https://doi.org/10.54890/EHJ-2024-1-32
УДК 616-002.7-036.12-057-053.2

CLINICAL OBSERVATION OF A 5-YEAR-OLD PATIENT WITH CHRONIC GRANULOMATOUS DISEASE ASSOCIATED WITH A MUTATION IN THE CYBB GENE

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Resume. Chronic granulomatous disease is a congenital primary immunodeficiency caused by a genetic defect of phagocytosis, characterized by the inability of leukocytes to synthesize reactive oxygen species and phagocytize microorganisms due to a defect in the enzyme NADP oxidase, which leads to a high susceptibility of the patient to bacterial and fungal infections. The frequency of occurrence of this pathology ranges from 1:100 thousand to 1:200 thousand people. In about 60% of cases, the disease is inherited linked to the X chromosome, and in 40% it is autosomal recessive. The most common and frequently occurring form is X-linked chronic granulomatous disease caused by a mutation of the CYBB gene, which explains the significantly higher prevalence of the disease in males. Chronic granulomatous disease is characterized by recurrent infections of any organ (lungs, skin, liver, lymph nodes, urinary system, intestines) with the formation of inflammatory granulomas, abscesses and fistulas; the development of severe pneumonia with extensive damage to the lung tissue involving the pleura. The article presents data on the prevalence, clinical manifestations and treatment of chronic granulomatous disease, as well as own clinical observation of the course of this disease in a 5-year-old child. The difficulties of diagnosing a primary immunodeficiency condition in routine pediatric practice are described, when the pediatrician must include primary immunodeficiency in the differential diagnosis plan.

Key words: children, primary immunodeficiency, chronic granulomatous disease.

КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ ПАЦИЕНТА 5 ЛЕТ С ХРОНИЧЕСКОЙ ГРАНУЛЕМАТОЗНОЙ БОЛЕЗНЬЮ, АССОЦИИРОВАННОЙ С МУТАЦИЕЙ В ГЕНЕ CYBB

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Резюме. Хроническая гранулематозная болезнь – врожденный первичный иммунодефицит, причиной которого служит генетический дефект фагоцитоза, характеризующийся неспособностью лейкоцитов синтезировать активные формы кислорода и фагоцитировать микроорганизмы в связи с дефектом фермента НАДФ-оксидазы, что приводит к высокой восприимчивости больного к бактериальным и грибковым инфекциям. Частота встречаемости данной патологии составляет от 1:100 тыс. до 1:200 тысяч человек. Примерно в 60% случаев заболевание наследуется сцеплено с Х-хромосомой, в 40% – аутосомно-рецессивно. Наиболее распространенной и часто встречающейся формой является Х-сцепленная хронической гранулематозной болезни, обусловленная мутацией гена CYBB, что объясняет значительно большую распространенность заболевания у представителей мужского пола. Для хронической гранулематозной болезни характерны рецидивирующие инфекции любого органа (легких, кожи, печени, лимфатических узлов, мочевой системы, кишечника) с формированием воспалительных гранулем, абсцессов и свищей; развитие тяжелой пневмонии с обширным поражением легочной ткани с вовлечением плевры. В статье приведены данные в отношении распространенности, клинических проявлений и лечения хронической гранулематозной

болезни, а также собственное клиническое наблюдение течения данного заболевания у ребенка 5 лет. Описаны сложности диагностики первичного иммунодефицитного состояния в рутинной педиатрической практике, когда педиатр должен в план дифференциальной диагностики включить первичный иммунодефицит.

Ключевые слова: дети, первичный иммунодефицит, хроническая гранулематозная болезнь.

Introduction. The inability of the human body to resist foreign antigenic aggression is commonly referred to as an "immunodeficiency condition" (IDC). There are several types of immunodeficiency: primary, secondary, selective, nonspecific and combined. By definition, primary immunodeficiency (PID) is a large group of severe genetically determined diseases caused by an irreversible violation of one or another link of immunity. To date, more than 250 genetic defects underlying PIDS have been described [1].

Manifestations of primary immunodeficiency occur from the first months of a child's life. However, the diagnosis of the disease is not always carried out at an early age due to the relatively low prevalence of primary immunodeficiency, pathogenetic heterogeneity and the absence of specific clinical markers [2].

By the Jeffrey Modell Foundation Medical Advisory Board (JMF, USA) and adapted for use in the Russian Federation since 2011 year 10 signs that allow suspecting primary immunodeficiency (PID). Among them: 4 or more otitis media per year; 2 or more severe exacerbations of sinusitis per year; antibiotic therapy for 2 or more months with insufficient effect; 2 or more pneumonia per year; the child's lag in growth and physical development; recurrent deep abscesses of the skin or internal organs; recurrent thrush on the oral mucosa and fungal skin lesion; the need for intravenous antibiotics to achieve control of the infectious process; 2 or more episodes of severe generalized infection, including septicemia; the presence of PID in family members) [3].

One of the variants of PIDs is chronic granulomatous disease – congenital primary immunodeficiency, the cause of which is a genetic defect of phagocytosis, characterized by the inability of leukocytes to synthesize reactive oxygen species and phagocytize microorganisms due to a defect in the enzyme NADP oxidase, which leads to a high susceptibility of the patient to bacterial and fungal infections. Chronic granulomatous disease (CGB) – is only one of the many variants of PID. The frequency of occurrence of this pathology, according to various authors, ranges from 1:100 thousand up to 1:200 thousand people. In about 60% of cases, the disease is inherited linked to the X chromosome, in 40% - autosomal recessive [4].

The most common and frequently occurring form is X-linked CGB (X-CGB), caused by a mutation of the CYBB gene, which explains the significantly greater prevalence of the disease in males. Autosomal recessive forms (AR-CGB), according to the IUIS (International Union of Immunological Societies) 2019 PID classification, are represented by defects in the following genes - NCF2, NCF1, CYBA, NCF4 or CYBC1 [5].

It is important to know that chronic granulomatous disease is characterized by recurrent infections of any organ (lungs, skin, liver, lymph nodes, urinary system, intestines) with the formation of inflammatory granulomas, abscesses and fistulas; the development of severe pneumonia with extensive damage to the lung tissue involving the pleura. Typical pathogens are catalase-producing microorganisms: Staphylococcus aureus, Escherichia coli, Salmonella, Noccardia, representatives of the genera Serratia, Klebsiella and Pseudomonas sp., fungi (Aspergillus) [6].

Patients with CGB retain normal antibody production, T-cell function, complement systems to most viruses and some types of bacteria and fungi, as a result of which patients are not permanently infected and can live for a long time without infections, and then get sick with a life-threatening infectious disease, the causative agent of which cannot be neutralized without hydrogen peroxide. Depending on the severity of the defect, there are 4 main types of CGB: complete absence of formation (X-linked form — 75% of cases), partial deficiency, structural defect leading to impaired function or regulation of NADPH oxidase formation [7].

Aggressive and timely use of appropriate antibiotics and antifungal drugs remains the most important basis for the treatment of infections. They should be empirically directed against CGB-associated organisms until bacteriological studies are confirmed. A high index of suspected fungal infection should be considered if symptoms, especially fever, persist despite treatment. Immunocorrection with gamma interferon is able to activate the bactericidal effect due to oxygen-independent mechanisms. However, these methods do not cure the genetic defect [8].

Surgery can be an important adjunctive treatment, especially for the removal of an invasive fungal disease, and tissue samples can help identify the

microorganism and sensitivity to antifungal drugs. Hematopoietic stem cell transplantation in patients with CGB began in the early 1970s, but was sporadic and considered experimental. Despite the fact that CGB is a life-threatening and potentially life-limiting primary immunodeficiency, the decision to transplant a patient with CGB is not an easy one. Patients with CGB have a normal lymphocytic response, and many have hyperinflammation, which increases the likelihood of rejection. Since the first description of CGB, significant progress has been made in approaches to treatment, prognosis, and a normal quality of life. Therefore, patients of any age with pneumonia caused by Aspergillus, Nocardia, Burkholderia cepacia, staphylococcal liver abscess, staphylococcal pneumonia, bone damage by the microorganism Serratia marcescens should be examined for the exclusion of CGB [9,10].

The aim of the work was to describe our own clinical observation of the course of chronic granulomatous disease in a 5-year-old child.

A clinical case. Patient N., born in 2017. It is known from the anamnesis that the boy is from the 7^{th} pregnancy, which took place against the background of anemia in the second and third trimesters, the fifth urgent spontaneous labor. At birth, body weight – 3300 g, body length – 54 cm, head circumference – 35 cm, chest circumference – 34 cm, Apgar score – 9/10. Neonatal jaundice was observed in the neonatal period. He has been on artificial feeding since birth. Preventive vaccinations – mother's refusal.

On the 2^{nd} day of life, the child was admitted to the Department of pathology of newborns and premature infants in the State Medical Institution of the Kolomna Central District Hospital with complaints of subfebrile body temperature. Upon admission, the general condition of the child was assessed as a state of moderate severity, body temperature 38.3℃. During auscultation, hard breathing, moist, small-bubbly wheezing, BH 63 per minute, SpO_2 95% were heard in the lungs.

In clinical blood analysis: leukocytes – 23.9×10^9/L, erythrocytes – 5.91×10^{12}/L, Hb – 200 g/L, platelets – 241×10^9/L, lymphocytes – 12.6%, neutrophils – 36%, monocytes – 1.8%, ESR – 2 mm/h.

In the biochemical analysis of blood: total bilirubin – 274 mmol/L, ALT – 10 IU/L, AST – 23 IU/L, creatinine – 32 mmol/L, urea – 3.38 mmol/L, C-reactive protein – 25 mg/L.

On the chest X-ray, right-sided polysegmental lower lobe pneumonia was determined. According to the results of laboratory and instrumental studies, a diagnosis was made: Congenital right-sided polysegmental lower lobe pneumonia. Neonatal jaundice.

There was a course of antibacterial treatment (ampicillin, amikacin, meropenem, vancomycin, linezolid, cefpar, metronidazole), phototherapy. Against the background of ongoing antibacterial therapy, the child was discharged home with recovery.

In March 2019, at the age of 2 years, the boy was hospitalized in the Moscow Regional Research Clinical Institute named after M.F. Vladimirsky (Moscow), where, after further examination, laparoscopic diagnostic surgery and drainage of a liver abscess were performed. During the revision, a lumpy cavity was revealed, covered with a strand of the omentum, located under the abdominal wall. The cavity came from the 4-5 segment of the liver. Partial immobilization of the stuffing box was performed. Percutaneous drainage of the cavity was performed under the control of a videolaparoscope, about 15 ml of creamy pus was obtained, sowing and cytology were taken. During further revision, additional liver formations were not visualized, liver tissue was not changed. The lymph nodes of the mesentery of the intestine are enlarged throughout and are inflammatory in nature. Drainage into the suprahepatic space is installed through the installed trocar in the right mesagastrium. The postoperative period proceeded smoothly. Positive dynamics was noted during the antibacterial and symptomatic treatment.

In January 2020, the child was undergoing a routine examination at the Moscow Regional Research Clinical Institute named after M.F. Vladimirsky (Moscow). During the control ultrasound examination of the abdominal organs, regression of liver abscesses and the formation of foci of fibrosis were observed. The therapy with ceftriaxone in combination with amikacin was prescribed.

In March 2020, the child was hospitalized in the children's infectious diseases department of the State Medical Institution of the Ministry of Health "Voskresenskaya Regional Hospital" (Voskresensk) with complaints of febrile fever, weakness, productive cough.

In the general blood test: hemoglobin – 75 g/L, leukocytes – 27.8×10^9/L, platelets – 690×10^9 /L, ESR – 50 mm/h, neutrophils – 45%, neutrophils – 6%, lymphocytes – 36%.

In a biochemical blood test: total bilirubin – 89 mmol/L, CRP – 24 mg/L, glucose is 4.49 mmol/L, ALT – 131 IU/e, AST – 494 IU/e.

Coagulograma: fibrinogen – 5.06, PTI – 105%, PT – 13.0 sec, PTT – 27.4 sec, DD – 1544.

According to the results of an X-ray of the chest organs, right-sided lower lobe pneumonia with hydrothorax on the right, hydropericardium was noted.

According to the ultrasound examination of the abdominal organs, ascites and hepatomegaly were determined.

On computed tomography of the chest organs: the pulmonary pattern is unevenly enhanced; in the middle lobe of the right lung, tissue infiltration is determined paracostally by the type of ovoid consolidation 50x31x40 mm. In S6 of the right lung, areas of local compaction of the lung tissue are visualized, with thickening of the underlying costal and interlobular pleura, characteristic of pneumopleurofibrosis.

Conclusion: CT data for the presence of pneumonia in the middle lobe of the right lung with the formation of an abscess. Areas of pneumopleurofibrosis in both lungs (Fig. 1).

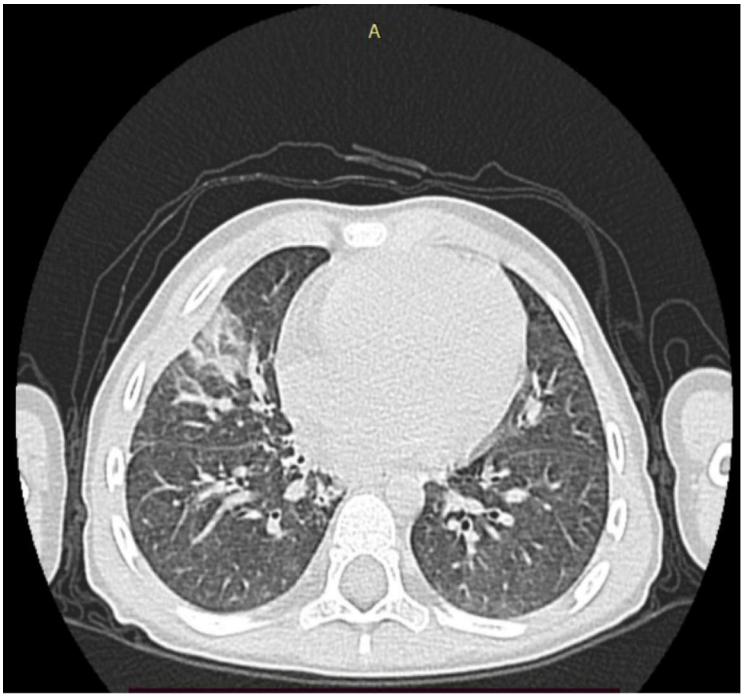

Fig. 1. Computed tomography of the chest organs, March 2020 (Voskresensk).

Due to the negative dynamics against the background of ongoing therapy, the child in a serious condition was transferred to the intensive care unit of the State Medical Institution of the Ministry of Defense "Khimki Regional Hospital" (Moscow). The boy was transferred to a ventilator due to an increase in respiratory failure. After 6 days, due to stabilization of the condition, he was extubated. He received treatment: antibacterial therapy, transfusion of erythrocyte mass, pulse therapy with corticosteroids, massive infusion therapy.

In May 2020, the boy urgently enters the children's infectious diseases department of the State Medical Institution of the Ministry of Health "Voskresenskaya Regional Hospital" (Voskresensk) with complaints of weakness, lethargy, unproductive, frequent cough, decreased appetite. Due to the severity of the condition caused by an increase in anemia with a drop-in hemoglobin to 75 g/l, respiratory disorders against the background of bilateral polysegmental pneumonia, an increase in colitis symptoms, the child was transferred to the intensive care unit in a serious condition. Transfusion of erythrocyte mass was performed. But against the background of the therapy, the child's condition is without positive dynamics.

The child was transferred to the Pediatric surgical department of the Moscow Regional Research Clinical Institute named after M. F. Vladimirsky (Moscow). The condition at admission is severe. The child is sluggish, whiny, adynamic. On examination, the skin and visible mucous membranes are pale pink with a gray tinge, nasal breathing is difficult. With percussion in the lungs, there is a pulmonary sound, with auscultation – hard breathing with different-sized wheezes on both sides. BH 30 per minute.

In the general blood test: hemoglobin – 90 g/L, leukocytes – 24×10^9/L, platelets – 254×10^9/L, ESR – 45 mm/h, s/I neutrophils – 57%, n/I neutrophils – 1%, lymphocyte – 31%.

In the biochemical analysis of blood: total bilirubin – 89 mmol/L, CRP – 24 mg/L, glucose – 4.49 mmol/L, ALT – 110 IU/e, AST I – 176 IU/e.

Immunogram: IgG – 17.2 (reference values - 5-13), IgA – 3.7 (reference values 0.4-1.8).

A study of a subpopulation of lymphocytes was conducted: an increase in CD3+(T-lymphocytes), CD3+ CD8+ (T-cytotoxic lymphocytes), CD3+ CD16+ CD56+ (NKT lymphocytes) values was observed.

A consultation was held, according to the results of which a diagnosis was made: Fungal-bacterial sepsis. Bilateral destructive pneumonia. Iron

deficiency anemia of the 2nd degree. Primary immunodeficiency? A molecular genetic study is recommended at the FSBI "NMIC DGOI named after Dmitry Rogachev" (Moscow).

In July 2020, the patient was hospitalized in the Federal State Budgetary Institution “Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology" of the Ministry of Health of the Russian Federation (FSBI "NMIC DGOI named Dmitry Rogachev”, Moscow).

In the general blood test: hemoglobin – 116 g/L, leukocytes – 16.3×10^9/L, platelets – 255×10^9/L, neutrophils – 8.07×10^9/L, lymphocytes – 5.9×10^9/L.

In a biochemical blood test: total bilirubin - 4.2 mmol/L (direct – 2.3 mmol/L), glucose – 4.93 mmol/L, ALT – 42 IU/e, AST – 33 IU/e.

Immunogram: IgG – 18.5 (reference values – 6.8-15.4), IgA – 4.39 (reference values 0.3-1.5).

Direct sequencing by Sanger: in exon 9, a replacement of one nucleotide c.925G> T in the hemizygous state was detected, leading to the formation of a stop codon and, as a consequence, to the termination of the synthesis of the protein P.Glu 309Ter (E309*). Evaluation of the oxidative activity of neutrophils (Burst-test): there is no oxidative activity of granulocytes after stimulation.

A multispiral computed tomography of the chest was performed, according to the results of which the course of bilateral polysegmental pneumonia was noted. A multispiral computed tomography of the abdominal cavity visualized a limited fluid accumulation in the subdiaphragmatic space on the right side of the liver, enlarged lymph nodes of the abdominal cavity and retroperitoneal space. According to ultrasound examination of the abdominal organs, hepatosplenomegaly was determined. Bronchoscopy with bronchoalveolar lavage was also performed: the growth of polyresistant Klebsiella pneumoniae was revealed.

A diagnostic lung biopsy was performed. Pathomorphological examination revealed atelectatically altered fragments of lung tissue with massive lymphocytic infiltration with the presence of multiple epithelioid granulomas with centrally located giant multinucleated cells. There is no expression of Mb, Zil-Nielsen, epithelioid cells express CD68, the lymphoid component is represented by CD20 positive B lymphocytes with an admixture of CD3/CD4 and CD3/CD8 positive T cells. There is no expression of EBER. Conclusion: in the studied material there are signs of granulomatous lesion of the lung tissue.

According to the results of laboratory and instrumental studies, the final diagnosis was made: primary immunodeficiency: Chronic granulomatous disease. Mutation in the gene CYBB c.925G>Tp.Glu309Ter in the hemizygous state.

Recommendations are given to continue therapy with voriconazole, sulfomethoxazole, azithromycin for six months, as well as conducting computed tomography of the chest organs once every 6 months at the place of residence. During 2021-2023, there were no exacerbations of the disease. Currently, the child is being dynamically monitored.

Conclusions. Primary immunodeficiency conditions always present difficulties for their timely diagnosis, especially in primary health care. A common clinical sign of immunodeficiency states is a tendency to develop recurrent bacterial and fungal infections of various localizations. The spectrum of immune disorders in primary immunodeficiency is quite wide, which makes it difficult to verify the disease. With early diagnosis of chronic granulomatous disease and a multidisciplinary approach to monitoring and treatment, it is possible to avoid life-threatening situations described by other authors.

References / Литература

1. *Щербина А.Ю. Маски первичных иммунодефицитных состояний: проблемы диагностики и терапии. Российский журнал детской гематологии и онкологии (РЖДГиО). 2016;3(1):52-58. [Shcherbina AYU. Maski pervichnyh immunodeficitnyh sostoyanij: problemy diagnostiki i terapii. Rossijskij zhurnal detskoj gematologii i onkologii (RZHDGiO). 2016;3(1):52-58. (In Russ.).] https://doi.org/10.17650/2311-1267-2016-3-1-52-58*
2. *Спиваковский Ю.М., Щербина А.Ю., Спиваковская А.Ю., Юхачева Д.В., Першин Д.Е. Хроническая гранулематозная болезнь у ребенка двух лет: путь к диагнозу (клинический случай). Саратовский научно-медицинский журнал. 2022;18(3):364-369. [Spivakovskij YUM, SHCHerbina AYU, Spivakovskaya AYU, YUhacheva DV, Pershin DE. Hronicheskaya granulematoznaya bolezn' u rebenka dvuh let: put' k diagnozu (klinicheskij sluchaj). Saratovskij nauchno-medicinskij zhurnal. 2022;18(3):364-369. (In Russ.).]*
3. *Шамраева В.В., Григоренко Г.В., Фурсова Н.В. Клинический случай первичного комбинированного иммунодефицита. Хронический кожно-слизистый кандидоз у девочки 5 лет. Аллергология и Иммунология в Педиатрии. 2022;(3):60-62. [SHamraeva VV, Grigorenko GV, Fursova NV. Klinicheskij sluchaj pervichnogo kombinirovannogo immunodeficita.*

Hronicheskij kozhno-slizistyj kandidoz u devochki 5 let. Allergologiya i Immunologiya v Pediatrii. 2022;(3):60-62. (In Russ.).] https://doi.org/10.53529/2500-1175-2022-3-60-62

4. *Arnold DE, Heimall JR. A Review of Chronic Granulomatous Disease. Adv Ther. 2017;34(12):2543-2557. https://doi.org/10.1007/s12325-017-0636-2*
5. *Бяловский Ю.Ю., Ракитина И.С. Влияние исходной величины подкрепления на физиологические показатели условного дыхательного рефлекса. Наука молодых (Eruditio Juvenium). 2021;(3):377-386. [Byalovskij YUYU, Rakitina IS. Vliyanie iskhodnoj velichiny podkrepleniya na fiziologicheskie pokazateli uslovnogo dyhatel'nogo refleksa. Nauka molodyh (Eruditio Juvenium). 2021;(3):377-386. (In Russ.).] https://doi.org/10.23888/HMJ202193377-386*
6. *Rawat A, Bhattad S, Singh S. Chronic Granulomatous Disease. Indian J Pediatr. 2016;83(4):345-53. https://doi.org/10.1007/s12098-016-2040-3*
7. *Губкина М.Ф., Стерликова С.С., Юхименко Н.В., Петракова И.Ю., Хохлова Ю.Ю. Трудности диагностики хронической гранулематозной болезни у ребенка 10 лет. Российский вестник перинатологии и педиатрии. 2021;66(6):97-102. [Gubkina MF, Sterlikova SS, YUhimenko NV, Petrakova IYU, Hohlova YUYU. Trudnosti diagnostiki hronicheskoj granulematoznoj bolezni u rebenka 10 let. Rossijskij vestnik perinatologii i pediatrii. 2021;66(6):97-102. (In Russ.).]*
8. *Kutluğ Ş, Şensoy G, Birinci A, Saraymen B, Yavuz Köker M, Yıldıran A. Seven chronic granulomatous disease cases in a single-center experience and a review of the literature. Asian Pac J Allergy Immunol. 2018;36(1):35-41.*
9. *Губенко М.С., Логинов В.И., Бурденный А.М., Пронина И.В., Хохлова С.В., Перцов С.С. Роль микроРНК в канцерогенезе немелкоклеточного рака легкого. Российский медико-биологический вестник им. академика И.П. Павлова. 2022; 30(1):123-132. [Gubenko MS, Loginov VI, Burdennyj AM, Pronina IV, Hohlova SV, Percov SS. Rol' mikroRNK v kancerogeneze nemelkokletochnogo raka legkogo. Rossijskij mediko-biologicheskij vestnik im. akademika I.P. Pavlova.2022;30(1):123-132. (in Russ.)]. https://doi.org/10.17816/PAVLOVJ71395*
10. *Gennery AR. Progress in treating chronic granulomatous disease. Br J Haematol. 2021;192(2):251-264. https://doi.org/10.1111/bjh.16939*

For citation

Belykh NA, Zakharova AV, Pisnyur IV. Clinical observation of a 5-year-old patient with chronic granulomatous disease associated with a mutation in the CYBB gene. Euroasian Health Journal. 2024;1:32-38. https://doi.org/10.54890/EHJ-2024-1-32

Для цитирования

Белых Н.А., Захарова А.В., Пизнюр И.В. Клиническое наблюдение пациента 5 лет с хронической гранулематозной болезнью, ассоциированной с мутацией в гене CYBB. Евразийский журнал здравоохранения. 2024;1:32-38. https://doi.org/10.54890/EHJ-2024-1-32

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