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PATHOPHYSIOLOGY AND TREATMENT OF ADRENOCORTICAL CANCER IN CHILDREN

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Annotation: Adrenocortical cancer in children is a malignant tumor that develops from cells of the adrenal cortex. The main cause of the disease is considered to be the Lee-Fraumeni syndrome and other hereditary pathologies. Manifestations of a hormone-active tumor: Cushing's syndrome, virilization, estrogen-genital syndrome. Hormone-inactive neoplasms occur without clinical symptoms. Ultrasound, MSCT and MRI of the adrenal glands, hormone tests, histological and immunohistochemical studies are used for diagnosis. Treatment includes adrenalectomy to remove the primary tumor, excision of regional lymph nodes, and adjuvant chemotherapy.

Key words: Adrenocortical cancer, hormone, lymph nodes.

Cancer of the adrenal cortex, or adrenocortical cancer (ACR), belongs to the group of orphan diseases in the Russian Federation. It occurs with a frequency of 1 case per 1 million population, and girls are 2.5 times more likely to get sick than boys. The peak diagnosis of pathology occurs in the first decade of a child's life. Despite its rarity, the disease does not lose its relevance in practical pediatric oncology and endocrinology. Adrenocortical cancer in children is characterized by rapid progression and an unfavorable prognosis, so it requires improvement of early diagnosis and treatment methods.

Adrenocortical cancer in children is associated with hereditary syndromes. About 50-80% of all cases of cancer pathology develop against the background of Lee-Fraumeni syndrome, which is caused by a mutation in TP53, a gene responsible for inhibiting tumor growth. Pathology is manifested by sarcomas, blood cancer, neoplasms of the brain, mammary glands and adrenal glands. Most often, this problem occurs in children in Brazil, where 0.3% of people are carriers of the mutation.

The proportion of other hereditary syndromes in the etiological structure of cancer pathology does not exceed 1%. Familial adenomatous polyposis (Gardner's syndrome), neurofibromatosis, Carney complex, Beckwith-Wiedemann syndrome can contribute to cancer development. The remaining cases of adrenocortical cancer are due to spontaneous de novo mutations that occur for no apparent reason.

Pathogenesis

The tumor process (carcinogenesis) in ACR is caused by driver gene mutations that activate various signaling pathways and affect cell growth and differentiation. Gene sequencing disorders occur in cells of the adrenal cortex, which begin to divide uncontrollably and become poorly differentiated or undifferentiated. The tumor can affect any part of the cortex: the glomerular, bundle or reticular layer.

Adrenocortical cancer is characterized by a large size of the primary focus-an average of about 10 cm, but isolated cases of tumors up to 25 cm in diameter have been described. In addition to affecting the hormonal background and general cancer symptoms, the disease is accompanied by compression of the surrounding tissues. AKR is characterized by kidney dysfunction on the affected side, compression of the stomach and intestines, which causes intestinal obstruction.

Classification

Staging of adrenocortical cancer is crucial in pediatric oncology for determining treatment tactics and long-term prognosis. At the present stage, the standard classification according to the TNM

system is used, which is approved by the American and European Committees for Cancer Research. There are 4 stages of ACRE development:

- Stage 1 . Corresponds to a primary adrenal tumor up to 5 cm in diameter without signs of metastasis.
- Stage 2. It is diagnosed with adrenocortical cancer larger than 5 cm, which is not accompanied by local or distant spread.
- Stage 3. It is determined with various sizes of neoplasms and metastatic lesions of the lymph nodes or signs of invasion of malignant tissue in neighboring organs.
- Stage 4. It is established in the presence of at least one distant metastasis, regardless of the characteristics of the primary tumor focus and the degree of damage to the lymph nodes.

In pediatrics, about 55% of hormone-active tumors manifest as viril syndrome. In girls, it is manifested by abundant growth of body hair in the male type, hypertrophy of the clitoris, a decrease in the timbre of the voice, an increase in muscle mass. Thickening and increased greasiness of the skin can cause acne. Adolescent girls have amenorrhea or irregular menstruation. In boys, virilization is manifested by suppression of testicular function.

In 10-15% of patients, adrenocortical cancer causes isolated cortisol overproduction and typical Itsenko-Cushing syndrome. It is characterized by a moon-shaped face, a central type of obesity with relatively thin limbs, atrophy of the skin and the appearance of purple stretch marks on it. In children, growth slows down, the rate of puberty is disrupted. 30% of patients have a combination of virilization and kushingoid symptoms.

A rare manifestation of adrenocortical cancer in children is estrogen-genital syndrome. In girls, it causes premature puberty: the appearance of pubic hair, enlargement of the mammary glands, changes in the proportions of the figure, early menarche. In boys, hyperestrogenia is characterized by gynecomastia, underdevelopment of the external genitalia, and female-type fat deposits. Also, isolated cases of manifestation in the form of primary aldosteronism are known in ACR.

Hormone-inactive adrenocortical neoplasms are rare in pediatric practice. In the early stages, they are asymptomatic. Clinical manifestations occur with the progression of the tumor process and are characterized by non-specificity: increased fatigue, decreased appetite, nausea, weight loss, prolonged subfebrility. With large neoplasms, pain in the upper abdomen and lower back is bothered.

Complications

In 87-95% of cases, children have hormone-active neoplasms of the adrenal glands, which are accompanied by undesirable body changes, sexual development disorders, and growth retardation. Pediatric patients are characterized by rapid progression of the disease, early appearance of regional metastases and distant foci in the liver, lungs, bones, and brain. The relapse rate after treatment is 80-85%.

The 5-year survival rate for adrenocortical cancer, which is limited to the adrenal gland, is 60-80%. With the spread of the tumor to neighboring tissues, the prognosis of survival decreases to 30-50%, with distant metastasis-it does not exceed 28%. When progressing, ACR causes cancer cachexia syndrome, secondary immunodeficiency, multiple organ failure, thrombosis, and thromboembolism.

Diagnostics

In case of viril and/or kushingoid syndrome, consultation with a pediatric endocrinologist is indicated, and if a tumor is detected and cancer is suspected, the examination continues with a pediatric oncologist. During physical examination, signs of hormonal disorders are determined, palpation of the abdomen is performed to detect large tumors, and the correspondence of physical

and sexual development to the patient's age is assessed. The following methods are used to diagnose ACR in children:

- Ultrasound of the adrenal glands. Normally, the adrenal glands are not detected during echosonography. An enlarged adrenal gland, the appearance of inhomogeneous hyperechoic formation, and signs of calcification are indirect criteria for cancer diagnosis. Additionally, ultrasound of the abdominal cavity and retroperitoneal space is performed to visualize regional lymph nodes.
- CT scan of the adrenal glands. Multispiral computed tomography (MSCT) is the "gold standard" for the diagnosis of adrenocortical cancer in children. It is used to determine the size and location of the tumor, the degree of its invasion into surrounding structures, and the density of tissues. The tumor is characterized by a high native density (over 40 HU) and its slow decrease in the delayed phase of contrast.
- Additional visualization methods. If there are contraindications to CT, MRI of the adrenal glands is used, which does not require radiation exposure to the child's body. For clarifying diagnostics, positron emission tomography (PET) is used, which has a specificity of 92% and sensitivity of 98.5%. PET is especially informative in relapses and metastasis.
- Study of biopsies. When examining biomaterial obtained during surgery, a high nuclear index is determined, more than 5 mitoses per 50 fields of vision, less than 25% of cells with light cytoplasm, and areas of necrosis. These criteria are used to assess the malignant potential on the Weiss scale. Additionally, an immunohistochemical examination of the tissue is performed.
- Hormonal studies. To assess the hormonal activity of the tumor, tests are performed for cortisol, aldosterone, estrogen, testosterone, and dehydroepiandrosterone sulfate. To clarify the nature of kushingoid syndrome, a study is shown for ACTH, which is produced in the pituitary gland and in adrenocortical cancer will be reduced due to the negative feedback mechanism.
- Genetic counseling. Given the high frequency of a combination of ACR and hereditary syndromes, children need to be examined by a geneticist. In addition to collecting a family history and physical examination, if there are alarming clinical signs, testing for a mutation in the TP53 gene is indicated.

Differential diagnosis

Adrenocortical cancer is differentiated with other types of adrenal tumors: adrenocortical adenoma, genital stroma tumor, schwannoma, hematolymphoid tumor. It is also necessary to exclude hormone-inactive incidentalomas: fibroids, lipomas, nonparasitic cysts. The circle of diagnostic search in children includes adrenogenital syndrome, Itsenko-Cushing's disease, complications after treatment with glucocorticoid hormones.

Radical surgery is recommended for patients with stages 1-3 of adrenal cancer. This is the most effective method of treatment, which allows achieving stable remission and improving the long-term survival of patients. The operation is performed as soon as possible after diagnosis and includes adrenalectomy within healthy tissues, lymph dissection in the aortocaval zone and in the area of the renal gate, and performing thrombectomies.

In most children, surgical treatment is performed by the classical method-by laparotomy. Laparoscopic adrenalectomy is possible only in the early stages of the disease, if the size of the focus does not exceed 6 cm, there are no signs of tumor invasion. The advantages of the method include low injury rate, good cosmetic results and rapid rehabilitation, but laparoscopy has an increased risk of dissemination of malignant cells along the peritoneum.

Conservative therapy

Adjuvant treatment is prescribed to destroy residual tumor cells after surgery, reduce the risk of recurrence and the formation of metastases. In adrenocortical cancer, special cytotoxic agents are used that inhibit the synthesis of hormones of the adrenal cortex. In case of inoperable cancer or

distant metastases, polychemotherapy is prescribed according to an individually selected scheme, remote radiation therapy.

Prognosis and prevention

In modern oncology, various methods of treating ACR have been developed that show good results in the early stages, so the long-term outcome depends on the timely diagnosis of the disease. The weighted average 5-year survival rate of patients is 50%. Prevention of adrenocortical cancer involves cancer awareness in children with hereditary diseases, in-depth examination of patients with signs of hormonal dysfunction of the adrenal glands.

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