A clinical case of autosomal recessive agammaglobulinemia with B-cell deficiency

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Annotation

Background. Primary agammaglobulinemia is the result of specific changes in B-cells that lead to low antibody production. A preliminary diagnosis is established if there is a history of frequent bacterial infections (otitis media, sinusitis, skin abscesses), including severe course, in some cases caused by opportunistic flora and atypical mycobacteria; low levels of immunoglobulins. The main symptoms of primary immunodeficiency in a child from this clinical example were frequent recidivating bronchial obstruction with the development of pneumonia.

Presentation of the clinical case. The publication presents a clinical case of autosomal recessive agammaglobulinemia with B-cell deficiency in a child of 2 years, 7 months. During the follow-up period from 4 months to 2 months, 7 months, the child had 3 episodes of pneumonia, 3 episodes of purulent otitis media. The child repeatedly underwent inpatient treatment, where he received broad-spectrum antibiotics as treatment. Based on the examination (IgA (0.02 g/l), IgG (0.3 g/l), IgM (0.07 g/l) and the absence of $CD19^+$ cells), the diagnosis of "Primary immunodeficiency, agammaglobulinemia" was made, which was subsequently confirmed by the RDC of Moscow. From the moment of diagnosis, the child receives intravenous immunoglobulins at a dose of 7.5 g. and antibacterial therapy.

Conclusion. Early recognition and diagnosis of these conditions is crucial to improve outcomes and prevent complications.

Keywords: Primary immunodeficiency, agammaglobulinemia, autosomal recessive form, children, clinical case.

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Клинический случай аутосомно-рецессивной агаммаглобулинемии с дефицитом В-клеток

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Аннотация

Введение. Первичная агаммаглобулинемия является результатом специфических изменений в В-клетках, которые приводят к низкой выработке антител. Предварительный диагноз устанавливается при наличии в анамнезе частых бактериальных инфекций (отиты, синуситы, абсцессы кожи), в том числе тяжелого течения, в некоторых случаях вызванных условно-патогенной флорой и атипичными микобактериями; низкого уровня иммуноглобулинов. Основными симптомами первичного иммунодефицита у ребенка из данного клинического примера являлись частые рецидивирующие бронхообструкции с развитием пневмонии.

Изложение клинического случая. В публикации представлен клинический случай аутосомно-рецессивной агаммаглобулинемии с дефицитом В-клеток у ребенка 2 лет 7 мес. В период наблюдения с 4 мес. до 2 лет 7 мес. у ребенка наблюдались 3 эпизода пневмонии, 3 эпизода гнойного среднего отита. Ребенок неоднократно проходил стационарное лечение, где в качестве лечения получал антибиотики широкого спектра действия. На основании обследования (IgA (0,02 г/л), IgG (0,3 г/л), IgM (0,07 г/л) и отсутствие $CD19^+$-клеток) был выставлен диагноз «Первичный иммунодефицит, агаммаглобулинемия», который в последующем был подтвержден в Российской детской клинической больнице (РДКБ) г. Москвы. С момента постановки диагноза ребенок получает ВВИГ в дозе 7,5 г и антибактериальную терапию.

Заключение. Раннее распознавание и диагностика этих состояний имеют решающее значение для улучшения результатов и предотвращения осложнений.

Ключевые слова: первичный иммунодефицит, агаммаглобулинемия, аутосомно-рецессивная форма, дефицит В-клеток.

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INTRODUCTION. Agammaglobulinemia is a type of primary immunodeficiency, characterized by severe forms of decrease in the level of all types of immunoglobulins in the blood serum and the absence of B-cells in the blood [1, 2, 3, 4]. Prevalence of agammaglobulinemia range from 1:100000 to 1:200000 [5]. Agammaglobulinemia should be considered in detail, paying special attention to the study of life and the disease history. The patient has frequent recidivating bronchial infections at the age of 5, severe bacterial infections, such as meningitis and septicemia, aplasia of lymphoid tissue [3, 6]. Laboratory evaluation includes the analysis of leukocyte formula, the state of the cellular component of immune system (immunophenotyping of B- and T-cells), levels of ɣ-globulins, quantitative levels of immunoglobulins in the serum (IgM, IgG, IgA, IgE) and specific antibody responses to both protein and polysaccharide antigens,

as well as whole-exome genome sequencing [3]. In the immunological study agammaglobulinemia is manifested in the form of IgG level decline in the blood below 1,0 g/l in combination with the decrease in IgM concentration below 0,2 g/l and IgA level below 0,1 g/l with a normal or reduced level of peripheral B-cells [5]. Nowadays there are several reported genes, defect in which might be the cause of agammaglobulinemia: BTK, IGHM, IGLL1, CD79A, CD79B, BLNK and PIK3R1 [7]. The diagnosis is confirmed by genetic analysis and the detection of mutations, associated with X- and autosomal recessive or dominant chromosome. X-linked form (XLA) is characterized by the absence of circulating B cells and a pronounced decrease in all serum immunoglobulins due to mutations in the BTK gene [2]. The only difference between autosomal recessive and XLA-agammaglobulinemia is that the former occurs in females. The incidence: 1:100000–1:500000 population [2, 5]. Inherited immune system disorders, XLA, or Bruton disease affects only men [2]. Autosomal recessive agammaglobulinemia is a rare type of primary immunodeficiency, characterized by mutations in genes, responsible for early differentiation and B-cell function [8]. These are mostly related to defects in the components of BCR complex. Transition from pro-B-cells to pre-B-cells, along with the consistent rearrangement of immunoglobulin genes and a normal development of B-cells, requires surface expression of pre-BCR functional complex. As a result, defects of the very BCR structure, including μ heavy chain, surrogate light chains (VpreB and λ5), Igα (CD79) and Igβ (CD79B) genes, which form heterodimeric transmembrane signal transduction elements, lead to autosomal forms of agammaglobulinemia. After BTK gene, encoding μ heavy chain, IGHM (located on chromosome 14q32.33) is the second most frequently mutated gene in patients with agammaglobulinemia, but it is still about 5% of patients [3, 9].

CLINICAL CASE REPORT

The girl A., at the age of 2 years and 7 months, was admitted to the emergency room of Pediatric Republican Clinical Hospital (PRCH), Saransk, December, 10, 2018 at 11:05 with complaints about an increase in body temperature to 38,0 °C, unproductive cough with sparse serous sputum, shortness of breath at rest, using accessory muscles, weakness and loss of appetite.

Life history. The child from the 2nd pregnancy, occurring against the background of mild iron-deficiency anemia, exacerbation of bronchial asthma, the presence of antibodies to herpes simplex virus in the blood, cytomegalovirus, toxoplasma, 2 births at 39 weeks. Natural delivery. The condition at birth is severe due to reduced neuro-reflex excitability. Birth weight is 3250 g, height is 50 cm. APGAR score is 7/7.

Disease history: the parents noted increased body temperature to 38 °C, productive cough, lethargy and loss of appetite for the first time at the age of 4 months. The child was hospitalized with the above described complaints, where, according to the results of physical (fine moist rales on the right side during auscultation), laboratory (leukocytosis with a shift of the leukocyte formula to the left and a moderate increase in the number of neutrophils) and hardware examination (low-intensity infiltration is determined in the lower lobe of the right lung on the radiograph of the thoracic organs in direct projection against increased pulmonary pattern) she was diagnosed with "Community-acquired right-sided lower lobe pneumonia of moderate severity. RF 0 degree". Against the background of antibiotic treatment (ceftriaxone solutions, 130 mg + NaCl 0,9 % 100 ml iv once per day for 7 days; azithromycin suspension 1,5 ml orally once per day for 5 day): there is a positive dynamic in the form of normalization of body temperature on the 4th day of hospital stay. With repeated radiographic examination on the 14th day: pulmonary pattern is enhanced, enriched, radiological signs of infiltrative changes in lung have not been defined.

At the age of 7 moths there was an episode of an increase in body temperature to 39 °C, tearfulness, irritability, abundant discharge of pus; examined by an otorhinolaryngologist at the place of residence, diagnosed with "Acute purulent otitis media", and symptomatic therapy and broad-spectrum antibiotic are prescribed as treatment— cefixime suspension, 3 ml orally, once per day for 7 days.

At the age of 11months (according to the parents, without documentary proof) there was hospitalization with the diagnosis "Left-sided bronchopneumonia".

According to the discharge summary, there was hospitalization to PRCH, Saransk, since the age of 1 year 5 months and for 2 months with the diagnosis "Obstructive bronchitis, acute laryngotracheitis, laryngeal stenosis of III degree, pseudomembranous candidiasis, immune thrombocytopenic, purpura complicated by intestinal bleeding and anemia of moderate severity. Immunodeficiency

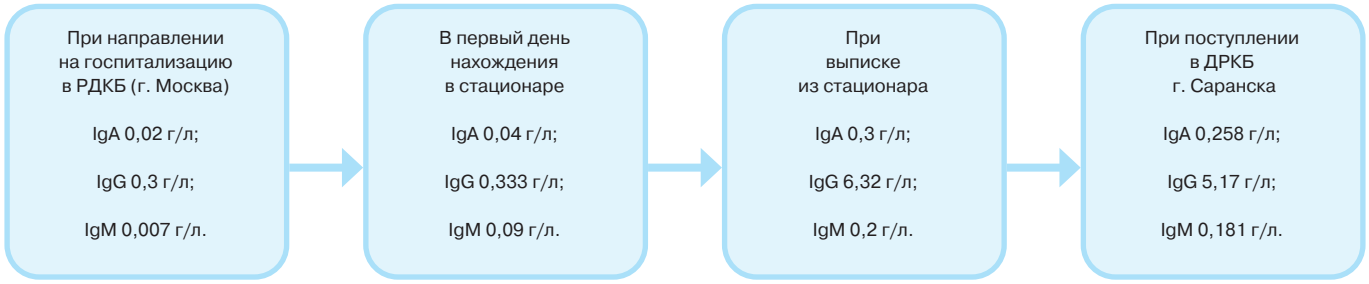

Fig. 1. **Immunoglobulin levels in the patient's blood serum**
Рис. 1. **Уровни иммуноглобулинов в сыворотке крови пациентки**

state is unspecified". There was red blood cell transfusion, replacement therapy with normal human immunoglobulin 5 g intravenous drip, antibiotic therapy in the form: ceftriaxone solution 200 mg + NaCl 0,9 % 200 ml IV once per day for 10 days; antifungal drug was prescribed: fluconazole suspension 3 ml orally once per day for 3 days.

Over the next4 months (according to the parents) she suffered from acute tracheitis and purulent otitis media. Follow-up and treatment were carried out on an outpatient basis.

According to the parents, there was an increase in temperature up to 38,5 °C, productive cough with purulent sputum discharge, tearfulness and irritability at the age of 2 years and 2 months. The radiograph of thoracic organs determines intensive infiltration on the left in the direct projection against the backdrop of increased pulmonary pattern. Hospitalized with the diagnosis "Community-acquired left-sided pneumonia of moderate severity. RF 0 degree". The child was first consulted by an allergist-immunologist, and immunological examination was recommended, according to which there was a significant decrease in the concentration of serum IgA (0,02 g/l), IgG (0,3 g/l), IgM (0,07 g/l) and lack of $CD19^+$ cells.

Due to the deterioration and reduction in serum immunoglobulins, the child was diagnosed with "Primary immunodeficiency, agammaglobulinemia" and sent to the Department of Clinical Immunology and Rheumatology of RPCH, Moscow. On admission there were complaints of cough and mucous discharge from the nose. According to x-ray data, signs of right-sided polysegmental pneumonia were visualized in the lungs. Data of immunological examination revealed a decrease in serum immunoglobulins: IgA to 0,04 g/l (1–3,5 g/l), IgM to 0,09 g/l (0,8–2,5 g/l), IgG to 0,33 g/l (9–18 g/l) and reduction in $CD19^+$ cells to 1% (5–19%). According to screening there was the clinical diagnosis of "Primary immunodeficiency with B-cell deficiency". By using a genetic research method, the child was diagnosed with autosomal recessive form of agammaglobulinemia. Replacement therapy was carried out during hospitalization — human normal immunoglobulin 7,5 r IV drops, antibiotic therapy in the form: cefepime solution 750 mg + NaCl 0,9 % 200 ml IV twice a day for 10 days, symptomatic therapy. There was positive dynamics during treatment in the form of improved overall well-being and increased concentration of serum immunoglobulins: IgA 0,3 g/l (1–3,5 g/l), IgG 6,32 g/l (9–18 g/l), IgM 0,2 g/l (0,8–2,5 g/l). In the future life-long replacement therapy with IVIG is recommended.

At the age of 2 years and 7 months the parents noted an increase in body temperature to 38 °C, the appearance of cough, nasal discharge of greenish colour, nasal congestion. Physical examination data: difficulty in nasal breathing, puromucous discharge from the nose, auscultatory puerile respiration, in all pulmonary fields, wheezing is not heard. Radiography of the thoracic organs identified: pulmonary pattern is enhanced, low-intensity infiltration is detected on the right. RT 24 per minute. According to immunological laboratory data: humoral immunity — IgA 0,258 g/l (1–3,5 g/l), IgM 0,181 g/l (0,8–2,5 g/l), IgG 5,17 g/l (9–18 g/l). There was an increase in the content of $CD4^+$- (46% (55–80%)) and $CD8^+$-lymphocytes (16% (31–51%)), single $CD19^+$-lymphocytes (2% (5–19%)). Broad-spectrum antibiotics were prescribed

— ceftriaxone solution 200 mg + NaCl 0,9 % 200 ml IV once per day for 10 days, symptomatic therapy; due to exacerbation of chronic foci of infection, it was decided to complement the planed course with IV administration of 5 g of normal human immunoglobulin.

CONCLUSION

Primary immunodeficiency and autosomal recessive agammaglobulinemia with B-cell deficiency were diagnosed in this clinical case. PID are severe life-threatening diseases in young children. Timely diagnosis before developing severe infectious processes in the patient significantly improves the prognosis for survival of this group of patients. Neonatal screening (TREC и KREC) is an important measure for early diagnosis of patients with PID.

INFORMED CONSENT

The legal representative of the patient provided voluntary informed consent for publishing the description of the clinical case in the journal "Allergology and Immunology in Paediatrics": the date of signing the document by the legal representative of the patient— 01.02.2018.

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Elena V. Negodnova, Maria S. Iskandyarova — creation of a research concept.
Evgenia N. Tyagusheva — preparation of a draft article.
Olga A. Radaeva, Galina V. Fominova — revision and editing of the article.

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