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ORIGIN AND ETIOPATHOGENESIS OF BEAN SYNDROME

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Annotation: Bean Syndrome - this is diffuse mucocutaneous angiomatosis. The disease occurs when there is a mutation in the TEK gene, which is located at the 9p21 locus. The pathology is manifested by multiple malformations of the veins – blue "rubber" formations located in the skin, mucous membranes of the gastrointestinal tract, and some internal organs. To diagnose Bean syndrome, a hemogram, coagulogram, endoscopic examination of the gastrointestinal tract, and other imaging methods are performed, taking into account clinical manifestations. Combined treatment: conservative therapy to suppress cell proliferation and correct signs of anemia, surgical or minimally invasive intervention to excise abnormal venous vessels.

Key words: mucocutaneous angiomatosis, abnormal venous vessel.

Vascular malformations occur in 1-1. 5% of people and are associated with morphogenetic abnormalities of the venous network. Bean syndrome is a multiple venous malformation with a low blood flow rate. The disease is named after the American physician William Bean, who described its clinical manifestations in 1958. An alternative name is "blue rubber nevus syndrome" (BRBNS). The estimated incidence of the disease is 1 case per 14,000 newborns, but accurate information is not available due to the rarity of the disease.

Bean syndrome occurs due to a somatic mutation of the TEK gene, which is located on the short arm of chromosome 9 at locus 21. Most often, point mutations are found in exons 17 and 23. Most cases of the disease are sporadic-they occur de novo in the absence of a burdened family history. However, if several family cases are observed, the probability of an autosomal dominant type of inheritance can be assumed.

Pathogenesis

The TEC gene encodes a specific protein TIE2, the intracellular part of the tyrosine kinase receptor. This protein is located only in endothelial structures. It is involved in the transmission of stimulating signals into the cell, regulates the activity of cell division, and maintains the stability of the vascular network. In Bin syndrome, TIE2 receptors are in an overactive state, so they constantly transmit differentiation signals to the endothelium.

The disease activates not only tyrosine kinase receptors, but also protein kinase PI3K/AKT. They play an important role in cell metabolism, growth, and differentiation. Bean syndrome is characterized by a violation of normal endothelial function in all cells containing the mutation, resulting in excessive growth and proliferation of blood vessels. Veins acquire an unusual convoluted structure and form malformations.

In 39% of patients with Bean syndrome, visible vascular malformations on or under the skin are observed already in the neonatal period or occur in infancy. In the remaining 61% of cases, symptoms first appear in older childhood or in adulthood. The timing of Bin syndrome manifestation does not correlate with the severity of the disease and the long-term prognosis.

The most common sign of the disease is venous malformations in the skin, which are mainly located on the trunk and distal parts of the limbs, especially on the pads of the fingers and toes. They have a blue color, an elastic "rubber" consistency, and are easily compressed when pressed. The size of the formations varies from 2-3 mm to several centimeters. Over time, existing vascular anomalies increase in size, and new ones appear next to them.

In 76% of patients, Bean syndrome is manifested by malformations in the mucosa and submucosal layer of the small intestine. The neoplasm has the same external characteristics as cutaneous vascular anomalies. In 13% of cases, in addition to typical localizations, there is damage to other organs: the central nervous system, eyes, lungs, kidneys and bladder. Occasionally, the disease affects smooth and striated muscles, bones, and serous membranes.

Venous malformations in the gastrointestinal tract cause acute and chronic bleeding. Low-volume blood loss goes unnoticed for a long time and leads to chronic post-hemorrhagic anemia. The patient has increased fatigue, shortness of breath, poor tolerance to physical exertion. It is characterized by painful pallor of the skin, perversion of taste, deterioration of hair and nails as a manifestation of sideropenic syndrome.

Complications

The main danger of Bean syndrome is the possibility of acute gastrointestinal bleeding. They are manifested by bloody vomiting, discharge of dark blood from the rectum, black tar-like stool (melena). In the absence of emergency medical care, massive hemorrhages can be fatal. Serious consequences of the disease include intestinal infarction, intestinal obstruction with an increase in the number and size of vascular formations.

Diagnostics

Most often, patients go to a dermatologist with complaints of a cosmetic defect or get an appointment with a general practitioner with non-specific signs of anemia. At the first consultation, the duration of the appearance and growth of vascular formations, the presence of subjective symptoms, and the presence or absence of such manifestations in blood relatives are evaluated. To make a diagnosis of Bean syndrome, the following research methods are prescribed::

- Endoscopic diagnostics. To detect venous malformations in the gastrointestinal tract, EFGDS and colonoscopy are used. Since most of the formations are located in the small intestine, which is inaccessible to examination by these methods, transoral or transrectal enteroscopy and video capsule endoscopy are additionally performed.
- Ultrasound scanning. Ultrasound is prescribed to confirm or exclude damage to soft tissues and internal organs. The study in the standard mode is supplemented with Dopplerography to assess the parameters of blood flow and determine the vascular nature of the detected formations.
- Neuroimaging. CT or MRI of the brain with contrast enhancement is an informative way to detect venous malformations. Neurosonography is actively used in infants to study intracranial structures as the simplest and safest method.
- Blood tests. To diagnose anemia, a hemogram is performed, which detects low levels of hemoglobin and red blood cells, a decrease in the color index and a decrease in the volume of red blood cells. Such data indicate hypochromic microcytic anemia, typical of chronic hemorrhages and iron deficiency. Blood clotting disorders are determined by the results of a coagulogram.
- Consultation of a geneticist. With characteristic pathomorphological changes, the diagnosis is not difficult. Genetic counseling will be required for atypical vascular malformations, suspected family variant of the disease. According to the indications, molecular genetic tests are performed.

Differential diagnosis

Clinical manifestations of Bean syndrome should be distinguished from other types of venous malformations (angiodysplasia): stem dilatation, obstructive stem, extratruncular diffuse or limited. Differential diagnosis is also performed with simple, cavernous and combined hemangioma – a benign vascular tumor that, unlike a malformation, can regress and decrease in size over time.

Treatment of Bean syndrome

Conservative therapy

The only specific drug that has been studied and is actively used in clinical practice is an immunosuppressant-an inhibitor of lymphocyte activation. The drug blocks intracellular signaling and interaction with the mTOR protein system, which is involved in the pathogenesis of Bean syndrome. Pharmacotherapy is aimed at suppressing cell proliferation, stopping further growth of malformations, and preventing new vascular anomalies.

Since most cases of Bean syndrome are accompanied by post-hemorrhagic iron deficiency, correction of anemia is necessary. Patients are prescribed iron supplements in oral or parenteral form, taking into account the level of hemoglobin and general condition. In severe anemic syndrome, blood transfusions are used, which can be supplemented with a platelet transfusion to correct signs of hypocoagulation.

Surgical treatment

In case of Bean syndrome, surgical interventions and new minimally invasive techniques for vascular removal are prescribed: sclerotherapy, ligation, laser or argon-plasma coagulation. Endoscopic manipulations are minimally traumatic and have a short rehabilitation period, but they present technical difficulties, especially in cases of deep malformations. Therefore, with multiple lesions, resection of the small intestine is required.

Prognosis and prevention

New methods of treatment show high efficiency, so the long-term outcome of the disease is favorable. The prognosis depends on the timely diagnosis – detection and removal of malformations at an early stage saves a person from threatening hemorrhages, severe anemia. There is no primary prevention of Bean syndrome. After treatment, patients are under the supervision of a doctor to exclude relapse, bleeding from hidden foci.

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