF2* postnatally develop adrenal hyperplasia (although not frank malignancy) (Weber et al. 1999). Taken together, the evidence strongly suggests that the IGF system is involved in adrenal growth and tumorigenesis. High local IGF2 levels combined with elevated *IGF1R* expression would provide a significant growth advantage, but additional steps are required for neoplastic transformation (Kirschner 2002; Barlaskar and Hammer 2007; Weber et al. 2000). Studies in several model organisms indicate the presence of undifferentiated multipotent adrenocortical cells, and a few molecular studies have implicated Wnt signaling pathway activation in ACC (Tissier et al. 2005). Further investigations are necessary to elucidate the contributions of developmental signaling pathways like Wnt in adrenal tumorigenesis.

The hypothetical multistep transformation process also requires intracellular signaling abnormalities other than dedifferentiation- and proliferation-inducing signals. *TP53* mutations appear to underlie such abnormalities in most cases, and ACT are strongly associated with germline *TP53* mutations. ACT are among the tumors most increased in frequency in families with Li–Fraumeni syndrome (Birch et al. 2001; Kleihues et al. 1997; Gonzalez et al. 2009), suggesting that germline *TP53* mutations exert tissue-specific effects. The diagnosis of ACT in a young patient should be considered a strong indicator of a germline *TP53* mutation, regardless of the family history (Gonzalez et al. 2009). A wide spectrum of germline *TP53* alterations have been described in ACT, and these mutations may contribute to the etiology of more than 80% of cases in children (Varley et al. 1999; Wagner et al. 1994). Consistent with the presence of a germline *TP53* mutation, relatives of children with ACT often have a high incidence of cancer; however, the lack of family history should not preclude investigation of *TP53* germline status (Varley et al. 1999; Wagner et al. 1994; Ariffin et al. 2008; Khayat and Johnston 2004; Rossbach et al. 2008). In North American children, the spectrum of germline *TP53* mutations in ACT is quite diverse, although germline mutations occur primarily in the *TP53* DNA-binding domains (exons 4–8) (Wagner et al. 1994; Reincke et al. 1994; Varley et al. 1999). In the Brazilian cases, by contrast, the patients' families do not have a high incidence of cancer, and a single mutation in exon 10 of the *TP53* gene is consistently observed. This mutation encodes an arginine in place of histidine at codon 337 (*TP53*-R337H) within the tetramerization domain. The families of these children do not share common ancestry. Recent studies have indicated that the R337H mutation is a relatively common polymorphism among southern Brazilians. Further, the penetrance of this mutation is low (only 10–15% of carriers develop ACT), and it appears not to predispose carriers to other malignancies later in life (Figueiredo et al. 2006). The wild-type allele is deleted in these tumors, and the mutant p53 protein accumulates in the nucleus. Functional analyses have shown that the mutant TP53 retains transactivation function and can induce apoptosis (Ribeiro et al. 2001). However, the mutant tetramerization domain is less stable than the wild-type domain and is sensitive to slightly increased pH, suggesting that a unique physiological condition within adrenocortical cells may contribute to the observed tissue-restricted pathogenesis (DiGiammarino et al. 2001). Thus, this inherited unique *TP53* mutation represents a low-penetrant, hypomorphic allele that contributes to the development of ACT in a tissue-specific manner (Ribeiro et al. 2001). Other *TP53* mutations, such as

the *TP53*R157L, with sufficient activity to suppress Li–Fraumeni syndrome but not ACC, have been described (West et al. 2006), thus the importance of in-depth evaluation and genetic counseling of children with ACT and their families.

Additional genetic alterations may be necessary for malignant transformation. ACT are characterized by a high frequency of chromosomal gains and amplifications, and several chromosomal subregions containing candidate proto-oncogenes are affected (Dohna et al. 2000; Figueiredo et al. 1999; Loncarevic et al. 2008). Interestingly, the pattern of genomic imbalances in pediatric ACT appears to be different from their adult counterparts. In a series of nine cases in Southern Brazil, the most consistent findings were a gain of all or part of chromosome arm 9q (eight cases) and amplification of band 9q34 (five cases) (Figueiredo et al. 1999). Loncarevic et al. analyzed 14 pediatric ACT by comparative genomic hybridization. Recurring genomic changes included gains of 1q, 12p, 12q, 1p, 7q, 9q, and 15q; and losses of 4q, 11q, 4p, and 16q (Loncarevic et al. 2008). Of particular interest is the consistent finding of gain of 9q in both series. The steroidogenic factor 1 gene (*SF1*, *NR5A1*) is located within this region and has been shown to be overexpressed in nearly all childhood ACT (Doghman et al. 2007). Enforced expression of *SF1* increases human adrenocortical cell proliferation and promotes adrenocortical tumorigenesis in transgenic mouse models. Collectively, these findings strongly implicate *SF1* as a driver in the initiation and/or progression of ACT. Additional studies are required to determine whether deregulation of *SF1* cooperates with *TP53* loss in ACT.

Microarray studies in childhood ACT show distinct patterns of gene expression that distinguish normal adrenal tissue, adenomas, and carcinomas (West et al. 2007). A significantly increased expression of *FGFR4* and *IGF2* was found in childhood ACC, although the degree of *IGF2* expression seems to be lower than adult tumors, and in contrast to adult ACT, this expression does not distinguish childhood adrenocortical adenoma from carcinoma. Also, there was a remarkable correlation in gene expression profiles between normal fetal adrenal tissue and pediatric ACT. There were very significant differences in gene expression between pediatric adenomas and carcinomas; remarkably, expression of major histocompatibility class II genes was lower in carcinomas than in adenomas, suggesting that malignant tumors may have evolved mechanisms to evade recognition by the immune system (West et al. 2007).

The distinctive clinical features suggest that ACT arises from the fetal zone of the fetal adrenal cortex. The fetal zone represents 85% of the adrenal cortex during fetal development, and it is oriented toward dehydroepiandrosterone production. It is thus possible that the presence of a constitutional *TP53* mutation increases the penetrance of ACT in the fetal adrenal cortex with lower risk for the remaining layers. Disruption of the *TP53* pathway under certain conditions may result in abnormalities of other cellular pathways leading to tumor formation.

42.2.4 Clinical Characteristics of Pediatric ACT

The clinical characteristics, treatment, and outcome of ACT have been described mainly in adults; because there are few reports about pediatric ACT, it is difficult to discriminate features unique to either age group. The degree and type of endocrine disturbance appear to be related to patient age (Wooten and King 1993; Wajchenberg et al. 2000). Older patients tend to have a much higher incidence of nonfunctional tumors, whereas more than 90% of childhood ACT are functional (Wajchenberg et al. 2000; Ribeiro et al. 1990; Ciftci et al. 2001; Driver et al. 1998). Adults usually have mixed virilization-hypercortisolism syndromes, whereas virilization syndrome is the most common presentation in children (Wajchenberg et al. 2000; Ribeiro et al. 1990; Ciftci et al. 2001; Driver et al. 1998).

Despite the rarity of childhood ACT, its clinical and pathologic characteristics have been well characterized in recent years (Ribeiro et al. 1990; Ciftci et al. 2001; Driver et al. 1998; Wieneke et al. 2003; Sandrini et al. 1997; Bugg et al. 1994; Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005; Teinturier et al. 1999). Significant information has been obtained from the International Pediatric Adrenocortical Tumor Registry (IPACTR) (www.stjude.org/ipactr), established in 1990 by the St. Jude Children's Research Hospital International Outreach Program, and institutions in Brazil. The registry has served as an information-exchange Web site, and more than 300 patients have been registered to date (Michalkiewicz et al. 2004). The registry now also includes a tumor bank component to collect from international sites both

normal and adrenal tumor tissue for detailed biological studies.

Childhood ACT typically present during the first 5 years of life (median age, 3–4 years), although there is a second, smaller peak during adolescence (Ribeiro et al. 1990; Ciftci et al. 2001; Wieneke et al. 2003; Sandrini et al. 1997; Teinturier et al. 1999; Michalkiewicz et al. 2004; Narasimhan et al. 2003). Female sex is consistently predominant in most studies, with a female to male ratio of 1.6:1 (Wieneke et al. 2003; Sandrini et al. 1997; Michalkiewicz et al. 2004; Ciftci et al. 2001; Narasimhan et al. 2003; Hanna et al. 2008). According to the IPACTR data, the female predominance is more significant for patients younger than 3 years of age (1.7:1) and for patients older than 13 years (6.2:1), but not for patients between 3 and 12 years (Michalkiewicz et al. 2004). Because pediatric ACT are almost universally functional, they cause endocrine disturbances, and a diagnosis is usually made 5–8 months after the first signs and symptoms emerge (Ciftci et al. 2001; Wieneke et al. 2003; Michalkiewicz et al. 2004). Virilization (pubic hair, accelerated growth, enlarged penis, clitoromegaly, hirsutism, and acne) due to excess of androgen secretion is seen, alone or in combination with hypercortisolism, in more than 80% of patients (Fig. 42.2.1). Isolated Cushing's syndrome is very rare (5% of patients), and it appears to occur more frequently in older children (median age 12.6 years in the IPACTR) (Ciftci et al. 2001; Wieneke et al. 2003; Teinturier et al. 1999; Michalkiewicz et al. 2004; Hanna et al. 2008).

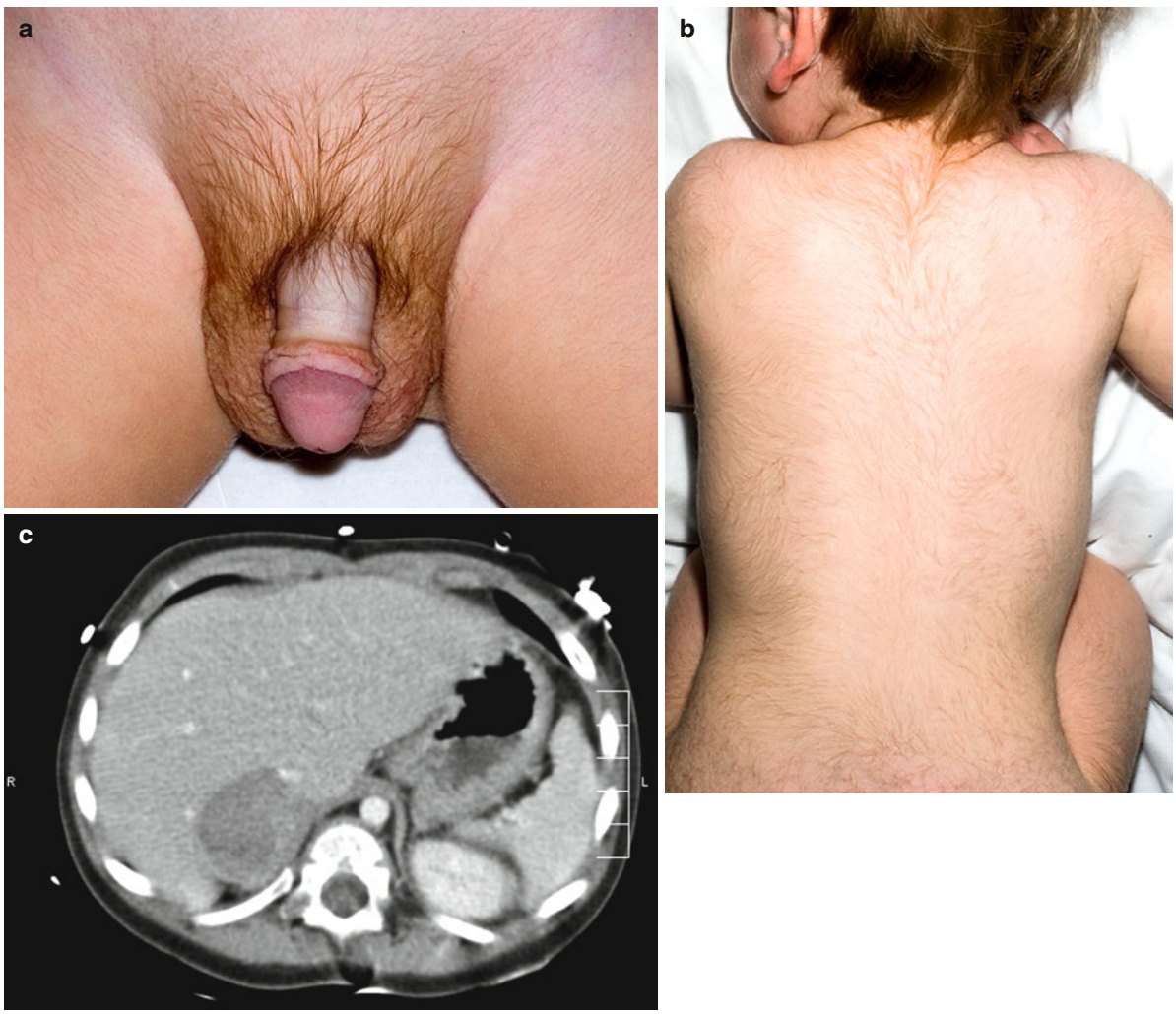

Fig. 42.2.1 Two-year-old boy presenting with virilization (**a**, **b**). CT scan demonstrated a right adrenal mass (**c**)

Likewise, nonfunctional tumors are rare (less than 10%) and tend to occur in older children (Michalkiewicz et al. 2004). Half of the patients have severe hypertension at presentation, and hypertensive crisis resulting in seizures is the presenting feature in 10% of cases (Ribeiro et al. 1990; Wieneke et al. 2003; Sandrini et al. 1997; Michalkiewicz et al. 2004; Wang et al. 2007). However, isolated Conn's syndrome with hypertension, hypokalemia, and pseudoparalysis resulting from hyperproduction of aldosterone or deoxycorticosterone is extremely rare (less than 1% in the IPACTR data) but has been described (Michalkiewicz et al. 2004; Narasimhan et al. 2003). An abdominal mass can be palpated in approximately half the patients (Ciftci et al. 2001; Teinturier et al. 1999).

At the time of diagnosis, two thirds of pediatric patients have limited disease (tumors are completely resected), and the remaining patients have either unresectable or metastatic disease (Michalkiewicz et al. 2004). In up to 20% of the cases, intracaval extension of the tumor is present (Michalkiewicz et al. 2004; Tucci et al. 2005). Unlike adult ACT, histologic differentiation of adenomas and carcinomas is difficult. However, approximately 10–20% of pediatric cases are adenomas (Wieneke et al. 2003; Michalkiewicz et al. 2004).

42.2.5 Diagnosis

Children with ACT usually present with striking endocrine syndromes, most commonly virilization, and thus are usually diagnosed earlier than adults. Because of the hormone hypersecretion, it is possible to establish an endocrine profile for each particular tumor, which may facilitate the evaluation of response to treatment and monitor for tumor recurrence. Laboratory evaluation can also help distinguish physiological adrenarche or congenital adrenal hyperplasia from ACC. Patients with adrenarche have elevated basal concentration of DHEAS and androstenedione, while those with congenital adrenal hyperplasia may show increased basal or ACTH-stimulated peak concentration of 17-OH-progesterone (Ribeiro and Figueiredo 2004). While the diagnosis of ACC is usually clinical, imaging studies are important to complete staging and for surgical planning. Magnetic resonance imaging (MRI) and computed tomography (CT) are needed for evaluation of the size and location of the primary tumor, the degree of invasion to surrounding structures, the presence of metastases, and involvement of venous structures. Although bone metastases at diagnosis are extremely rare, scintigraphic studies are recommended. On CT, large tumors usually have a central area of stellate appearance caused by hemorrhage, necrosis, and fibrosis; this central area is usually hyperintense on T2-weighted MRI and STIR images. Calcifications are also common (Ribeiro et al. 2000). In order to evaluate tumor extension into the vena cava, ultrasound or MRI are always recommended, and a careful evaluation of the presence of a tumor thrombus must always be performed prior to surgery (Ribeiro and Figueiredo 2004; Tucci et al. 2005). Because ACT are metabolically active, whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) is being increasingly used. Although the experience in pediatrics is limited, available information suggests that this may be a very useful technique in the imaging of the regional and metastatic extension, and in the diagnosis of recurrences in areas not typically imaged (Mackie et al. 2006; Murphy et al. 2008).

The distinction between benign (adenomas) and malignant (carcinomas) tumors can be problematic. In fact, adenoma and carcinoma appear to share multiple genetic aberrations and may represent points on a continuum of cellular transformation (Dohna et al. 2000; Figueiredo et al. 1999). Macroscopically, adenomas tend to be well defined and spherical, and they never invade surrounding structures. They are typically small (usually <200 cm^3), and some studies have included size as a criterion for adenoma. Microscopically, they may resemble normal adrenal cortex. By contrast, carcinomas have macroscopic features suggestive of malignancy; they are larger, and they show marked lobulation with extensive areas of hemorrhage and necrosis. Microscopically, carcinomas comprise larger cells with eosinophilic cytoplasm, arranged in alveolar clusters. Several authors have proposed histologic criteria that may help to distinguish the two types of neoplasm (Weiss 1984; Slooten et al. 1985). However, morphologic criteria may not allow reliable distinction of benign and malignant ACC. Mitotic rate is consistently reported as the most important determinant of aggressive behavior (Weiss et al. 1989; Kendrick et al. 2001; Stojadinovic et al. 2002; Harrison et al. 1999). *IGF*2 expression also appears to discriminate between carcinomas and adenomas in adults but not in children (Almeida et al. 2008; West et al. 2007; Rosati et al. 2008; Erickson et al. 2001). Other histopathologic

variables are also important, and risk groups may be identified on the basis of a score derived from characteristics, such as venous, capsular, or adjacent organ invasion; tumor necrosis; mitotic rate; and the presence of atypical mitoses (Stojadinovic et al. 2002). Two retrospective studies have investigated histological criteria of malignancy in pediatric ACT. Bugg et al. analyzed histology, ploidy, proliferative index, and tumor size in 54 cases (Bugg et al. 1994). The histologic criteria for malignant tumors were the mitotic index, the presence of confluent necrosis and atypical mitoses, and the nuclear grade, as previously defined by Weiss (Weiss 1984; Weiss et al. 1989). The most statistically significant predictors of outcome were tumor histology and tumor weight (<100 g vs. >100 g). Ploidy and proliferative index were not predictive of outcome (Bugg et al. 1994). More recently, Wienecke et al. analyzed features associated with increased probability of a malignant behavior in a series of 83 pediatric ACC (Wieneke et al. 2003). Tumor weight >400 g, tumor size >10.5 cm in the largest diameter, vena cava, capsular or vascular invasion, extension into periadrenal soft tissues, confluent necrosis, presence of severe nuclear atypia, atypical mitoses, and presence of >15 mitotic figures/20 high-power field were all associated with adverse outcome. However, on multivariate analysis, only vena cava invasion, presence of necrosis, and high mitotic rate retained prognostic significance. The incorporation of gene expression techniques to the diagnostic evaluation of ACT may provide additional means to anticipate the clinical and biological behavior, both in adult (Reynies et al. 2009) and pediatric (West et al. 2007) tumors. However, still unknown biological events rather than histopathologic tumor characteristics are likely to dictate clinical behavior.

42.2.6 Prognostic Factors

In an analysis of 40 cases in Southern Brazil, Ribeiro et al. (1990) found tumor volume >200 mL or weight >80 g, and age >3.5 years to be associated with worse outcome, although only tumor size was independently predictive. In the IPACTR data, several clinical features, including age, sex, clinical syndrome, interval between first symptoms and diagnosis, blood pressure, disease stage, tumor spillage, tumor thrombus, and tumor weight were examined for their association with outcome. In patients with localized disease, age between 0 and 3 years, virilization alone, normal blood pressure, disease stage I, absence of spillage during surgery, and tumor weight ≤200 g were associated with a greater probability of survival. In a Cox regression model analysis, only stage I, virilization alone, and age 0–3 years were independently associated with a better outcome (Michalkiewicz et al. 2004) (Figs. 42.2.2 and 42.2.3).

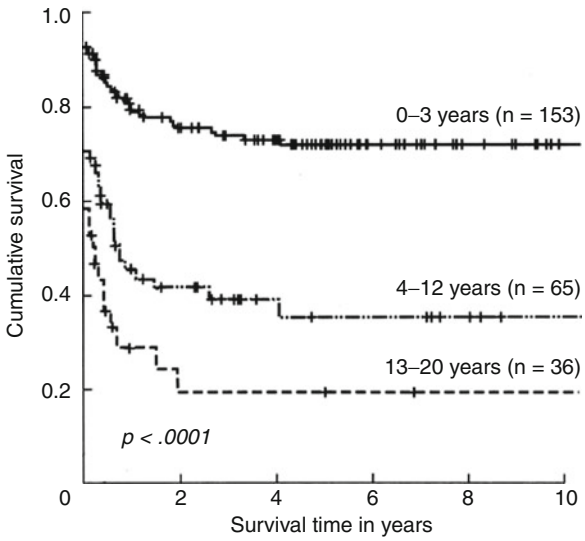

Fig. 42.2.2 Probability of 5-year event-free survival according to age at the time of diagnosis in 254 children with ACT (From Michalkiewicz et al. (2004) With permission)

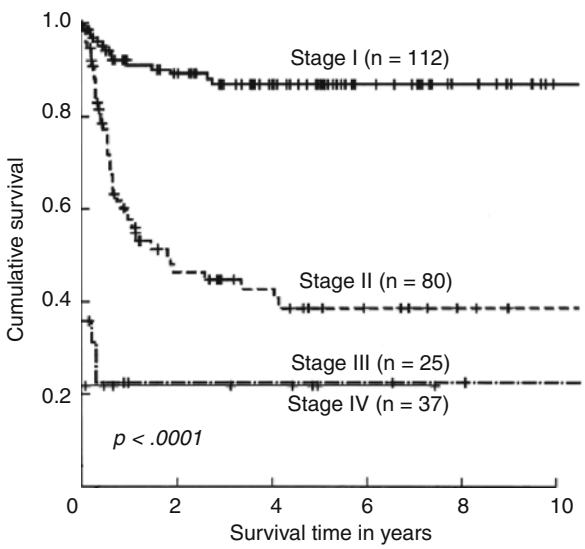

Fig. 42.2.3 Probability of 5-year event-free survival according to disease stage at the time of diagnosis in 254 children with ACT (From Michalkiewicz et al. (2004) With permission)

Table 42.2.1 Proposed staging of adrenocortical tumors in children

- *Stage I*
  - Completely resected, small tumors (<100 g and <200 cm^3) with normal postoperative hormone levels
- *Stage II*
  - Completely resected, large tumors (≥100 g or ≥200 cm^3) with normal postoperative hormone levels
- *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 metastases

Modified from Sandrini et al. (1997)

Thus, available data suggest that tumor size is especially important in children; patients with small tumors have an excellent outcome with surgery alone, regardless of histologic features (Ribeiro et al. 1990; Wieneke et al. 2003; Bugg et al. 1994; Michalkiewicz et al. 2004; Michalkiewicz et al. 1997). A staging system based on disease extent and tumor size has been proposed on the basis of these findings (Table 42.2.1) (Rodriguez-Galindo et al. 2005; Sandrini et al. 1997). The overall probability of 5-year survival for children with ACT is reported to be 54–74% (Ciftci et al. 2001; Wieneke et al. 2003; Sandrini et al. 1997; Teinturier et al. 1999; Michalkiewicz et al. 2004; Hanna et al. 2008; Tucci et al. 2005). Data from the IPACTR and other series show the staging system to be highly predictive of outcome in children with stage I or stage IV disease: more than 90% of patients with stage I disease, but only 10% of those with stage IV disease, are long-term survivors (Fig. 42.2.3). Determining the prognosis of patients with intermediate-stage disease is much more difficult. Despite presumed complete tumor resection, local recurrence is the most common adverse event in patients with stage II disease (30–50% of cases) (Michalkiewicz et al. 2004; Tucci et al. 2005).

42.2.7 Treatment of Pediatric ACT

Treatment of childhood ACT has evolved from the data derived from the adult studies, and same guidelines are used; surgery is the most important mode of therapy, and mitotane- and cisplatin-based regimens are recommended for patients with advanced disease (Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005; Zancanella et al. 2006; Hovi et al. 2003). An aggressive surgical approach of the primary tumor and all metastatic sites is recommended when feasible (Tucci et al. 2005; Stewart et al. 2004). Because of tumor friability, rupture of the capsule with resultant tumor spillage is frequent (approximately 20% of initial resections and 43% of resections after recurrence) (Sandrini et al. 1997; Michalkiewicz et al. 2004). In fact, spontaneous tumor rupture resulting in acute abdomen as presentation of a pediatric ACT has been described (Leung et al. 2002). When the diagnosis of ACT is suspected, laparotomy and a curative procedure are recommended rather than fine-needle aspiration, to avoid the risk of tumor rupture (Kardar 2001). Laparoscopic resection is associated with a high risk of rupture and peritoneal carcinomatosis; thus, open adrenalectomy remains the standard of care (Gonzalez et al. 2005). The lymph node drainage of the adrenal gland is complex. There is an extensive subserosal network of lymphatic channels around the gland, crossing several levels in different directions inside the fascia and connective tissue involving the adrenal gland. The incidence of lymph node involvement is not known, although some studies report it to be close to 40% in adults (Crucitti et al. 1996; Lee et al. 1995). In children, available data suggests that nodal involvement is present in approximately 30% of the cases (Stewart et al. 2004). Whether ipsilateral retroperitoneal lymph node dissection may improve local control is a matter of debate and a question currently being investigated in the Children's Oncology Group ARAR0332 study (see below).

Chemotherapeutic regimens used for patients with advanced disease have derived from the standard treatments used in adults. A cisplatin-based combination, usually incorporating doxorubicin and etoposide, is most commonly used (Ribeiro and Figueiredo 2004; Rodriguez-Galindo et al. 2005; Ciftci et al. 2001; Teinturier et al. 1999; Michalkiewicz et al. 2004; Zancanella et al. 2006). Because of cisplatin's renal dose-limiting toxicity, Ayass and coworkers substituted carboplatin for cisplatin given in combination with etoposide to a 17-month-old boy with ACT that had metastasized to the brain and chest. After complete resection of the primary tumor and eight cycles of etoposide and carboplatin, the metastatic dis-

ease responded completely and the patient survived long-term (Ayass et al. 1991).

Little information is available about the use of mitotane in children, although response rates appear to be similar to those seen in adults (Ribeiro and Figueiredo 2004; Zancanella et al. 2006). There have been several reports of complete responses in children with advanced or metastatic ACT, but these appear to be rare events (Coelho Netto et al. 1963; Ostuni and Roginsky 1975). In a review of 11 children with advanced ACT treated with mitotane and a cisplatin-based chemotherapeutic regimen, measurable responses were seen in seven patients. The mitotane daily dose required for therapeutic levels was around 4 g/m^2, and therapeutic levels were achieved after 4–6 months of therapy (Zancanella et al. 2006). Compliance with daily mitotane administration is a major limitation to therapy in young children; nausea, vomiting, diarrhea, and neurologic alterations are common (Zancanella et al. 2006). Monitoring for neurotoxicity is particularly important in young patients as the use of mitotane has been associated with motor and speech developmental delays (De Leon et al. 2002).

The use of radiotherapy in pediatric ACT has not been consistently investigated. ACT are generally considered to be radioresistant (Wajchenberg et al. 2000). Furthermore, because many children with ACT carry germline *TP53* mutations that predispose to cancer, radiation may increase the incidence of secondary tumors. Driver et al. reported that three of five long-term survivors of pediatric ACT died of secondary sarcoma that arose within the radiation field (Driver et al. 1998). For most patients with metastatic or recurrent disease that is unresponsive to mitotane and chemotherapy, repeated surgical resection is the only alternative. However, given the infiltrative nature of the disease, complete resection is difficult to achieve. Image-guided tumor ablation with radiofrequency currently offers a valid alternative for these patients. Radiofrequency ablation is a minimally invasive and safe treatment for patients in whom surgery may not be possible. Using this technique, Wood et al. reported responses in 53% of the adult patients treated; these results suggest that radiofrequency ablation has a role in the management of this aggressive malignancy (Wood et al. 2003). Data regarding the use of this treatment modality in children is limited; however, it appears to offer a valid alternative for children with unresectable ACT (Hoffer et al. 2009).

Finally, advances in our understanding of ACT biology may lead to the identification of new molecular targets (Kirschner 2006). In particular, new developments in IGF pathway inhibition, such as monoclonal antibodies against the IGF1R, may provide effective alternatives and are currently being investigated (Table 42.4.1) (Almeida et al. 2008; Barlaskar et al. 2009).

42.2.8 A Collaborative Research Initiative for Childhood ACT

Cooperative multi-institutional efforts have been pivotal in the advancement of pediatric oncology during the past several decades. Rare pediatric tumors, however, have remained research orphans, and children with these rare malignancies have yet to benefit from group-wide initiatives. In recent years, the Children's Oncology Group (COG) has made a commitment to develop research programs in rare childhood malignancies. Part of this effort is a collaboration between COG and Brazilian institutions to develop a study protocol for childhood ACC (ARAR0332) (Table 42.2.2). This protocol investigates three main clinical questions: (1) the efficacy of surgery alone for stage I tumors; (2) the role of retroperitoneal lymph node resection in reducing local recurrence of stage II tumors; and (3) the impact of mitotane- and cisplatin-based chemotherapy for unresectable and metastatic disease.

The ARAR0332 protocol also attempts to provide further insight into the biology of ACC and the different patterns of *TP53* mutations. In addition to the near-requisite germline *TP53* mutations, a number of consistent chromosomal gains and losses have been observed in childhood ACT. These genetic alterations

Table 42.2.2 Treatment on the COG ARAR 0332 protocol

Stage	Treatment
Stage I	• Surgery alone
Stage II	• Surgery • RPLN dissection
Stage III	• Mitotane • CDDP/ETO/DOX • Surgery + RPLN dissection
Stage IV	• Mitotane • CDDP/ETO/DOX • Surgery + RPLN dissection

RPLN retroperitoneal lymph node, *CDDP* cisplatin, *ETO* etoposide, *DOX* doxorubicin

Table 42.4.1 Guidelines for diagnosis and management of pediatric adrenocortical tumors

Physical examination	Virilization is a hallmark. Other signs of hormone hyperproduction such as Cushing's syndrome or hypertension are also common. Less frequently, signs of Beckwith–Wiedemann or MEN-I syndromes
Laboratory assessment	High adrenal hormones, primarily DHEA, DEHA-S, and Androstendione; less frequently cortisol, deoxycorticosterone
Radiological assessment	Always try to limit radiation exposure in young children with possible or documented germline *TP53* mutation
– First assessment	Ultrasonogram or computed tomography (CT) of the abdomen
– Local staging	CT or MRI of the abdomen. Important to visualize adrenal veins and inferior vena cava for tumor thrombus, and retroperitoneal structures for nodal metastases (rare). Tumor implants may be present in tumor spillage
– Diagnostic work	CT chest to rule out lung metastases and to visualize superior vena cava for tumor thrombus. PET scan has proven to be helpful in diagnosis and monitoring of recurrence
Pathological assessment	Always avoid needle biopsy due to risk of tumor spillage. Distinction between adenomas and carcinomas often difficult. Size and presence of mitosis, necrosis, and nuclear atypia are associated with adverse outcome
Staging systems for risk-adapted treatment strategy	*Stage I* – Completely resected, small tumors (<100 g and <200 cm^3) with normal postoperative hormone levels *Stage II* – Completely resected, large tumors (≥100 g or ≥200 cm^3) with normal postoperative hormone levels *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 metastases
General treatment guidelines	Importance of a multidisciplinary approach, with aggressive surgery of primary and metastatic lesions
– Surgery	Keystone of therapy; upfront resection if possible
	Risk of tumor rupture and spillage is high, and therefore, laparoscopic procedures should be avoided
– Radiotherapy	Should be avoided when possible given the high frequency of germline *TP53* mutations in young children with ACT
	Role limited to palliation
– Chemotherapy	For patients with locally advanced and metastatic disease
	Cisplatin-based regimens, usually including etoposide and doxorubicin
	Long-term treatment with mitotane is recommended, but levels must be monitored closely
– Radiofrequency ablation	Helpful in cases of unresectable disease
– Supportive care	Importance of close endocrinologic monitoring; patients on mitotane often develop long-term adrenal insufficiency, hypothyroidism, and other hormonal dysfunctions

presumably favor the expression of tumor-promoting oncogenes while eliminating potential tumor suppressors. Genomic DNA analyses used with microarray gene expression profiling should allow the identification of the genes that cooperate with p53 inactivation to promote development of ACT.

42.3 Medulloepithelioma

Gianni Bisogno

Medulloepithelioma (MEP) is a rare tumor derived from the primitive neuroepithelium located in the ciliary body of the eye; however, tumors arising from the optic nerve or from the central nervous system have also been described (Vajaranant et al. 2005; Molloy et al. 1996).

Ocular medulloepitheliomas occur in early childhood with a mean age at diagnosis of 4 years. Rarely, these tumors can affect adults possibly as a late malignant transformation of a benign asymptomatic MEP arisen in childhood (Carrillo and Streeten 1979). It is a locally aggressive tumor that may extend anteriorly into the iris or posteriorly into the vitreous cavity involving the retina, with the entire globe filled with tumor similar to retinoblastoma. In advanced cases, it may present with extraocular extension and involve the regional lymph nodes. Distant metastasis to lungs and parotid gland have been rarely described (Broughton and Zimmerman 1978; Viswanathan et al. 2008). There is no racial or sexual predilection, and both eyes are equally affected (Vajaranant et al. 2005).

MEP can be associated with central nervous system malignancies (i.e., pinealoblastoma) or malformations (i.e., corpus callosum agenesia, schizencephaly) (Vajaranant et al. 2005). In addition, it has recently been suggested that MEP is a manifestation of a familiar tumor predisposition associated with pleuropulmonary blastoma (Priest et al. 2011).

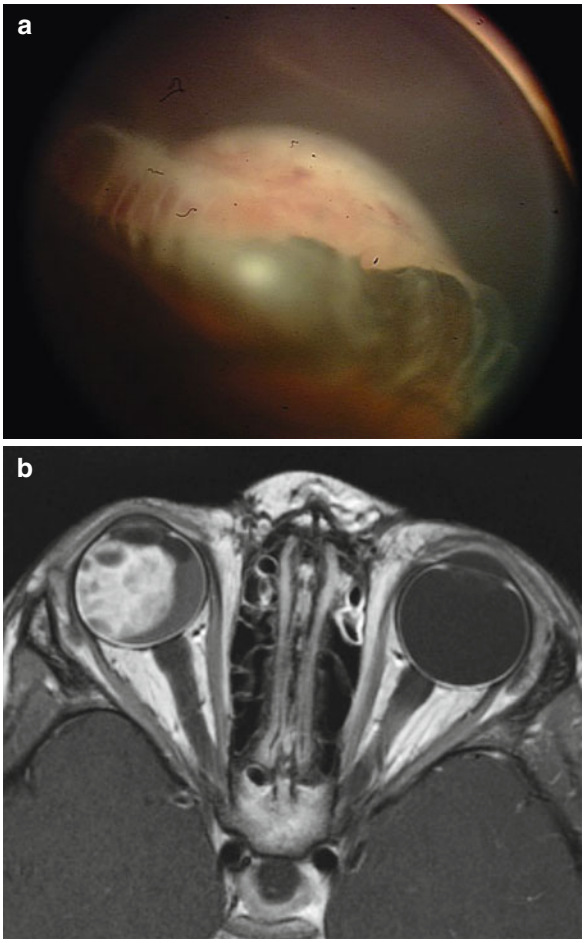

Fig. 42.3.1 (**a**) Medulloepithelioma-Variably pigmented cilliary body mass. (**b**) MRI highlights characteristic intralesional cysts.

42.3.1 Clinical Characteristics

The most common presenting symptoms are pain and poor vision, related to secondary lens subluxation, glaucoma, or cataract formation. Leukocoria and the evidence of a mass in the iris or ciliary body are also part of the initial signs (Chung et al. 2007).

On fundoscopic examination, the tumor presents an irregular surface with characteristic cystic lesions (Fig. 42.3.1a). In up to 60% of patients, cysts break off the surface and float freely in aqueous or vitreous humor. Retinal detachment is seen in many cases. MEP may also contain calcifications in some cases (Chung et al. 2007).

On ultrasound, MEP appears as an echogenic irregular mass with a cystic structure and calcification in some cases. CT scan shows a dense irregular mass in the region of the ciliary body with marked to moderate enhancement after contrast. On MRI, the mass is moderately hyperintense compared to vitreous on T1-weighted images, hypointense on T2-weighted images with marked enhancement after gadolinium administration (Fig. 42.3.1b) (Vajaranant et al. 2005).

42.3.2 Diagnosis

The diagnosis requires a histopathologic examination. MEP is characterized by proliferating sheets and cords of poorly differentiated neuroepithelium with cystic

spaces in between and rosette-like structures visible in some cases. It has been classified as teratoid and nonteratoid types. The nonteratoid MEP medulloepithelioma is a pure proliferation of cells of the medullary epithelium. The teratoid subtype includes also heteroplastic elements, such as cartilage, skeletal muscle, and brain-like tissue, and account for 30–50% of cases. Benign MEPs medulloepitheliomas exist, but more than two third of cases are malignant. The histopathological criteria for malignancy are the presence of poor cellular differentiation, cellular pleomorphism, sarcomatous changes, and invasion of surrounding ocular tissues (Broughton and Zimmerman 1978).

When MEP is very extensive and includes calcification, it may be difficult to distinguish it from an anteriorly located retinoblastoma. Differential diagnosis should also include benign conditions such xanthogranuloma, a cyst of the ciliary body, or the persistence and hyperplasia of the primary vitreous (PHPV) (Vajaranant et al. 2005; Chung et al. 2007).

42.3.3 Treatment

MEP treatment is usually based on the surgical removal of the tumor. Limited procedures can be adopted with small tumors, but enucleation may be necessary in larger lesions and exenteration when there is evidence of extraocular extension. Unfortunately, there is a substantial risk of relapse even after a complete tumor resection. The prognosis is less favorable for tumors with extraocular extension. In these cases, chemotherapy and/or radiotherapy have been adopted. Recent reports have showed tumor response after the administration of a regimen including vincristine, carboplatin and etoposide underlining the possible use of preoperative chemotherapy to limit the aggressiveness of surgery (Meel et al. 2010). The successful use of brachytherapy after conservative surgery has also been reported (Cassoux et al. 2010).

MEP may also arise from the optic nerve from where it may extend anteriorly into the ocular globe or posteriorly, intracranially. Enucleation with resection of the optic nerve is the usual therapeutic approach. When radiotherapy and chemotherapy have been implemented, there is conflicting results (Chavez et al. 2004).

A small series of MEP arising in the central nervous system has been published, and the most common location is the periventricular region; however, the prognosis is poor (Molloy et al. 1996).

42.4 Chordoma

Gianni Bisogno

Chordoma is a rare but aggressive tumor that occurs in the spine. It is believed to arise from notochord remnants located along the craniovertebral axis. The notochord develops during the third week of gestation and is located in the central portion of the future vertebral bodies. When vertebrae develop, the notochord cells form the nucleus pulposis of the intervertebral discs. It has never been shown that intravertebral discs are the site of origin of chordoma, but the fact that this tumor most frequently arises in the sacrococcygeal and sphenooccipital regions, where ectopic notochord remnants are most often found in fetuses, and with the morphological similarities between notochord and chordoma cells supports this view.

It has been estimated that about 300 new cases of chordoma/year occur in the United States, and this correspond to an incidence of approximately one case per million people/year (McMaster et al. 2001).The median age at presentation is 60 years. It is extremely rare in children and young adults where it represents less than 5% of all chordomas. No sex predisposition has been described.

Chordoma etiology is unknown. Rarely, families with multiple affected members have been reported, suggesting an inherited condition. Although extremely rare, chordoma in children and young adults present distinctive clinical and pathological characteristics but share with adults the same unsatisfactory prognosis.

42.4.1 Clinical Characteristics

In younger patients, chordoma more frequently arises at the base of the skull, including the clivus, rather than in the mobile spine and sacrum which are the typical site in adults (Hoch et al. 2006). Very rarely, chordoma can occur outside the spine.

The tumor tends to remain localized, but the risk of distant dissemination seems higher in children under 5 years, with metastasis most frequently in the lungs, but also in lymph nodes, bone, liver kidney, adrenal gland, and heart (Borba et al. 1996).

Chordoma is generally a slow-growing neoplasm and causes symptoms from invading the nearby structures. Pain and neurological signs are more often reported: skull base tumors cause headache, cranial

nerves palsy, and torticollis, while chordoma of the spine cause alteration of bowel and/or bladder function, pain, tingling, and numbness or weakness of the arms and legs.

42.4.2 Diagnosis

Chordoma usually presents as a soft tissue mass associated with bone destruction and may extend into the intracranial compartment and sphenoid bone and sphenoid sinus. Both MRI and CT scan are employed to have a clear picture of tumor extension and bone involvement. CT shows an enhancing soft tissue mass with internal densities thought to represent fragments of bone and invasion of surrounding structures. On MRI, the lesion presents variable intensity and enhancement on T1-weighted images and high signal intensity on T2-weighted images (Lui et al. 2011).

A total body CT scan is also indicated to exclude distant metastasis. Conventional (or classic) chordoma is histologically characterized by a lobular pattern of growth with epithelioid cells arranged in nests, sheets, and syncytial cords in an abundant mucoid matrix.

The cells show some degree of nuclear atypia, the number of mitosis is usually low, and some necrosis may be present. Immunohistochemistry is usually positive for cytokeratin, epithelial membrane antigen, vimentin, S-100 protein, and variably for carcinoembryonic antigen and NSE. According to Louis et al. (2007), two more subtypes are recognized: the chondroid chordoma that contains elements that resembles neoplastic hyaline cartilage and behaves less aggressively than the conventional type, and the dedifferentiated chordoma, rarely encountered in children. Two more subtypes have been described in the pediatric age: (a) the cellular chordoma, possibly a conventional chordoma that lacks stroma, and (b) the poorly differentiated chordoma composed of sheets of epithelioid cells tightly packed with high nuclear/cytoplasmic ratio and distinct nucleoli. This latter variant affects very young children, behaving aggressively, tending to grow rapidly, and is often associated with metastasis (Hoch et al. 2006).

The differential diagnosis with chondrosarcomas may be difficult as they can occur in the same locations and share some morphological similarities (Rosenberg et al. 1999).

42.4.3 Treatment

Due to the small number of cases described in the literature, the management of pediatric cases of chordoma mainly derives from the experience gathered with adults.

Surgery has an established role, and complete tumor resection at diagnosis provides the best chances for local control and long-term survival (Park et al. 2006; Tzortzidis Elahi et al. 2006). Unfortunately, aggressive surgery is often required with a high risk of postoperative death (Borba et al. 1996) and significant morbidity (Sekhar et al. 2001). In most cases, only partial tumor resection is feasible and high-dose radiotherapy is administered. Doses in excess of 60 Gy are required, and this represents a major limitation in children. Techniques to maximize the dose of radiation to the tumor, while sparing adjacent critical structures, have been used, including proton therapy and intensity-modulated radiation therapy (IMRT). A limited number of patients have been treated so far, and the results seem promising: an overall survival of 81% has been reported in a series of 73 children and adolescents treated with proton bean radiotherapy after surgery. This compares favorably with a 55% 5-year survival described in adults with chordoma treated at the same institution (Hoch et al. 2006).

Chordomas are generally resistant to chemotherapy with only few reports describing a response to chemotherapy, including ifosfamide and doxorubicin (Scimeca et al. 1996), ifosfamide and etoposide (Dhall et al. 2011), or cisplatinum, vinblastine, and bleomycin (Azzarelli et al. 1988). The administration of 9-nitro-camptothecin in a phase 2 study including 15 patients with chordoma reported only one patient with an objective response (Chugh et al. 2005).

Recently, imatinib has been shown to have antitumor effects in some patients with advanced chordomas (Casali et al. 2004). The use of other targeted therapies such as cetixumab and gefinitinib has been reported (Hof et al. 2006).

42.4.4 Prognosis and Survival

Currently, the overall survival rate for chordoma in adults in the United States is 68% at 5 years and 40% at 10 years, with a median survival of about 7 years (McMaster et al. 2001).

Reports describing pediatric cases have shown conflicting results with some series describing worse results than in adults (Coffin et al. 1993). Recent reports of patients treated at single institutions have shown better outcome with four out of six patients alive at a median follow-up of 9 years described by Dhall et al. (2011) and an overall survival rate of 81% (median follow-up 7.2 years) in a cohort of patients with skull base chordoma referred to the Boston Massachusetts General Hospital for proton beam radiotherapy (Hoch et al. 2006). Complete tumor resection (Hug 2001) and histological subtype (Hoch et al. 2006) seem to be the major prognostic determinants. Patients with conventional chordoma have the best prognosis, while the chance of survival in the poorly differentiated subtype remains very low.

References

Intra-adrenal (Pheochromocytoma) and Extra-adrenal Paraganglioma

Auerbach SD, Steakley LS, Young Rc et al (1988) Malignant phaeochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine and dacarbazine. Ann Intern Med 109:267–273

Barontini M, Levin G, Sanso G (2006) Characteristics of pheochromocytoma in a 4- to 20-year-old population. Ann N Y Acad Sci 1073:30–37

Beltsevich DG, Kuznetsov NS, Kazaryan AM et al (2004) Pheochromocytoma surgery: epidemiologic peculiarities in children. World J Surg 28:592–596

Benn DE, Gimenez-Roqueplo AP, Reilly JR et al (2006) Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab 91: 827–836

Borba LA, Al-Mefty O (1996) Intravagal paragangliomas: report of four cases. Neurosurgery 38:569–575

Bravo EL, Kalmadi SR, Gill I (2009) Clinical utility of temozolomide in the treatment of malignant paraganglioma: a preliminary report. Horm Metab Res 41(9):703–706

Brunt LM, Lairmore TC, Doherty GM et al (2002) Adrenalectomy for familial pheochromocytoma in the laparoscopic era. Ann Surg 235:713–720

Caty MG, Coran AG, Geagen M et al (1990) Current diagnosis and treatment of pheochromocytoma in children. Experience with 22 consecutive tumors in 14 patients. Arch Surg 125:978–981

Chrisoulidou A, Kaltsas G, Ilias I et al (2007) The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 14:569–585

Criftci AO, Tanyel FC, Senocak ME et al (2001) Phaeochromocytoma in children. J Pediatr Surg 36: 447–452

Dardik A, Eisele DW, Williams GM et al (2002) A contemporary assessment of carotid body tumor surgery. Vasc Endovascular Surg 36:277–283

Deal JE, Sever PS, Barratt TM et al (1990) Pheochromocytoma – investigation and management of 10 cases. Arch Dis Child 65:269–274

de Krijger RR, Petri BJ, van Nederveen FH et al (2006) Frequent genetic changes in childhood pheochromocytomas. Ann N Y Acad Sci 1073:166–176

Dickinson PH, Griffin SM, Guy AJ et al (1986) Carotid body tumor: 30 years experience. Br J Surg 73:14–16

Ein SH, Standling B, Wesson D et al (1990) Recurrent phaeochromocytomas in children. J Pediatr Surg 25:1063–1065

Ein SH, Pullerits J, Creighton R et al (1997) Pediatric phaeochromocytoma. A 36-year review. Pediatr Surg Int 12:595–598

Eisenhofer G, Walther MM, Huynh TT et al (2001) Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. J Clin Endocrinol Metab 86:1999–2008

Fletcher CDM, Unni KK, and Mertens F (2002) WHO Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone. IARC Press, Lyon

Goldstein RE, O'Neill JA Jr, Holcomb GW III et al (1999) Clinical experience over 48 years with pheochromocytoma. Ann Surg 229:755–764

Gonias S, Goldsby R, Matthay KK et al (2009) Phase II study of high-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. J Clin Oncol 27(25):4162–4168

Gounot E, Couillault G, Maingueneau C et al (1990) Paraganglioma of the carotid body. Apropos of a case in a 14-year-old child. Chir Pediatr 31:125–126

Gujrathi CS, Donald PJ (2005) Current trends in the diagnosis and management of the head and neck paragangliomas. Curr Opin Otolaryngol Head Neck Surg 13:339–342

Hack HA (2000) The perioperative management of children with phaeochromocytoma. Paediatr Anaesth 10:463–476

Hajnzic TF, Kruslin B, Belicza M (1999) Carotid body paraganglioma in a 9-year-old boy with extensive pulmonary metastases. Med Pediatr Oncol 32:399–400

Havekes B, Corssmit EP, Jansen JC et al (2007) Malignant paragangliomas associated with mutations in the succinate dehydrogenase D gene. J Clin Endocrinol Metab 92:1245–1248

Haws R, Joseph M, Adelman R (2007) Two cases of pheochromocytoma presenting with ADHD (attention deficit hyperactivity disorder)-like symptoms. Pediatr Nephrol 23: 473–475

Ilias I, Pacak K (2004) Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 89:479–491

Lenders JW, Pacak K, Walther MM et al (2002) Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 287:1427–1434

Lenders JW, Eisenhofer G, Mannelli M et al (2005) Phaeochromocytoma. Lancet 366:665–675

Loh KC, Fitzgerald PA, Matthay KK et al (1997) The treatment of malignant phaeochromocytoma with iodine-131 metaiodobenzylguanidine (131I-MIBG): a comprehensive review of 116 reported patients. J Endocrinol Invest 29:648–658

Ludwig AD, Feig DI, Brandt ML et al (2007) Recent advances in the diagnosis and treatment of pheochromocytoma in children. Am J Surg 194:792–796

Ong KR, Woodward ER, Killick P et al (2007) Genotype-phenotype correlations in von Hippel-Lindau disease. Hum Mutat 28:143–149

Ophir D (1991) Familiar multicentric paragangliomas in a child. J Laryngol Otol 105:376–380

Pacak K, Linehan WM, Eisenhofer G et al (2001) Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 134:315–329

Pacak K, Eisenhofer G, Ahlman H et al (2007) Pheochromocytoma: recommendations for clinical practice from the first international symposium, October 2005. Nat Clin Pract Endocrinol Metab 3:92–102

Pellitteri PK, Rinaldo A, Myssiorek D et al (2004) Paragangliomas of the head and neck. Oral Oncol 40:563–575

Pham TH, Moir C, Thompson GB et al (2006) Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. Pediatrics 118:1109–1117

Sawka AM, Jaeschke R, Singh RJ et al (2003) A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 88:553–558

Shamblin WR, ReMine WH, Sheps SG et al (1971) Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. Am J Surg 122:732–739

Sisson JC, Shapiro B, Shulkin BL et al (1999) The treatment of malignant phaeochromocytoma with 131-I metaiodobenzylguanidine and chemotherapy. Am J Clin Oncol 22:364

Spoudeas HA, Harrison B (2005) Paediatric endocrine tumours. The British Society of Paediatric Endocrinology and Diabetes and the UK Children's Cancer Study Group, West Sussex

Stringel G, Ein SH, Creighton R et al (1980) Pheochromocytoma in children – an update. J Pediatr Surg 15:496–500

Takautz TM, Pratt CB, Jenkins JJ et al (2003) Pediatric extraadrenal paragaglioma. J Pediatr Surg 38:1317–1321

Thompson JW, Cohen SR (1989) Management of bilateral carotid body tumors and a glomus jugulare tumor in a child. Int J Pediatr Otorhinolaryngol 17:75–87

Timmers HJ, Kozupa A, Chen CC et al (2007a) Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. J Clin Oncol 25:2262–2269

Timmers HJ, Kozupa A, Eisenhofer G et al (2007b) Clinical presentations, biochemical phenotypes, and genotype-phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. J Clin Endocrinol Metab 92:779–786

van der Mey AG, Jansen JC, van Baalen JM (2001) Management of carotid body tumors. Otolaryngol Clin North Am 34:907–924

Velchik M, Alavi A, Kresse LH (1989) Localisation of phaeochromocytoma. MIBG, CT and MR correlation. J Nucl Med 30:328–336

Weise M, Merke DP, Pacak K et al (2002) Utility of plasma free metanephrines for detecting childhood pheochromocytoma. J Clin Endocrinol Metab 87:1955–1960

Zaupa P, Höllwarth ME (2007) Carotid body paraganglioma: rare tumor in a 15-year-old adolescent boy. J Pediatr Surg 42:E13–E17

Adrenocortical Tumors in Children

Almeida MQ, Fragoso MCBV, Lotfi CFP et al (2008) Expression of insulin-like growth factor-II and its receptor in pediatric and adult adrenocortical tumors. J Clin Endocrinol Metab 93:3524–3531

Ariffin H, Martel-Planche G, Daud SS, Ibrahim K, Hainaut P (2008) Li-Fraumeni syndrome in a Malaysian kindred. Cancer Genet Cytogenet 186:49–53

Ayass M, Gross S, Harper J (1991) High-dose carboplatinum and VP-16 in treatment of metastatic adrenal carcinoma. Am J Pediatr Hematol Oncol 13:470–472

Barlaskar FM, Hammer GD (2007) The molecular genetics of adrenocortical carcinoma. Rev Endocr Metab Disord 8:343–348

Barlaskar FM, Spalding AC, Heaton JH et al (2009) Preclinical targeting of the type I insulin-like growth factor receptor in adrenocortical carcinoma. J Clin Endocrinol Metab 94: 204–212

Bernstein L, Gurney JG (1999) Carcinomas and other malignant epithelial neoplasms. In: Ries LAG, Smith MA, Gurney JG et al (eds) Cancer and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, SEER program, Bethesda, pp 139–147

Birch J, Alston RD, McNally RJQ et al (2001) Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene 20:4621–4628

Boulle N, Logie A, Gicquel C, Perin L, Le Bouc Y (1998) Increased levels of insulin-like growth factor II (IGF-II) and IGF binding protein-2 are associated with malignancy in sporadic adrenocortical tumors. J Clin Endocrinol Metab 83:1713–1720

Bugg MF, Ribeiro RC, Roberson PK et al (1994) Correlation of pathologic features with clinical outcome in pediatric adrenocortical neoplasia. Am J Clin Pathol 101:625–629

Ciftci AO, Senocak ME, Tanyel FC, Buyukpamukcu N (2001) Adrenocortical tumors in children. J Pediatr Surg 36:549–554

Coelho Netto AS, Wajchenberg BL, Ravaglia C et al (1963) Treatment of adrenocortical cancer with o,p′-DDD. Ann Intern Med 59:74–78

Crucitti F, Bellantone R, Ferrante A, Boscherini M, Crucitti P (1996) The Italian registry for adrenal cortical carcinoma: analysis of a multiinstitutional series of 129 patients. The ACC Italian Registry Study Group. Surgery 119:161–170

De Leon DD, Lange BJ, Walterhouse D, Moshang T (2002) Long-term (15 years) outcome in an infant with metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 87:4452–4456

de Reynies A, Assie G, Rickman DS et al (2009) Gene expression profiling reveals a new classification of adrenocortical tumors and identifies molecular predictors of malignancy and survival. J Clin Oncol 27:1108–1115

DiGiammarino EL, Lee AS, Cadwell C et al (2001) A novel mechanism of tumorigenesis involving pH-dependent destabilization of a mutant p53 tetramer. Nat Struct Biol 9:12–16

Doghman M, Karpova T, Rodrigues GA et al (2007) Increased steroidogenic factor-1 dosage triggers adrenocortical cell proliferation and cancer. Mol Endocrinol 21:2968–2987

Dohna M, Reincke M, Mincheva A, Allolio B, Solinas-Toldo S, Lichter P (2000) Adrenocortical carcinoma is characterized by a high frequency of chromosomal gains and high-level amplifications. Genes Chromosomes Cancer 28:145–152

Driver CP, Birch J, Gough DCS, Bruce J (1998) Adrenal cortical tumors in childhood. Pediatr Hematol Oncol 15:527–532

Erickson LA, Jin L, Sebo TJ et al (2001) Pathologic features and expression of insulin-like growth factor-2 in adrenocortical neoplasms. Endocr Pathol 12:429–435

Figueiredo BC, Stratakis CA, Sandrini R et al (1999) Comparative genomic hybridization analysis of adrenocortical tumors of childhood. J Clin Endocrinol Metab 84:1116–1121

Figueiredo BC, Sandrini R, Zambetti GP et al (2006) Penetrance of adrenocortical tumours associated with the germline TP53 R337H mutation. J Med Genet 43:91–96

Gicquel C, Bertagna X, Gaston V et al (2001) Molecular markers and long-term recurrences in a large cohort of patients with sporadic adrenocortical tumors. Cancer Res 61: 6762–6767

Gonzalez RJ, Shapiro S, Sarlis N et al (2005) Laparoscopic resection of adrenal cortical carcinoma: a cautionary note. Surgery 138:1078–1086

Gonzalez KD, Noltner KA, Buzin CH et al (2009) Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 27:1250–1256

Hanna AM, Pham TH, Skegard-Giesmann JR et al (2008) Outcome of adrenocortical tumors in children. J Pediatr Surg 43:843–849

Harrison LE, Gaudin PB, Brennan MF (1999) Pathologic features of prognostic significance for adrenocortical carcinoma after curative resection. Arch Surg 134:181–185

Hoffer FA, Daw NC, Xiong X et al (2009) A phase 1/pilot study of radiofrequency ablation for the treatment of recurrent pediatric solid tumors. Cancer 115:1328–1337

Hovi L, Wikström S, Vettenrante K, Heikkilä P, Saarinen-Pihkala UM (2003) Adrenocortical carcinoma in children: a role for etoposide and cisplatin adjuvant therapy? Preliminary report. Med Pediatr Oncol 40:324–326

Hoyme HE, Seaveer LH, Jones KL, Procopio F, Crooks W, Feingold M (1998) Isolated hemihyperplasia (Hemihypertrophy): report of a prospective multicenter study of the incidence of neoplasia and review. Am J Med Genet 79:274–278

Ilvesmaki V, Kahri AI, Miettinen PJ, Voutilainen R (1993) Insulin-like growth factors (IGFs) and their receptors in adrenal tumors: high IGF-II expression in functional adrenocortical carcinomas. J Clin Endocrinol Metab 77: 852–858

Kardar AH (2001) Rupture of adrenal carcinoma after biopsy. J Urol 166:984

Kendrick ML, Lloyd R, Erickson L et al (2001) Adrenocortical carcinoma: surgical progress or status quo? Arch Surg 136:543–549

Khayat CM, Johnston DL (2004) Rhabdomyosarcoma, osteosarcoma, and adrenocortical carcinoma in a child with a germline p53 mutation. Pediatr Blood Cancer 43:683–686

Kirschner LS (2002) Signaling pathways in adrenocortical cancer. Ann N Y Acad Sci 968:222–239

Kirschner LS (2006) Emerging treatment strategies for adrenocortical carcinoma: a new hope. J Clin Endocrinol Metab 91:14–21

Kleihues P, Schäuble B, zur Hausen A, Estève J, Ohgaki H (1997) Tumors associated with p53 germline mutations. A synopsis of 91 families. Am J Pathol 150:1–13

Langer P, Cupisti K, Bartsch DK et al (2002) Adrenal involvement in multiple endocrine neoplasia type 1. World J Surg 26:891–896

Lee JE, Berger DH, el-Naggar AK et al (1995) Surgical management, DNA content, and patient survival in adrenal cortical carcinoma. Surgery 118:1090–1098

Leung LYJ, Leung WY, Chan KF, Fan TW, Chung KW, Chan CHS (2002) Ruptured adrenocortical carcinoma as a cause of paediatric acute abdomen. Pediatr Surg Int 18: 730–732

Loncarevic IF, Herin A, Pososrki N, Linden T, Hoyer H, Bucksy P (2008) Number of genomic imbalances correlates with the overall survival for adrenocortical cancer in childhood. Pediatr Blood Cancer 51:356–362

Mackie GC, Shulkin BL, Ribeiro RC et al (2006) Use of [18F] fluorodeoxyglucose positron emission tomography in evaluating locally recurrent and metastatic adrenocortical carcinoma. J Clin Endocrinol Metab 91:2665–2671

Michalkiewicz EL, Sandrini R, Bugg MF et al (1997) Clinical characteristics of small functioning adrenocortical tumors in children. Med Pediatr Oncol 28:175–178

Michalkiewicz E, Sandrini R, Figueiredo B et al (2004) Clinical and outcome characteristics of children with adrenocortical tumors. An analysis of 254 cases from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol 22:838–845

Murphy JJ, Tawfeeq M, Chang B, Nadel H (2008) Early experience with PET/CT scan in the evaluation of pediatric abdominal neoplasms. J Pediatr Surg 43:2186–2192

Narasimhan KL, Samujh R, Bhansali A et al (2003) Adrenocortical tumors in childhood. Pediatr Surg Int 19:432–435

Ostuni JA, Roginsky MS (1975) Metastatic adrenal cortical carcinoma: documented cure with combined chemotherapy. Arch Intern Med 135:1257–1258

Pianovski MAD, Maluf EMCP, de Carvalho DS et al (2006) Mortality rate of adrenocortical tumors in children Under 15 years of age in Curitiba, Brazil. Pediatr Blood Cancer 47:56–60

Reincke M, Karl M, Travis WH et al (1994) p53 mutations in human adrenocortical neoplasms: immunohistochemical and molecular studies. J Clin Endocrinol Metab 78: 790–794

Ribeiro RC, Figueiredo B (2004) Childhood adrenocortical tumours. Eur J Cancer 40:1117–1126

Ribeiro RC, Sandrini Neto R, Schell MJ, Lacerda L, Sambaio GA, Cat I (1990) Adrenocortical carcinoma in children: a study of 40 cases. J Clin Oncol 8:67–74

Ribeiro J, Ribeiro RC, Fletcher BD (2000) Imaging findings in pediatric adrenocortical carcinoma. Pediatr Radiol 30: 45–51

Ribeiro RC, Sandrini F, Figueiredo B et al (2001) An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci USA 98:9330–9335

Rodriguez-Galindo C, Figueiredo BC, Zambetti GP, Ribeiro RC (2005) Biology, clinical characteristics, and management of

adrenocortical tumors in children. Pediatr Blood Cancer 45:265–273
Rosati R, Cerrato F, Doghman M et al (2008) High frequency of loss of heterozygosity at 11p15 and IGF2 overexpression are not related to clinical outcome in childhood adrenocortical tumors positive for the R337H TP53 mutation. Cancer Genet Cytogenet 186:19–24
Rossbach H-C, Baschinsky D, Wynn T, Obzut D, Sutcliffe M, Tebbi C (2008) Composite adrenal anaplastic neuroblastoma and virilizing adrenocortical tumor with germline TP53 R248W mutation. Pediatr Blood Cancer 50:681–683
Sandrini R, Ribeiro RC, DeLacerda L (1997) Childhood adrenocortical tumors. J Clin Endocrinol Metab 7:2027–2031
Slooten HV, Schaberg A, Smeenk D, Moolenaar AJ (1985) Morphologic characteristics of benign and malignant adrenocortical tumors. Cancer 55:766–773
Steenman M, Westerveld A, Mannens M (2000) Genetics of Beckwith-Wiedemann Syndrome-associated tumors: common genetic pathways. Genes Chromosomes Cancer 28:1–13
Stewart JN, Flageole H, Kavan P (2004) A surgical approach to adrenocortical tumors in children: the mainstay of treatment. J Pediatr Surg 39:759–763
Stojadinovic A, Ghossein RA, Hoos A et al (2002) Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol 20:941–950
Sutter JA, Grimberg A (2006) Adrenocortical tumors and hyperplasias in childhood – etiology, genetics, clinical presentation and therapy. Pediatr Endocrinol Rev 4:32–39
Teinturier C, Pauchard MS, Brugieres L, Landais P, Chaussain JL, Bougneres PF (1999) Clinical and prognostic aspects of adrenocortical neoplasms in childhood. Med Pediatr Oncol 32:106–111
Tissier F, Cavard C, Groussin L et al (2005) Mutations of {beta}-catenin in adrenocortical tumors: activation of the Wnt signaling pathway Is a frequent event in both benign and malignant adrenocortical tumors. Cancer Res 65:7622–7627
Tucci JR, Martins ACP, Suaid HJ et al (2005) The impact of tumor stage on prognosis in children with adrenocortical carcinoma. J Urol 174:2338–2342
Varan A, Unal S, Ruacan S, Vidinlisan S (2000) Adrenocortical carcinoma associated with adrenogenital syndrome in a child. Med Pediatr Oncol 35:88–90
Varley JM, McGown G, Thorncroft M et al (1999) Are there low-penetrance TP53 alleles? Evidence from childhood adrenocortical tumors. Am J Hum Genet 65:995–1006
Wagner J, Portwine C, Rabin K, Leclerc J-M, Narod SA, Malkin D (1994) High frequency of germline p53 mutations in childhood adrenocortical cancer. J Natl Cancer Inst 86:1707–1710
Wajchenberg BL, Pereira MAA, Medonca BB et al (2000) Adrenocortical carcinoma: clinical and laboratory observations. Cancer 88:711–736
Wang X, Liang L, Jiang Y (2007) Nine cases of childhood adrenal tumour presenting with hypertension and a review of the literature. Acta Paediatr 96:930–934
Weber MM, Fottner C, Schmidt P et al (1999) Postnatal overexpression of insulin-like growth factor II in transgenic mice is associated with adrenocortical hyperplasia and enhanced steroidogenesis. Endocrinology 140:1537–1543
Weber MM, Fottner C, Wolf E (2000) The role of the insulin-like growth factor system in adrenocortical tumorigenesis. Eur J Clin Invest 30(suppl 3):69–75
Weiss LM (1984) Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol 8:163–169
Weiss LM, Medeiros LJ, Vickery AL (1989) Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol 13:202–206
West AN, Ribeiro RC, Jenkins J et al (2006) Identification of a novel germ line variant hotspot mutant p53-R175L in pediatric adrenal cortical carcinoma. Cancer Res 66:5056–5062
West AN, Neale GA, Pounds S et al (2007) Gene expression profiling of childhood adrenocortical tumors. Cancer Res 67:600–608
Wieneke JA, Thompson LDR, Heffess CS (2003) Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. Am J Surg Pathol 27:867–881
Wood BJ, Abraham J, Hvizda JL, Alexander HR, Fojo T (2003) Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. Cancer 97:554–560
Wooten MD, King DK (1993) Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. Cancer 72:3145–3155
Zancanella P, Pianovski MAD, Oliveira BH et al (2006) Mitotane associated with cisplatin, etoposide, and doxorubicin in advanced childhood adrenocortical carcinoma. Mitotane monitoring and tumor regression. J Pediatr Hematol Oncol 28:513–524

Medulloepithelioma

Broughton WL, Zimmerman LE (1978) A clinicopathologic study of 56 cases of intraocular medulloepitheliomas. Am J Ophthalmol 85(3):407–418
Carrillo R, Streeten BW (1979) Malignant teratoid medulloepithelioma in an adult. Arch Ophthalmol 97(4):695–699
Cassoux N, Charlotte F, Sastre X et al (2010) Conservative surgical treatment of medulloepithelioma of the ciliary body. Arch Ophthalmol 128(3):380–381
Chavez M, Mafee MF, Castillo B et al (2004) Medulloepithelioma of the optic nerve. J Pediatr Ophthalmol Strabismus 41(1):48–52
Chung EM, Specht CS, Schroeder JW (2007) From the archives of the AFIP: pediatric orbit tumors and tumor like lesions: neuroepithelial lesions of the ocular globe and optic nerve. Radiographics 27(4):1159–1186
Meel R, Chawla B, Mohanti BK et al (2010) Ocular medulloepithelioma chemosensitivity. Ophthalmology 117(12):2440.e1–2440.e2
Molloy PT, Yachnis AT, Rorke LB et al (1996) Central nervous system medulloepithelioma: a series of eight cases including two arising in the pons. J Neurosurg 84:430–436
Priest JR, Williams GM, Manera R et al (2011) Ciliary body medulloepithelioma: four cases associated with pleuropulmonary blastoma–a report from the International Pleuropulmonary Blastoma Registry. Br J Ophthalmol 95(7):1001–1005
Vajaranant TS, Mafee MF, Kapur R et al (2005) Medulloepithelioma of the ciliary body and optic nerve: clinicopathologic, CT, and MR imaging features. Neuroimaging Clin N Am 15(1):69–83

Viswanathan S, Mukul S, Qureshi S et al (2008) Orbital medulloepitheliomas – with extensive local invasion and metastasis a series of three cases with review of literature. Int J Pediatr Otorhinolaryngol 72:971–975

Chordoma

Azzarelli A, Quagliuolo V, Cerasoli S et al (1988) Chordoma: natural history and treatment results in 33 cases. J Surg Oncol 37(3):185–191

Borba LA, Al-Mefty O, Mrak RE et al (1996) Cranial chordomas in children and adolescents. J Neurosurg 84(4): 584–591

Casali PG, Messina A, Stacchiotti S et al (2004) Imatinib mesylate in chordoma. Cancer 101(9):2086–2097

Chugh R, Dunn R, Zalupski MM et al (2005) Phase II study of 9-nitro-camptothecin in patients with advanced chordoma or soft tissue sarcoma. J Clin Oncol 23(15): 3597–3604

Coffin CM, Swanson PE, Wick MR et al (1993) Chordoma in childhood and adolescence. A clinicopathologic analysis of 12 cases. Arch Pathol Lab Med 117(9):927–933

Dhall G, Traverso M, Finlay JL et al (2011) The role of chemotherapy in pediatric clival chordomas. J Neurooncol 103(3):657–662

Dr. Ferrari or Dr. Bisogno, Tsai EC, Santoreneos S, Rutka JT (2002) Tumors of the skull base in children: review of tumor types and management strategies. Neurosurg Focus. May 15;12(5):e1

Hoch BL, Nielsen GP, Liebsch NJ et al (2006) Base of skull chordomas in children and adolescents: a clinicopathologic study of 73 cases. Am J Surg Pathol 30(7):811–818

Hof H, Welzel T, Debus J (2006) Effectiveness of cetuximab/gefitinib in the therapy of a sacral chordoma. Onkologie 29(12):572–574

Hug EB (2001) Review of skull base chordomas: prognostic factors and long-term results of proton-beam radiotherapy. Neurosurg Focus 10(3):E11

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (2007) WHO Classification of Tumours of the Central Nervous System, 4th edn. International Agency for Research on Cancer: Lyon

Lui YW, Dasari SB, Young RJ (2011) Sphenoid masses in children: radiologic differential diagnosis with pathologic correlation. AJNR Am J Neuroradiol 32(4):617–626

McMaster ML, Goldstein AM, Bromley CM et al (2001) Chordoma: incidence and survival patterns in the United States, 1973-1995. Cancer Causes Control 12:1–11

Park L, Delaney TF, Liebsch NJ et al (2006) Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. Int J Radiat Oncol Biol Phys 65(5):1514–1521

Rosenberg AE, Nielsen GP, Keelet SB et al (1999) Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol 23(11):1370–1378

Scimeca PG, James-Herry AG, Black KS et al (1996) Chemotherapeutic treatment of malignant chordoma in children. J Pediatr Hematol Oncol 18(2):237–240

Sekhar LN, Pranatartiharan R, Chanda A et al (2001) Chordomas and chondrosarcomas of the skull base: results and complications of surgical management. Neurosurg Focus 10(3):E2

Tzortzidis Elahi F, Wright D et al (2006) Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. Neurosurgery 59:230–237