Olimjonov Mirzohid Yusufjon o'g'li
Andijan State Medical Institute

THE MOST MODERN DIAGNOSTIC TESTS AND TREATMENTS FOR CHARGE SYNDROME

Annotation: CHARGE syndrome is a rare congenital disorder characterized by a pronounced clinical polymorphism. The cause of development is a genetic mutation CHD7. The name of the disease is an English abbreviation and reflects the main clinical symptoms: C-coloboma of the choroid, H-abnormalities of the heart and blood vessels, A-choan atresia, R-growth retardation, G-urogenital abnormalities, E-abnormalities of the hearing organ. The diagnosis is made based on the presence of clinical criteria and the detection of a mutation. Treatment consists of surgical correction of existing abnormalities and hormone replacement therapy.

Key words: Hall-Hittner syndrome, A-choan atresia, R-growth retardation, G-urogenital abnormalities.

CHARGE-syndrome (Hall-Hittner syndrome) was first described in 1979 by American doctors B. D. Hall and H. M. Hittner. This disease is more often associated with congenital choan atresia than other hereditary pathologies. The prevalence of CHARGE syndrome is 1 in 12,000 children, and it occurs with the same frequency in boys and girls. It mostly occurs sporadically, but hereditary transmission of the disease by autosomal dominant type is possible.

In the vast majority of cases, CHARGE syndrome develops due to a mutation of the CHD7 gene encoding the DNA-binding protein of chromodomain helicase. The gene is located on chromosome 8, locus 8q12.2. This protein is one of the key transcription factors of early stages of embryonic development. It regulates gene expression and chromatin structure.

Some varieties of CHARGE syndrome that differ from the classical phenotype are caused by a mutation of the semaphorin 3E gene located on chromosome 7q21.Most often, mutations occur de novo, which explains the mostly sporadic nature of the appearance of CHARGE syndrome. Mostly there are nonsense mutations and mutations with a read shift, while splicing mutations are quite rare. The influence of teratogenic effects as risk factors for the occurrence of the disease is assumed.

Since the CHARGE syndrome involves proteins that regulate the main stages of embryogenesis in the pathological process, maturation and differentiation of organs and systems are disrupted. The most pronounced defect in the formation of the mesoderm (middle germ leaf), which is necessary for the development of the cardiovascular, nervous system, bone skeleton, reproductive organs, etc. Due to the small amount of data, the exact pathogenetic mechanisms of the effect of a genetic defect in chromodomain helicase on certain stages of embryonic development remain unknown.

Symptoms

The clinical picture of CHARGE syndrome can be extremely diverse. The main symptom that causes a serious condition of the patient almost immediately after birth is the overgrowth of the holes connecting the nasal cavity and nasopharynx (choan atresia). Because of this anomaly, the child's breathing is sharply difficult. Also, problems with swallowing are often noted (70-90% of cases) due to underdevelopment of the bulbar cranial nerves. Feeding the child is significantly difficult, it is accompanied by coughing, choking with food, regurgitation.
Some of the most characteristic are ophthalmic symptoms. Some of them represent only a cosmetic defect. These include coloboma of the iris. More serious, causing visual impairment, sometimes up to blindness, are considered anomalies of the choroid and optic disc.

Severe hearing impairment caused by defects in the middle and inner ear (incomplete separation of the cochlea, hypoplastic semicircular canals) is observed in almost all patients. Due to congenital heart defects with hemodynamic disorders (for example, Fallot's tetrads), the child has a characteristic bluish coloration of the lips, tip of the nose, and fingers.
In half of the children with CHARGE syndrome, growth hormone and sex hormone deficiency is caused by short stature and signs of hypogonadotropic hypogonadism – delayed puberty, micropenis and cryptorchidism in boys, and hypoplasia of the labia in girls.
The defeat of the central system is manifested by a delay in psychomotor, psycho-speech development. The child cannot sit, stand, or walk independently. Half of the patients have paresis of the facial nerve. There are also skeletal anomalies – the absence of ribs, clinodactyly, polydactyly, etc.
The following anomalies are less common in CHARGE syndrome::

- cleft lip or palate;
- kidney hypoplasia;
- vesicoureteral reflux;
- tracheesophageal fistula;
- omphalocele;
- hypoplasia of the thymus and parathyroid glands.

Complications

Due to the wide range of congenital anomalies that can occur in CHARGE syndrome, the number of complications in this disease is also high. With bilateral choan atresia, respiratory distress syndrome can develop even during the newborn period, which often causes neonatal mortality. Due to dysphagia, aspiration and aspiration pneumonia are often observed.
Heart defects can cause acute heart failure. Defects in the structure of the urinary tract in some patients provoke hydronephrosis and acute renal failure. The delay in mental development leads to the fact that the child lacks self-service skills.

Diagnostics

Patients with CHARGE syndrome are managed by doctors of several profiles – pediatricians, geneticists, specialists from various fields of surgery (otorhinolaryngologists, cardiac surgeons, urologists). Many anomalies and their manifestations can be detected already during a general examination of the patient – cyanosis of the skin, defects of the bone skeleton, etc.
The face has a characteristic appearance-a wide bridge of the nose, a square face, a triangular shape of the auricle. During auscultation of the heart, you can listen to rough systolic and diastolic murmurs. Additional examinations are scheduled, including::

- Blood tests. In the case of kidney underdevelopment, an increase in the concentration of urea and creatinine may be noted in the biochemical analysis of blood. An increased NT-proBNP level is a marker of heart failure. Hypogonadism is characterized by a decrease in the content of reproductive hormones – LH, FSH, estradiol (in girls), testosterone (in boys).
- Electrocardiography. The ECG may show signs of hypertrophy of the right and left parts of the heart, various rhythm disorders – blockage of the bundle branch legs, etc.
- Echocardiography. On an echo-CT scan, you can visualize defects in the atrial or interventricular septum, an open ductus arteriosus, and dilation of the heart chambers. An unfavorable sign is a reduced emission fraction.
- An MRI scan. On targeted MRI of the inner ear, it is possible to detect underdevelopment or complete absence of the semicircular channels of the bone labyrinth.
- Ophthalmological examination. Using slit lamp biomicroscopy and ophthalmoscopy, it is possible to assess the presence of defects in the choroid of the eye, retina and optic nerve.
- Endoscopy. In CHARGE syndrome, endoscopic diagnostic methods are mainly used to identify choan atresia.

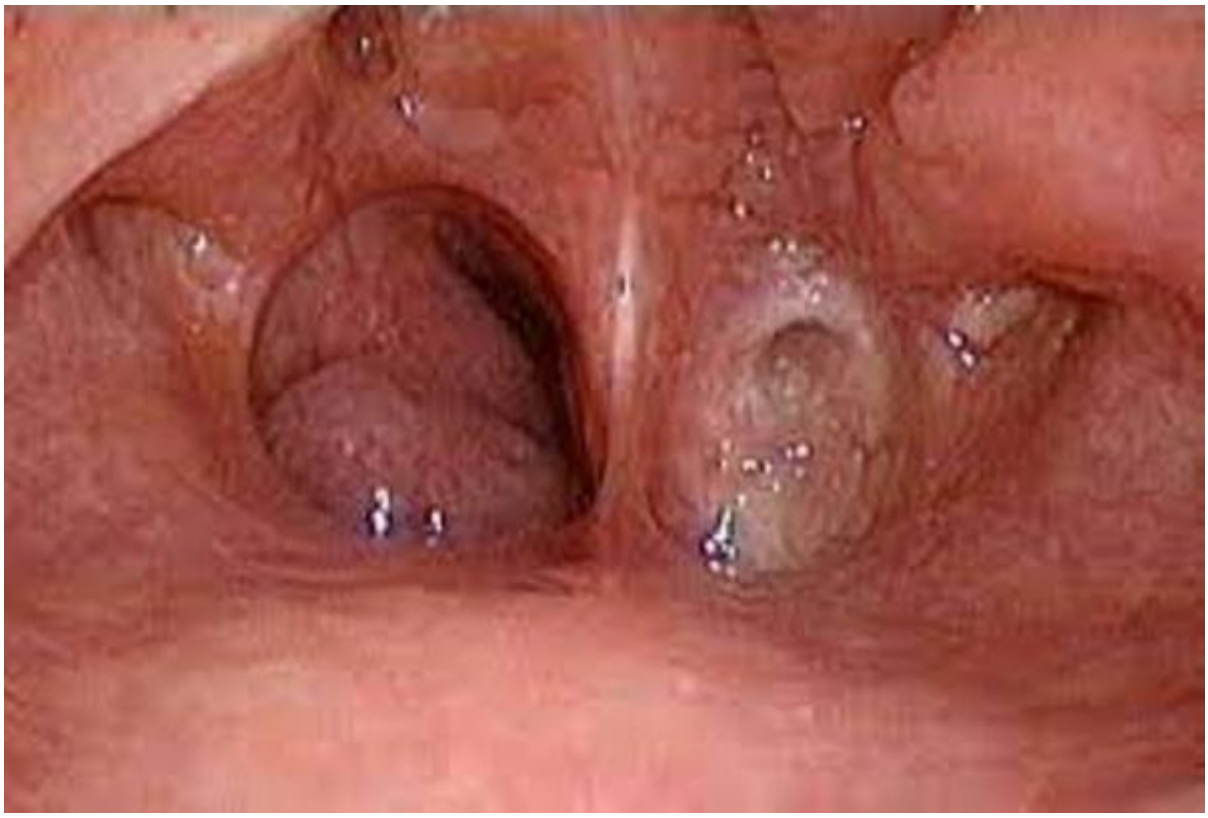
- Genetic research. The CHD7 mutation is detected by molecular genetic research methods-DNA sequencing.

Approximately 30% of patients have no mutations. In such clinical situations, the diagnosis is established in the presence of 3 main symptoms included in the abbreviation CHARGE or 2 main and 1 additional symptom.

Differential diagnosis

Differential diagnosis is performed with the following diseases::

- papillorenal syndrome;
- Kallman's syndrome;
- Joubert syndrome;
- brachyotorenal syndrome;
- VACTERL-an association.



Treatment of CHARGE syndrome

Conservative therapy

Among the medicinal methods of pathogenetic treatment, hormone replacement therapy with synthetic androgens and estrogens is used. In Fallot's tetrad, the administration of prostaglandin preparations is recommended in order to preserve the arterial duct in an open state. This increases the volume of blood in the small circulatory system, which is saturated with oxygen.

Surgical treatment

The main place in the treatment of patients with CHARGE syndrome is occupied by surgical correction of anomalies. With choan atresia, choanotomy is indicated. Which can be done in 4 different ways. The endonasal method carries a lower risk of blood loss, but has a high probability of restenosis. The greatest effectiveness in the formation of choan in congenital atresia was demonstrated by transeptal access, so most specialists resort to it.

Many children with CHARGE syndrome undergo cochlear implantation. In Fallot's tetrad, radical correction is indicated - resection of muscles to expand the ventricular outlet, elimination of septal defects, and application of patches. In some cases, they resort to the imposition of an anastomosis. With severe renal hypoplasia with the development of renal failure, kidney transplantation is indicated.

Prognosis and prevention

CHARGE-syndrome is a very serious disease with an unfavorable prognosis. The most dangerous period in terms of the frequency of deaths is considered to be the neonatal period, when respiratory failure develops with complete atresia of the choan. Also, one of the main causes of death is circulatory disorders due to congenital heart defects. Delayed neuropsychiatric development and hearing loss greatly disrupt the child's social adaptation. There are no methods of specific prevention other than prenatal diagnosis.

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