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Pediatric adrenal incidentaloma as a rare and difficult to diagnose finding – review

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Abstract

Adrenal incidentaloma (AI) is an asymptomatic mass localized in the adrenal gland, usually detected during diagnostic imaging performed due to other health issues than the suspected adrenal disease. It occurs in 2% of adults and 0,2% of children. Pediatric AI may cause many difficulties in the diagnostic processes. Neuroblastoma is one of the most common malignant tumors in children. Usually, it is localized in the medulla of the adrenal gland. Many patients do not have any symptoms, but some may present with fever, weariness, weight loss, pain, enlarging mass, etc. The majority of cases are high- risk and the survival rate is less than 50%. The diagnostic protocol consists of laboratory tests and radiological imaging. Treatment depends on the risk group that the patient is assigned to. Pheochromocytoma is a rare catecholamine-secreting tumor in children originating in the adrenal medulla. Most pediatric patients present with sustained hypertension. 60% of pheochromocytoma cases are sporadic. The surgical removal of the tumor through adrenalectomy is a standard procedure. To the group of pediatric adrenocortical tumors (ACT), benign adrenocortical adenoma (ACA) and malignant adrenocortical carcinoma (ACC) are included. ACA is found in only 20% of cases of ACT. Most of the patients present with signs of virilization, Cushing Syndrome, or both. The 5-years survival rate of ACC in the pediatric population is 46-55%. An adrenal incidentaloma is an unpredictable and possibly dangerous disorder in the pediatric population. Due to the rarity

of the finding and their variety, there is not much data and clear recommendations about AI management. Doctors need to know about the prevalence of different types of adrenal tumors in the pediatric population based on age.

Key words: Pediatric adrenal incidentaloma; neuroblastoma; pheochromocytoma; adrenocortical carcinoma

Introduction

Adrenal incidentaloma (AI) is an asymptomatic mass localized in the adrenal gland, usually detected during diagnostic imaging performed due to other health issues than the suspected adrenal disease (1). It occurs in 2% of adults, however, the prevalence is over 7% in the population of those over 70 years old(2). Pediatric adrenal incidentalomas bring many difficulties in the process of medical diagnosis and treatment. Firstly, AI is an extremely rare discovery in the pediatric population(3). The prevalence is around 0,2% in the pediatric population and it is increased with age(4).

If found in children, it is recommended to perform urgent additional assessment due to the increased risk of malignancy (3). However, the imaging does not allow for differentiating the benign and the malignant mass with 100% accuracy in young patients. Therefore, pediatric adrenal masses, whether benign or malignant, are surgically removed and then moved to histopathological evaluation. Secondly, adrenal tumors may not fit into certain histological criteria of malignancy (1). Due to the rarity and diversity of AI in children, limited data is available to establish histopathological criteria to distinguish benign mass from malignant tumor, especially when thinking of adrenocortical adenoma and adrenocortical carcinoma (5). The aim of this work is to raise awareness of risks and difficulties connected with the diagnostic process of pediatric adrenal incidentaloma and approximate the most common types of adrenal tumors and their prevalence in children.

Structure of adrenal gland

The adrenal gland consists of two components: cortex and medulla. Medulla produces catecholamines, adrenaline, and noradrenaline. Cortex takes part in steroidogenesis which is a process of making steroid hormones such as glucocorticoids, mineralocorticoids, and androgens. It is built of three unique layers differing histologically and functionally: the zona glomerulosa as the most outer zone, the zona fasciculate in the middle, and the most inner of layers- the zona reticularis. Each hormone is produced from the precursor cholesterol in a specific layer of the cortex due to the presence of enzymes needed in the process (6).

Neuroblastoma

Neuroblastoma is one of the most common malignant tumors in children. It represents 8-10% of cancer in the pediatric population (7,8). Neuroblastoma occurs in early childhood, with a peak incidence around 17-18 months of age. Almost 40% of diagnosed patients are under one year old and less than 5% of children with neuroblastoma are older than 10 years old (9). The tumor origins in the sympathetic nervous system and is most often found in the medulla of the adrenal gland (47%) (10,11). Other locations of the tumor are the abdominal/retroperitoneal region (24%), thorax (15%) and pelvis (3%) regions, and neck (3%) (11). Most of the cases happen sporadically, however, the autosomal dominant inheritance is noted (12). The anaplastic

lymphoma kinase (ALK) is observed in almost all the familial cases of neuroblastoma that account for 1-2% of all cases of the disease (9). Many patients do not have any symptoms, but some may present with fever, weariness, weight loss, pain, enlarging mass, etc. At the diagnosis, 50% of patients have localized disease, but 35% of them present with metastasis in regional lymph nodes (12). Neuroblastoma typically metastasizes to mentioned before regional lymph nodes and bone marrow, the metastatic tumors may also be found in the liver. Neuroblastoma is quite unpredictable- there may be spontaneous regression of the mass or a sudden and aggressive progression, even after applied treatment (11). The prognosis depends on a few factors, especially the age of the patient at diagnosis and stage of the disease according to the International Neuroblastoma Staging System (INSS). The majority of cases are high-risk and the survival rate is less than 50% contrary to patients with low or intermediate risk where 85-90% of them are cured (9). The initial diagnostic protocol includes basic laboratory tests such as morphology, electrolytes, and liver function tests. In the results, there may be an increased level of catecholamines or their metabolites such as dopamine, vanillylmandelic acid, or homovanillic acid in urine or serum. Also, nonspecific biomarkers such as lactate dehydrogenase, ferritin, and neuron-specific enolase could be found in patients, especially with a possible advanced stage of the disease and/or relapse (12). Radiological imaging of the neck, thorax, and pelvis is essential to localize the mass, evaluate the regional extent of the disease, and assess image-defined risk factors (IDRFs) which show a relationship of the neuroblastoma to vital structures such as vessels, organs, nerves, etc. To achieve that, magnetic resonance imaging (MRI) is used as it is preferred over computed tomography (CT) because of the absence of radiation, higher soft tissue contrast resolution, and better visualization of intraspinal extension (13). Iodine-meta-iodobenzylguanidine (MIBG) scan helps particularly with the detection of metastases, controlling response to the therapy, and checking for recurrence (12). MIBG is a norepinephrine analog and it accumulates in neuroblastoma due to connection with the norepinephrine transporter (NET) receptor which is detected in the tumor and any sympathetic tissue (14). The sensitivity and specificity of the MIBG scan are around 90% for neuroblastoma (13). The treatment depends on the risk group according to the International Neuroblastoma Risk Group (INRG) classification. In the INRG staging system, there are four stages describing the location of the tumor and its relation to other tissues or organs, the presence or not of metastases, and IDRFs. It is essential to choose the best therapy for patients- for low-risk to minimize or refrain from medical intervention and for the high-risk group to intensify the treatment. In the low-risk group, there is a strong possibility of spontaneous regression so the protocol is to observe (15). Some patients may need surgery or minimal chemotherapy. For the intermediate-risk group of children, milder chemotherapy followed by surgical removal of the remaining tumor is preferable. Treatment of high-risk patients consists of aggressive chemotherapy as induction therapy and then surgery followed by a high dose of chemotherapy with autologous stem cells transplantation and local radiotherapy (9). As post-consolidation isotretinoin combined with an anti-ganglioside 2 (GD2) antibody is used to prevent relapse (15).

Pheochromocytoma

Pheochromocytoma is a rare catecholamine-secreting tumor in children originating in the adrenal medulla. It is usually diagnosed between ages 9 and 12 years, two times more often in boys than girls (16). The incidence is 0.2-0.5 cases per million, however, pheochromocytoma is the most common endocrine tumor in the pediatric population, responsible for 0.5-1% of hypertensive cases in children (17). According to the rule of 10, which was created to help remember characteristic features of pheochromocytoma/ paraganglioma in adults, 10% happen in children, 10% of tumors are normotensive, 10% are extra-adrenal, 10% are malignant, 10% of cases are localized bilateral and 10% are familial (18,19), however, it is not as accurate

nowadays (18). The symptom triad of pheochromocytoma in children consists of headache, excessive sweating, and palpitations as a result of catecholamine overflow in the bloodstream (20). Most pediatric patients with pheochromocytoma present with sustained hypertension, however, the data from various studies showed that approximately around 70% of children have high blood pressure, not 90% as the rule says (18). Other symptoms may include anxiety, weight loss, visual disturbance, polyuria, and polydipsia (17). The percentage of malignant tumors in pediatrics varies from 9% to 16% (18). 60% of pheochromocytoma cases are sporadic, and the rest is hereditary. The familial cases may be associated with genetic syndromes, and Men2, VHL, Nand F1, and SDHx are the best-known from the group (17). However, it was noticed that even in children with apparently sporadic cases of pheochromocytoma the germline mutation could be present (18). Even 70-80% of pediatric patients do have an associated germline mutation that may be hereditary or not. The three most common defects are found in VHL (45,5%) SDHB and SDHD gene (18). At the beginning of a diagnostic process, it is recommended to perform metanephrine measurement in plasma and urine. Increased levels of adrenaline and norepinephrine metabolites are an indicator of the excessive secretion of catecholamines by the tumor. The second step is MRI or CT to find and evaluate the tumor to plan an adequate therapeutic approach (21). For both imaging methods, the sensitivity is around 90-100% and specificity stands at 70-80%. However, some voices favor MR scans over CT in children due to less radiation exposure (22). MIBG scan may also be used to look for metastases, offering 95-100% specificity of finding pheochromocytoma (21). The surgical removal of the tumor through adrenalectomy is a standard procedure (22). To avoid hypertensive crisis during the surgery, as a preoperative procedure selective alpha-blockers or a combination of alpha and beta blockers are applied (19). In the second protocol, the first alpha-blocker is used and then a beta blocker to suppress reflex tachycardia from antagonism of alpha- 2 receptors. The beta blocker must be always after the alpha-blocker to prevent a severe hypertensive crisis. The aim of blood pressure reduction is below 50 percentile for age and height (22). Calcium Chanel blockers may also be used to control blood pressure due to suppression of calcium-dependent norepinephrine release as well as tyrosine hydroxylase inhibitors which inhibit catecholamine synthesis (19,22). The patient should use a high sodium diet and high fluid intake to avoid hypertension from the vasodilatory characteristics of the medication. After the surgery, for malignant tumors, 131I-MIBG or chemotherapy may be offered. External beam radiotherapy is recommended to control metastatic pheochromocytoma (22).

Adrenocortical tumors (ACT)

To the group of pediatric ACT, adrenocortical adenoma (ACA) and adrenocortical carcinoma (ACC) are included. ACA is a benign mass, whereas ACC is highly aggressive. ACA is found in only 20% of cases of ACT and differentiation of a malignant tumor from a benign mass is troublesome (23). In their study, M.D. Traynor Jr and co. noted that among 40 children, 15% of them had incidentaloma and after histopathological evaluation in 20% of patients ACC was identified (24). ACT are very rare- 0,2-0,3 cases per 1 million children per year are noted but the incidence rate of ACT in Southern Brazil is 10-15 times higher probably due to the prevalence of TP53 mutation in the population (23). ACT are usually observed either under 4 years of age or to have a biphasic age distribution- under 5 years and over 10 years. 12% of cases may be found during the first year of life (5). According to a study by E. Michalkiewicz and co, generally, the most of patients are girls but it varies in different age groups (25). Majority of the patients present with signs of virilization, Cushing Syndrome, or both. Less than 10% of cases are asymptomatic but in laboratory tests, some of them may have abnormal levels of adrenal cortex hormones (26). Pediatric ACT are usually a part of a clinical presentation of congenital disorders such as Carney Complex (CNC), Beckwith- Wiedemann (BWS), or Li-

Fraumeni (LFS) Syndrome (23). CNC is an extremely rare syndrome characterized by pigmented skin lesions, endocrine dysfunctions, and myxoma (27). Association of CNC with ACC is rare but one of the components of the disorder is a primary pigmented nodular adrenal disease (23). BWS, apart from overgrowth, macroglossia, neonatal hypoglycemia, or abdominal wall defects, is characterized by a high predisposition to tumors. Wilms tumor occurs the most often (52%) followed by hepatoblastoma (14%). ACC is found in 3% of tumors in BWS (28). LFS is also a disorder with a high risk of cancer due to germline mutation in TP53. The most common types of cancer are soft-tissue sarcomas, osteosarcomas, ACC, central nervous system tumors, and breast cancer in females, occurring even before 31 years. The TP53 alterations are usually discovered among children with cancers or adult females with breast cancer. Moreover, they often do not have any familial history of cancer. 70-50% of pediatric ACC have TP53 mutation (23). The 5-years survival rate of ACC in the pediatric population is 46-55% (29). The factors indicating a good prognosis are younger age (<4 years), the weight of the tumor ≤ 200 g, total resection of the mass, and clinical presentation of virilization alone (25). The initial diagnostic protocol includes excluding other types of adrenal tumors such as neuroblastoma or pheochromocytoma. We may achieve that using hormonal assessment tests and they should be performed on all patients. Laboratory tests check glucocorticoid excess by performing dexamethasone suppression test, free 24-hours cortisoluria, basal adrenocorticotropin hormone, and salivary cortisol dosage. For assessment of mineralocorticoid excess, it is recommended to do an aldosterone level test, aldosterone/renin ratio, and kalemia. Also, sex steroids, their precursors, and urinary catecholamines and metanephrines levels should be examined. As far as radiological imaging, USG of the abdomen and pelvis, as well as abdominal CT, need to be done. For patients with a family history of early onset of tumors, abdominal MRI or whole-body MRI may be executed. When ACC is a strong possibility, the recommendation mentions performing chest CT and PET scan. Genetic counseling should be advised to the patient and their family. The most essential procedure in the treatment of ACT is an open approach surgery. The minimally invasive techniques are not recommended and could be considered only in young children with small tumors, likely to be benign without invasion of local tissues or lymph nodes. When removal of the tumor alone is not possible due to local invasion, wide en bloc resection is acceptable. The approach to metastatic tumors is neoadjuvant chemotherapy and surgery followed by adjuvant chemotherapy plus mitotane. Resection of metastases, at the same time as primary tumor removal or more often as a second operation later, may be considered in patients with a good clinical condition. Radiotherapy usually is avoided due to radioresistance of ACC and potential mutagenic effect, especially in children with germline TP53 mutation or LFS (30).

Summary

An adrenal incidentaloma is an unpredictable and possibly dangerous disorder in the pediatric population. Due to the rarity of the finding and their variety, there is not much data and clear recommendations about AI management. Doctors need to know about the prevalence of different types of adrenal tumors in the pediatric population based on age. AI is a multidisciplinary issue and the management of the disorder should be done in cooperation with a few medical professionals such as a pediatrician, oncologist, pediatric surgeon, pediatric endocrinologist, radiologist, geneticist, and pathologist.

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