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Rare adrenal tumors in children

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ABSTRACT

Apart from neuroblastomas, adrenal tumors are exceedingly rare in children and young adults. In this age group, the vast majority of patients present with clinical signs associated with excess hormone production. The most common tumor to arise from the adrenal cortex is an adrenocortical carcinoma (ACC). Similar to the situation in adults, this tumor is frequently diagnosed at a late stage and carries a very poor prognosis. ACCs require extensive/aggressive local resection followed by mitotane chemotherapy. A multidisciplinary approach is essential, and these children should be referred to units that have previous experience in managing ACCs. International registries are an invaluable source for evidence-based care, and such collaborations should be further developed in the future.

Pheochromocytomas are derived from the adrenal medulla and present with symptoms caused by high secretion of catecholamines. At least one-third of these children will be found to carry genetic mutations, most commonly the RET gene (MEN2 syndrome) or the VHL gene.

Open radical adrenalectomy should be offered to children with adrenocortical cancers. For all other cases, laparoscopic adrenalectomy is the treatment of choice. It is possible that the retroperitoneoscopic approach will gain increasing favor. The role of robotic adrenalectomy remains controversial.

Introduction

Tumors of the adrenal gland, other than neuroblastomas, are extremely rare in children. Consequently, adrenal surgery is seldom indicated in children and young adults, and the experience of the majority of individual surgeons remains very limited. For example, the national audit maintained by the *British Association of Endocrine Surgeons* (BAETS) has logged only 33 adrenalectomies in patients under 21 years of age out of a total of 1359 such operations performed by BAETS members (http://www.baets.org.uk/wp-content/uploads/2013/05/4th-National-Audit.pdf).

This article discusses the common indications and technical aspects of adrenal surgery in children by reviewing articles published in the last 10 years in the English literature. All information is based on non-randomized cohort studies from centers with large practice, as well as a few individual case reports that illustrate these conditions. This article does not address any issues related to neuroblastomas.

Etiology of adrenal tumors in children

The adrenal gland has two distinct parts: the cortex and the medulla. Each part has a different embryological origin, each produces different hormones, and each is the origin of different types of tumors.

The cortex arises from the mesoderm and starts to develop in the fourth week of gestation as a proliferation of the coelomic mesothelium into the underlying mesenchyme, between the root of the dorsal mesogastrium (the root of the mesentery) and the urogenital ridge (the mesonephros and the developing gonad). This close proximity explains why the ectopic adrenal tissue has been described to be located below the kidneys and associated with the testes or the ovaries.

In the initial phase, the *adrenogonadal primordium* (AGP) first gets distinguished and then expresses the essential transcription factor SF1 (steroidogenic factor 1). In the second phase (the 8th week of gestation in humans), the AGP separates into two distinct structures, the adrenal and the gonadal primordial. This second phase is followed by migration of neural crest cells through the fetal cortex to establish the medulla.

The embryogenesis of the adrenal medullary cells starts in the second month of gestation. Before this, during the fourth week of embryonic life, the neural plate develops and then infolds to form the neural tube. A portion of the neuroectoderm, adjacent to the tube, separates and remains between the neural tube and the definitive ectoderm as the neural crest. Cells derived from the neural crest (sympathogonia, primitive spinal ganglia) migrate ventrally from the apex of the neural tube to the dorsal aorta (where they aggregate and differentiate into neuroblasts to form sympathetic neurons) or to the adrenal primordia

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(where they differentiate into pheochromoblasts to form chromaffin cells).

At the end of gestation, the adrenal gland is organized into distinct zones: the *glomerulosa*, *transitory* (that appears between weeks 22 and 24, the future zona fasciculata) and the *dominant fetal zone*. Immediately after birth, the fetal zone undergoes rapid involution. Moreover, the zona reticularis starts to develop at the age of 4–6 or even 8 years, while structure typical to adults stabilizes at the age of 10–20 years. The fascicular and the reticular zones of the adult cortex proliferate from the glomerular zone after birth and are fully differentiated by about the 12th year.

Therefore, it appears that the adrenal gland in children is in a process of continuous transformation. In this context, tumors that develop in children are either sporadic or, more commonly, appear in the context of genetic syndromes associated with a risk of adrenal tumors. The most well-known associations are the development of pheochromocytomas in multiple endocrine neoplasia type 2 (MEN2) and in von Hippel–Lindau (VHL) syndromes and the appearance of adrenocortical carcinoma (ACC) as a hallmark cancer in families with Li–Fraumeni syndrome resulting from mutations in the TP53 gene.

Adrenocortical cancer

Incidence

Adrenocortical carcinomas (ACCs) are very rare tumors, with an incidence of 1–1.5 per million population per year. Data published by the *International Association of Cancer Registries* showed that there is a peak of incidence in childhood and 1 in the 5th decade of life. The situation differs in Brazil, where a disproportionately large number of children are diagnosed with an ACC due to p53 mutations.

Clinical presentation

Most children present with clinical signs. In a series of 20 children operated in a single center at a mean age of 7 years (range: 2.5–13), endocrine dysfunction was noted in 83% of the patients, with virilization being the most common presentation followed by Cushing's syndrome. A total of 14 patients presented with a palpable abdominal mass and three patients presented with distant metastases. The mean time from initial symptoms to diagnosis was 8 months. The majority (80%) had regional or metastatic disease by the time of presentation.[1] Similar findings from another series of 23 children with a mean age of 9 years reported tumor hormone production in 74% of patients and advanced stage of disease in 66%.[2] These findings were confirmed in a multicentre registry of 254 patients, of whom the majority (84.2%) had virilization, while Cushing's syndrome without virilization was uncommon (5.5%).[3] The high percentage of children with functioning tumors suggests that earlier detection is possible if there is increased awareness of this possible diagnosis amongst clinicians who assess these children at the onset of their symptoms.[2]

Diagnosis

In some patients, the diagnosis is suggested by the clinical presentation if signs of virilization are observed in a girl or rapid onset of “early puberty” occurs in a young child.

In the absence of signs of metastatic disease, the radiological suspicion of malignancy is generally based on the size of the tumor. For adults, the risk of an adrenal tumor representing an ACC increases from 4 cm (risk $< 5\%$) to > 10 cm (risk close to 100%). Likely, these dimensions have to be interpreted based on the age of the child. Further signs suggestive of malignancy include a high Hounsfield unit on unenhanced scans (> 10 HU) and rapid washout of the contrast. There are no studies assessing the role of PET scanning in children with adrenal tumors, but in adults the technique is commonly used to assess for metastatic disease. Furthermore, the SUV ratio between the liver and the adrenal tumor is used in some centers as a sign of malignancy. There is no role of biopsy of the adrenal gland as the cytological diagnosis of ACCs is unreliable, and the procedure can increase the risk of contamination of normal anatomical planes.

The histological diagnosis is based on assessing how many of the nine characteristics summarized on the Weiss score are present (nuclear grade, mitoses/50 high-power fields, atypical mitoses, clear cells, diffuse architecture, confluent necrosis, venous invasion, sinusoidal invasion, and capsular infiltration). Tumors with a score < 3 are benign, a score > 6 are malignant, and a score of 3–6 are indeterminate.

Surgical treatment

In all reported series, radical surgery is considered necessary in order to ensure complete excision; hence, in addition to adenalectomy, ipsilateral nephrectomy and/or right hepatic lobectomy plus nephrectomy should be considered.[1] The aim of such an aggressive approach is to limit the risk of local recurrence.

Postoperative treatment

Adjuvant chemotherapy consisting of mitotane or mitotane plus cisplatin and etoposide is commenced postoperatively. Systemic chemotherapy and mitotane therapy are both important therapeutic options in the treatment of advanced pediatric ACC patients. Neoadjuvant therapy should be considered for patients with primarily incompletely resectable or inoperable tumors, and tumor spillage is an indication for adjuvant chemotherapy and mitotane therapy. In the GPOH-MET-97 study, over half of the children had undergone chemotherapy (neoadjuvant, adjuvant, and salvage) and mitotane therapy. Duration of mitotane treatment longer than 6 months and mitotane levels greater than 14 mg/L were found to be associated with significantly better survival.[4]

Prognosis

The prognosis for these tumors is poor with an overall 5-year survival of less than 30%. In this context, it remains distressing to know that the vast majority of patients are treated in units that have minimal previous experience. The expectation is that all pediatric ACC patients should be treated in pediatric oncological centers according to a consistent protocol in a highly interdisciplinary setting (including surgeons experienced in radical adrenalectomy), but the rarity of the disease makes it difficult to monitor adherence to such guidelines worldwide. Nevertheless, in Germany, this approach has been followed since 1997, with all pediatric ACC patients being treated according to the non-randomized, single arm study—GPOH-MET-97. Data regarding 60 patients with ACC (age: 0.24–18 years, with a M:F gender ratio of 1:2) treated according to the GPOH-MET-97 protocol showed that among all patients, event-free survival and overall survival were 43% and 65%, respectively.[4] Children with a tumor volume > 300 mL ($n = 25$) showed an increased rate of operative complications and a poorer overall survival rate. A total of 14 patients showed metastatic spread, particularly to the lungs and lymph nodes. R2 resection only was achievable in 5 patients, and surgery was not feasible in 3 patients. Interestingly, preoperative biopsy and/or experienced tumor rupture was associated with poorer overall survival rate, reinforcing the view that biopsy