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DISEASE TAKAYASUS IN A TEENAGER. CLINICAL OBSERVATION AND COMMENT

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Abstract. Nonspecific aortoarteritis (NAA), or Takayasu disease, is a rare pathology related to large vascular vasculitis. Its characteristic feature is the weakening and asymmetry of the pulse. Diagnosis of NAA is difficult due to nonspecific manifestations in the onset of the disease, an extremely wide range of differential diagnostics and insufficient awareness of primary care physicians. The features of NAA in children have not been sufficiently studied. The article provides a clinical observation of a 14-year-old girl with Takayasu disease proven in accordance with international criteria.

Key words*: nonspecific aortoarteritis; Takayasu disease; children; pulse asymmetry.*

БОЛЕЗНЬ ТАКАЯСУ У ПОДРОСТКА. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ И КОММЕНТАРИЙ

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Резюме. Неспецифический аортоартериит (НАА), или болезнь Такаясу, — редкая патология, относящаяся к васкулитам крупных сосудов. Его характерной особенностью является ослабление и асимметрия пульса. Диагностика НАА затруднена из-за неспецифических проявлений в дебюте заболевания, чрезвычайно широкого круга дифференциальной диагностики и недостаточной осведомленности врачей первичного звена. Особенности НАА у детей изучены недостаточно. В статье приводится клиническое наблюдение девочки 14 лет с доказанной в соответствии с международными критериями болезнью Такаясу.

Ключевые слова: *неспецифический аортоартериит; болезнь Такаясу; дети; асимметрия пульса.*

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INTRODUCTION

Nonspecific aortoarteritis (NAA), or Takayasu's disease, is a rare pathology related to vasculitis, predominantly affecting large arteries — the aortic arch, its branches, and less often the descending aorta. NAA, along with giant cell arteritis (GCA), belongs to large-vessel vasculitis (LVVs). While GCA is the most common primary vasculitis in adults, Takayasu's disease occurs at a frequency of 1,2 to 6,3 cases per 1 million population. NAA was first described in 1908 as a series of retinal vascular disorders by Japanese ophthalmologist Mikito Takayasu [1]. The association of this pathology with absent or weakened pulses in the peripheral vessels has led to the term "pulseless disease" [2]. Synonyms are used in the literature: Takayasu's arteritis, Takayasu's disease, pulseless disease (ICD-10 code: M31) [3]. Early descriptions of the disease included persons of Japanese ancestry, but NAA is now found worldwide. The classification of NAA was proposed in 1994 (Takayasu Conference, 1994) and is based on the predominant localization of vascular lesions [4]. There are 5 types:

- Type I — aortic arch and arteries branching from it;
- Type IIa — ascending aorta, arch and its branches;
- Type IIb — ascending aorta, arch and its branches, descending thoracic aorta;
- Type III — descending thoracic, abdominal aorta and (or) renal arteries;
- Type IV — abdominal aorta and (or) renal arteries;
- Type V is a mixed version of types IIb and IV.

In children, the prevalence and clinical features have not been sufficiently studied. It is known that the manifestation of the disease in most patients occurs in early adolescence. Rapid diagnosis and early treatment are key to good patient outcomes, but diagnosis of NAA is challenging and typically delayed because clinical manifestations are nonspecific, the range differential diagnosis is quite broad, and assessment of disease activity is difficult.

EPIDEMIOLOGY OF NONSPECIFIC AORTOARTERITIS

In Japan, where Takayasu's disease was first described, it is detected annually at a frequency of 1–2 cases per million people. In Europe, the annual incidence ranges from 0,4 to 3,4 per million. Age of onset usually ranges from 10 to 40 years and is the main epidemiological feature that distinguishes NAA from GCA, although late-onset NAA has become more common [5]. In Europe, 80–90% of NAA are female; in China, India, Japan, and Thailand, the ratio of female to male varies from 3:1 to 4:1 [6, 7]. It is noteworthy that the nature of the disease may vary depending on the patient's age at the onset of the disease, as well as between men and women. In the national literature, the largest number of observations of children with Takayasu's disease (51 children) were presented by Moscow pediatricians [8]. According to their data, the ratio of the frequency of NAA between boys and girls under 7 years of age is almost the same: 1:1.25; in the group of children over 7 years old, girls significantly predominated — 1:7,4. The most common symptoms were malaise (90%) and fever (67.3%). Remarkably, the authors noted the absence or weakening of the pulse only in 35% of cases.

PATHOGENESIS

The pathogenesis of LVV has been studied mainly in relation to GCA as a more common pathology, but the main links also apply to NAA. Under physiological conditions, the walls of medium and large arteries are protected from inflammation and autoimmune reactions by immune tolerance. LVV is characterized by a loss of immune tolerance, which leads to the launch of a cascade of pro-inflammatory mediators and progressive tissue damage. At the onset of the disease, vasculitis is difficult to notice and quantify. Aneurysm formation and progressive arterial occlusion occur decades after onset. Over the past few years, the role of mast cells in the pathogenesis of NAA lesions has been identified. In a series of *in vitro* and *in vivo* experiments using serum and aortic tissue from both healthy individuals and patients with NAA, mast cells were responsible for increased vascular permeability, neovascularization, and fibrosis; these cells represent a potential therapeutic target [9]. Vascular inflammation in LVV is often combined with extravascular systemic inflammation. This systemic inflammatory response manifests as anemia, thrombocytosis, liver dysfunction, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in the blood, with clinical symptoms of fever, malaise, and myalgia. Systemic inflammation is associated with a change in the number of circulating B cells and an increase in their ability to produce interleukin-6 (IL-6). Identification of anti-endothelial cell antibodies in patients with NAA suggests vascular autoimmune reactions [10].

We present our own observation of clinical case of Takayasu's disease in a 14-year-old teenager

Girl M., 14 years old, was admitted to the clinic urgently with a diagnosis of community-acquired pneumonia. From the anamnesis it is known that 3 months before hospitalization, pain appeared in the left hypochondrium, which intensified in the supine position and at the depth of inspiration. The onset of pain could

not be associated with any disease, injury, or stress. At the local clinic she was examined several times by a pediatrician and a neurologist; intercostal neuralgia was diagnosed, for which she received symptomatic therapy with NSAIDs and physiotherapy treatment, but the pain syndrome persisted over time. Upon repeated examination, a neurosis-like condition was diagnosed, treatment was also without effect. Due to the child's persistent complaints of pain in the left hypochondrium, an outpatient chest x-ray was performed, which revealed infiltrative changes in the lower parts of the left lung. The condition was considered pneumonia, and therefore the patient was hospitalized.

From the anamnesis vitae it is known that the girl was born from a second, normal pregnancy, an urgent physiological delivery. Breastfed up to 1.5 years. She grew and developed according to age. Vaccinated according to the National calendar. *Menses* from the age of 13, regular periods. She was rarely sick and suffered from a mild form of acute upper respiratory infection. No allergic pathology was observed in relatives. Heredity is burdened: the first child in the family died from a congenital pulmonary malformation.

Upon admission, the child's condition was moderate. Body temperature — 36.8 °C, heart rate — 102 beats/min. Weak filling pulse, respiratory rate — 18 per min. Blood pressure on the right arm is 150/70 mm Hg, on the left arm — 130/75 mm Hg. The pulse in the legs was almost not palpable, and blood pressure was not determined. General well-being is satisfactory. Consciousness is clear. There are no meningeal symptoms. The position in bed is active. The skin and visible mucous membranes pale coloration, there are no pathological rashes. The body type is asthenic. The subcutaneous fat layer is not sufficiently developed. Tissue turgor and skin elasticity are preserved. Nasal breathing is free. The mucous membrane of the pharynx is pale pink. The tonsils are hypertrophied, grade 1–2, there are no plaques. Peripheral lymph nodes are small, mobile. Heart sounds are muffled, rhythmic, rough systolic murmur over the entire surface of the heart, carried out extracardially, the murmur is heard along the entire abdominal aorta. There is no peripheral edema. The chest is of normal shape. Percussion sound is pulmonary. There is vesicular breathing in the lungs, carried out in all fields, there are no wheezes, during forced inhalation the girl complains of chest pain on the left. The abdomen is soft, painless. The lumbar region is visually unchanged, the symptom of tapping on both sides is negative. The liver and spleen are not enlarged. Physiological functions are normal.

Urine analysis: pH 6.5; specific gravity — 1.025; white blood cells — 8–10 per HPF; squamous epithelial cells — a large number per HPF; protein — 0.34 g/L.

Examination by an ophthalmologist: vessels of the eye fundus without pathology. A disseminated bronchopulmonary process has been excluded (Mantoux test with 2TE dated 29.10.21 — 12 mm, the girl was consulted by a phthisiatrician — there is no tuberculosis data).

Laboratory examination data upon admission are shown in Tables 1–3.

As can be seen from Tables 1 and 2, the patient has moderate iron-deficiency anemia, and markers of active inflammation are sharply increased.

An immunological study (Table 3) revealed high titers of immunoglobulins of classes A and M and anti-beta 2-glycoprotein I antibodies of IgGAM class (antiphospholipid antibodies).

Table 1. Complete blood count

Таблица 1. Клинический анализ крови

Hb, g/L / Hb, г/л	RBC, 10^{12}/L / Эр., 10^{12}/л	CI / ЦП	Ht, % Ht, %	MCV, fl / MCV, фл	MCHC / MCHC	Plt, 10^9/L / Тромбоциты, 10^9/л	WBC, 10^9/l / Лей 10^9/л	Neu, % / Нейт. %	Lym, % / Лимф. %.	Bas, % / Баз. %	Eos, % / Эоз. %	Mon, % / Мон. %	ESR, mm/hr / СОЭ мм/ч
80	4,64	55,6	27,9	60	285	383	7,8	57,9	26,2	0,8	2,7	12,4	67

Table 2. Biochemical blood test

Таблица 2. Биохимический анализ крови

Parameter / Показатель	Result / Результат	Normal /Норма
Total protein, g/L / Общий белок, г/л	82	60–80
CRP, mg/L / СРБ, мг/л	55,71	0,00–5,00
Iron, µmol/L / Железо, мкмоль/л	3,4	4,7–19,7
Transferrin, g/L / Трансферрин, г/л	2,1	3,0–3,8
TIBS of serum, µmol/L / ОЖСС сыворотки, Мкмоль/л	45	52–79

Table 3. Immunogram
Таблица 3. Иммунограмма

Parameter, g/L / Показатель, г/л	Result / Результат	Normal / Норма
Immunoglobulin A / Иммуноглобулин А	6,14	0,47–2,40
Immunoglobulin M / Иммуноглобулин М	2,76	0,15–1,88
Immunoglobulin G / Иммуноглобулин G	21,5	6,58–15,34

Instrumental examinations

- According to the results of computed tomography of the chest organs with intravenous bolus contrast-enhanced of the lungs, there is a picture of diffuse lesion of the thoracic, abdominal parts of the aorta and its branches, the pulmonary trunk, focal consolidation in the lower lobe of the left lung (pulmonary infarction localized in S_8 on the left) (Fig. 1), subcortical defect of contrast of the left kidney (infarction in the upper pole of the left kidney) (Fig. 3).
- By the data of duplex imaging of the abdominal aorta and its visceral branches, there is a picture of aortoarteritis of abdominal aorta, arteritis of the superior mesenteric artery, severe stenosis of the celiac trunk (Fig. 2, 4); Duplex imaging of the renal arteries — signs of stenosis at the mouth of the right renal artery, stenosis of the left renal artery.
- Color-coded triplex scanning of the transcranial and brachiocephalic arteries revealed stenosis of the right subclavian artery, arteritis of the common carotid artery, the upper third of the internal carotid artery on both sides (Fig. 5).
- As the results of echocardiography — moderate dilatation of the ascending aorta, mild aortic insufficiency; left ventricular concentric remodeling, increased fluid content in the pericardial cavity.

During the examination, the range of differential diagnosis included a disseminated pulmonary process, pneumonic infiltration, diffuse connective tissue diseases and small-vessel vasculitis, pulmonary infarction, infectious endocarditis, rheumatoid arthritis, neoplastic process, primary immunodeficiency.

Based on the totality of the results of the anamnesis, clinical, laboratory and instrumental examinations, namely the presence of 4 out of 5 criteria proposed by EULAR/PRINTO/PReS [11], the diagnosis was established: "Systemic vasculitis: nonspecific aortoarteritis (Takayasu's disease), debut, type V. Secondary antiphospholipid syndrome.

Complications: pulmonary infarction localized in S_8 on the left. Infarction in the upper pole of the left kidney. Moderate microcytic hypochromic anemia. Arterial hypertension. Mild aortic insufficiency".

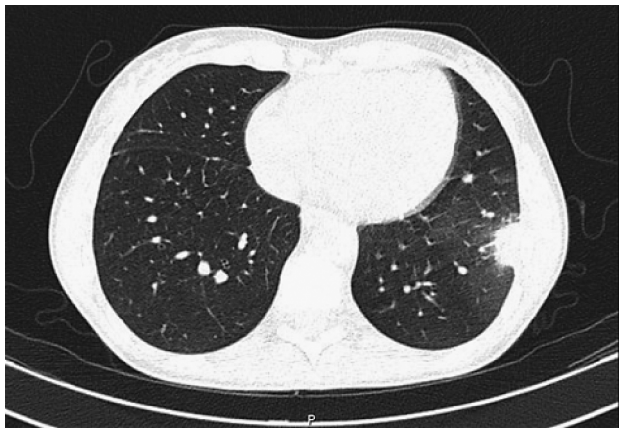

Fig. 1. Computed tomography of the chest organs with intravenous bolus contrast-enhanced: focal consolidation in the lower lobe of the left lung (pulmonary infarction localized in S_8)

Рис. 1. Компьютерная томография органов грудной полости с внутривенным болюсным контрастированием: очаговое уплотнение в нижней доле левого легкого (инфаркт легкого с локализацией в S_8)

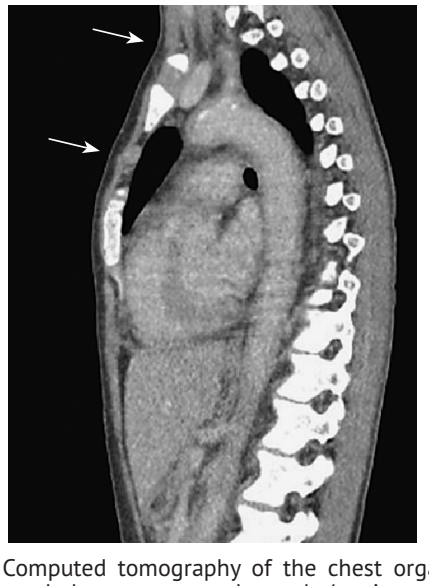

Fig. 2. Computed tomography of the chest organs with intravenous bolus contrast-enhanced (angiography): CT picture of diffuse lesion of the thoracic, abdominal parts of the aorta and its branches, the pulmonary trunk. Arrows indicate calcifications in the aortic arch and diffuse lesions of the thoracic aorta

Рис. 2. Компьютерная томография органов грудной полости с внутривенным болюсным контрастированием (ангиография): КТ-картина диффузного поражения грудного, брюшного отделов аорты и ее ветвей, легочного ствола. Стрелками обозначены кальцинаты в дуге аорты и диффузное поражение грудного отдела аорты

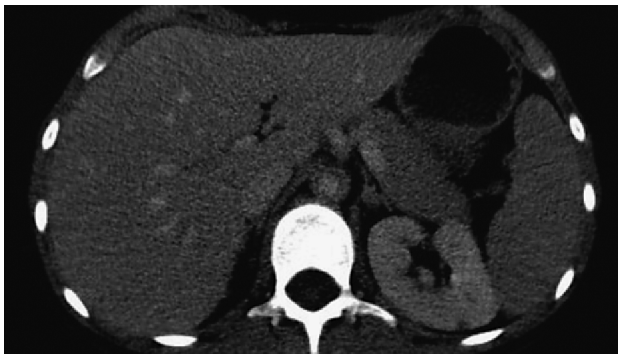

Fig. 3. Computed tomography of the chest organs with intravenous bolus contrast-enhanced: subcortical defect of contrast of the left kidney (infarction in the upper pole of the left kidney)

Рис. 3. Компьютерная томография органов грудной полости с внутривенным болюсным контрастированием: субкортикальный дефект контрастирования левой почки (инфаркт в верхнем полюсе левой почки)

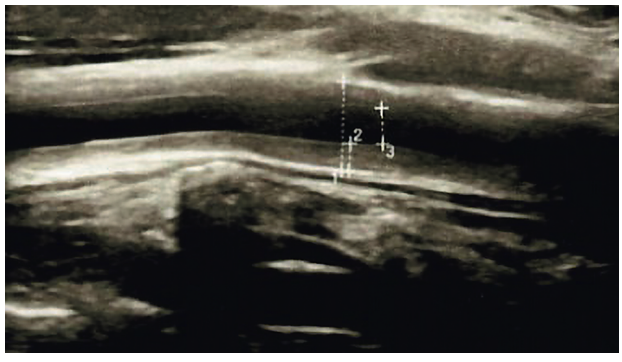

Fig. 5. Color-coded triplex scanning of the transcranial and brachiocephalic arteries: stenosis of the right subclavian artery, arteritis of the common carotid artery, the upper third of the internal carotid artery on both sides

Рис. 5. Цветовое триплексное сканирование транскраниальных и брахиоцефальных артерий: стеноз правой подключичной артерии, артериит общей сонной артерии, верхней трети внутренней сонной артерии с обеих сторон

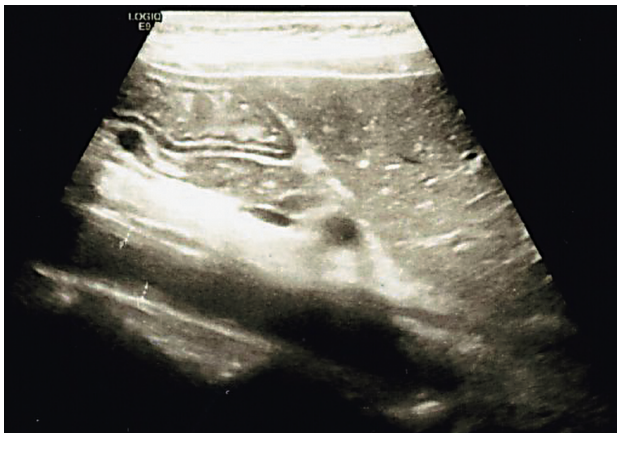

Fig. 4. Duplex imaging of the abdominal aorta and its visceral branches: picture of aortoarteritis of abdominal aorta, arteritis of the superior mesenteric artery, severe stenosis of the celiac trunk

Рис. 4. Дуплексное исследование брюшного отдела аорты и ее висцелярных ветвей: картина аортоартериита брюшного отдела аорты, артериита верхней брыжеечной артерии, выраженного стеноза чревного ствола

At the department, intravenous methylprednisolone pulse therapy was started at a dose of 1000 mg once a daily for 3 days, with subsequent administration of oral prednisolone at a dose of 50 mg once a day. Anticoagulant, antihypertensive, antibacterial and symptomatic therapy were also carried out. A positive effect was achieved: pain in the left half of the chest, dizziness, headaches were relieved; an increase in hemoglobin was noted (from 80 to 104 g/L), a decrease in ESR was observed (from 67 to 34 mm/hr), as well as a decrease in CRP (from 55 to 10 mg/L), and normalization of coagulogram parameters.

According to the results of control instrumental examinations (ultrasound of the abdominal aorta and its visceral branches, renal vessels, echocardiography) — no dynamics.

MSCT of the chest circumference described positive dynamics — a reduction in the size of the focal consolidation of the left lung; Ground-glass opacities are marked on both sides.

To continue treatment of systemic vasculitis and secondary antiphospholipid syndrome, the patient was transferred to a specialized pediatric rheumatology center, where she was prescribed targeted therapy: infliximab (anti-TNF-α group), methotrexate, and combination antihypertensive therapy.

CONCLUSION

Diagnosis of NAA is difficult; clinical manifestations depend on the preferential damage to certain vessels. This pathology can occur under the "masks" of other diseases, have a polymorphic course and not be recognized for a long time. This requires special alertness of pediatricians and doctors of other specialties to this pathology. Correct diagnosis and timely initiation of therapy help prevent the development of serious complications that are associated with a high risk of disability, morbidity and mortality of patients.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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