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Lung diseases in adult patients with primary immunodeficiencies with defects of antibody production according to real clinical practice

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Abstract

Introduction. The problem of lung diseases in patients with primary defects in antibody production has not been sufficiently studied, especially depending on the climatic, geographical and demographic conditions of real clinical practice.

Aim. To study the structure of lung disorders in adult patients with primary antibodies defects in the Middle Urals in real clinical practice.

Materials and methods. Register of adult patients with primary immunodeficiencies (PID) were created in 2013 in the Sverdlovsk region. Now it contains 209 people. The main group of the register is patients with primary antibodies defects (PAD, n = 143, 68.4%: agammaglobulinemia (AGG, n = 11, common variable immune deficiency (CVID, n = 37), PIK3-Kinase deficiency (n = 3), Selective IgA deficiency (SD IgA, n = 92). The diagnosis of PID was established on the criteria for the Russian Association of Allergists and Clinical Immunologists and European Societies of Immunodeficencies, in some cases it has a genetic confirmation. We used medical history of patients, radiological, functional studies to establish lung lesions. We occurred immunological examination for all PID patients.

Results. Repeated pneumonia were observed in all patients with AGG and CVID, especially in the onset of PID. Patients also had diseases such as bronchiectasis (up to 37.6% of patients), chronic obstructive lung disease (up to 70.3% of patients), bronchial asthma (only SD IgA), interstitial lung disease (only CVID).

Conclusion. According to our data, in the Middle Urals, lung diseases, especially pneumonia and bronchiectasis, are the most common clinical manifestations in patients with DA. Analysis of immunoglobulins' level is necessary in patients with repeated pneumonia, bronchiectasis and interstitial lung disease, bronchial asthma and early onset of chronic obstructive lung disease without smoking status.

Keywords: primary immunodeficiencies, primary antibodies defects, repeated pneumonias, bronchiectasis, immunoglobulin level

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Заболевания легких у взрослых пациентов с первичными дефектами антителообразования по данным реальной клинической практики

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Резюме

Введение. Проблема заболеваний легких у пациентов с первичными дефектами антителообразования недостаточно исследована, особенно в зависимости от климатогеографических и демографических условий реальной клинической практики.

Цель. Исследовать структуру заболеваний легких у взрослых пациентов с первичными дефектами антителообразования на Среднем Урале в условиях реальной клинической практики.

Материалы и методы. В 2013 г. в Свердловской области создан регистр взрослых пациентов с первичными иммунодефицитами (ПИД), в котором в настоящее время состоят 209 человек. Основную группу регистра составляют пациенты с дефектами антителообразования (ДА) (n = 143, 68,4%): пациенты с агаммаглобулинемией (АГГ, n = 11), общей вариабельной

иммунной недостаточностью (ОВИН, n = 37), дефицитом PIK3-киназы (n = 3), с селективным дефицитом IgA (СД IgA, n = 92). Диагноз ПИД был установлен на основании критериев Российской ассоциации аллергологов и клинических иммунологов и European Societies of Immunodeficienties, в ряде случаев имеет генетическое подтверждение. Для диагностики поражений легких использовали данные анамнеза пациентов, рентгенологические, функциональные, иммунологические исследования.

Результаты. Неоднократные пневмонии наблюдались у всех пациентов с АГГ и ОВИН, особенно в дебюте заболевания. Также регистрировались бронхоэктазы (37,6% пациентов), хроническая обструктивная болезнь легких (70,3%), бронхиальная астма (только у пациентов СД IgA), интерстициальное поражение легких (только у пациентов с ОВИН).

Выводы. На Среднем Урале заболевания легких, особенно пневмонии и бронхоэктазы, являются наиболее частыми клиническими проявлениями у пациентов с ДА. Исследование уровня IgG, IgM, IgA необходимо у пациентов с неоднократными пневмониями, бронхоэктатической болезнью, интерстициальным поражением легких, бронхиальной астмой, при раннем дебюте хронической обструктивной болезни легких без статуса курения.

Ключевые слова: первичные иммунодефициты, первичные дефекты антителообразования, неоднократные пневмонии, бронхоэктазы, уровень иммуноглобулинов

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INTRODUCTION

Primary immunodeficiencies (PID) are the group of genetically determined diseases of the immune system associated with the loss, reduction or malfunction of one or more of its components [1–4]. Congenital disorders of the immune system are manifested by increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergies and/or malignancies. The number of known genetic defects identified as causing PID is currently about 500 [4]. The incidence of PID in international registries is 11.2 per 100,000 births [5], of which 71% are diagnosed before the age of 18 years. Defects that primarily affect the humoral immune system account for about 60% of all PIDs. The frequency of occurrence of primary immunodeficiencies with antibody defects varies depending on the identified defect: selective IgA deficiency – 1:300–1:700; Common variable immunodefficiency (CVID) – 1:7 000–1: 200 000; X-linked agammaglobulinemia – 1:50 000–1 000 000. In 80% of cases, the age of patients at diagnosis definition does not exceed 20 years [6].

In real clinical practice, patients with primary immunodeficiencies can occur at an appointment with any doctor, but more often with a pediatrician, therapist and pulmonologist. This is due to the fact that clinical manifestations of bronchopulmonary pathology, first of all infections, are the most common manifestation of PID [7, 8]. In domestic and foreign literature there are many indications of lung disorders in patients with PID [9–13]. However, there is insufficient data on the climatic, geographical and demographic features of the prevalence of PID and lung diseases associated with congenital immune deficiency. For example, information about patients with PID in Central Asia is sporadic; there are indications of 9 patients in Kyrgyzstan and 6 patients in Uzbekistan [14, 15]. There are large territories, a high enough population density and extensive travels of people in all historical periods in this geographical area (for example, the Silk Roads caravan way) make research the problem of inborn errors of the immune system in this region very demand. A comparison of the incidence and prevalence of lung disorders in patients with primary antibody production defects in contrasting climatic and geographical regions, for example, the Middle Urals and Central Asia, constitutes unquestionable scientific interest. In this regard, the goal of our work was to study the structure of lung disorders in adult patients with primary antibody production defects in the Middle Urals in real clinical practice.

MATERIALS AND METHODS

The register of adult patients with PID was conducted in Sverdlovsk region (the Middle Urals) at 2013. The register includes 209 patients (*Table 1*).

The information about the patient, nosological form of PID, the onset of the disease, family history, the main clinical and laboratory symptoms of the disease, the therapy performed and its effectiveness, all these include registry information [7]. The main group of the register consists of patients with predominantly antibody deficiencies (PAD) –143 people (68.4%). The PAD group is the largest in the PID registers of other regions of Russian Federation and other countries [9, 16–20].

The part of PAD patients needs immunoglobulin replacement therapy. In our registry, these are patients with agammaglobulinemia (AGG, n = 11), and common variable immune deficiency (CVID, n = 37), PIK3-kinase deficiency (n = 3). Another part of PAD patients does not need immunoglobulin replacement therapy, these are patients with selective IgA deficiency (SD IgA, n = 92).

The diagnosis of PID in our patients was established based on the criteria of the Russian Association of Allergologists and Clinical Immunologists (RAACI) and the European Societies of Immunodeficiencies (ESID) [21]. The diagnosis

● ***Table 1.*** The Register of adult patients with PID, data for June 2024
● ***Таблица 1.*** Регистр взрослых пациентов с первичными иммунодефицитами, данные на июнь 2024 г.

PID groups	Nosology of PID	Number of patients, n		
		total	male	female
I. Combined immunodeficiencies with associated or syndromic features	HyperIgE syndrom	5	3	2
	Ataxia-telangiectasia	1	1	-
	DiGeorge/velocardiofacial Syndrome/ Chromosome 22q11.2 deletion syndrome (22q11.2DS)	2	-	2
	Wiskott-Aldrich syndrome	1	1	-
	Kabuki syndrome	1	1	-
	Nijmegen breakage syndrome	1	-	1
II. Predominantly antibody deficiencies	Agammaglobulinemia	11	10	1
	Common variable immune deficiency	37	6	31
	Selective IgA deficiency	92	48	44
	PIK3kinase deficiency	3	1	2
III. Diseases of immune dysregulation	Autoimmune Lymphoproliferative Syndrome	1	1	-
	BACH2 deficiency	1	1	-
IV. Congenital defects of phagocyte number or function	X-linked chronic granulomatous disease	2	1	1
	Congenital Neutropenia	1	1	-
V. Autoinflammatory disorders	Familial Mediterranean fever	5	4	1
	Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	1	-	1
VI. Complement deficiencies	Hereditary angioedema	30	8	22
VII. Phenocopies of inborn errors of immunity	Thymoma with hypogammaglobulinemia (Good syndrome	1	-	1
VIII. Non verification PID		13	9	4
Total		209	96	113

PID – primary immunodeficiencies.

of patients with X-linked agammaglobulinemia was confirmed genetically (defect in the *BTK* gene). The registry also includes patients with CVID and PIK3-kinase deficiency, which has genetic confirmation of the disease.

To establish lung diseases, we used patient history data, first of all the presence of repeated pneumonia at the onset and during the course of the disease, as well as bronchiectasis and lung resections. Chest X-ray was performed using Axion Luminos (Siemens), spiral computed tomography was performed using Siemens Somatom 64. The lung function was performed using Erich Jaeger GmbH spirograph, determined: FEV_1, FVC, FEV_1/FVC; in this case, functional confirmation of chronic obstructive pulmonary disease (COPD) was a decrease in FEV_1/FVC less than 0.7 as a result of a bronchodilator test with 400 mcg of salbutamol.

The immunological examination was performed in all groups of patients to evaluate the following indicators:

- number of populations and subpopulations of lymphocytes (quantitative and percentage content in peripheral blood): CD3+, CD4+, CD8+, CD 19+, CD16+, CD56+, HLA-DR;
- blood levels of immunoglobulins G, A, M, E;
- phagocytosis features: determination of the absorption and metabolic activity of peripheral blood phagocytes, identification of the formation of reactive oxygen species by leukocytes.

Lymphocyte populations and subpopulations were determined by flow cytometry using monoclonal antibodies (Beckman Coulter, USA). Levels of serum immunoglobulins (IgA, IgM, IgG, IgE) were determined by turbodimetry (Cobas Integra 400). Phagocytosis parameters were assessed using spontaneous and stimulated nitroblue tetrazolium reduction test (Sigma-Aldrich). The stimulated test was performed in whole blood with neutrophils activated with 0.1 ml of a latex suspension with a particle size of 1.5 μm.

Quantitative indicators were assessed for normality using the Kolmogorov-Smirnov test (for a sample of more than 50) and the Shapiro-Wilk test (for a sample of less than 50). Quantitative data were described using the median (Me) and the lower and upper quartiles (Q1–Q3), since the distribution differed from normal.

Statistical indicators were performed using the Statistica Program for Windows, version 13.3.

RESULTS

The average age of patients with CVID was 37.4 years (Q1-Q3: 19.2–50.1), patients with AGG was 22.1 years (Q1-Q3: 19.6–29.1), with SD IgA 24.2 years (Q1-Q3: 18.9–27.4). At the same time, the average age at the time of disease onset in patients with CVID was 22.1 years (Q1-Q3: 19.4–34.2), in patients with AGG – 3.7 years (Q1-Q3: 1.7–5.1), PIK3-kinase deficiency – 8.0 years (Q1-Q3: 3.5–11.6), CD IgA – 10.7 years (Q1-Q3: 7.6–13.4). Thus, the majority of patients with CVID were identified in adulthood, other patients - in childhood and transferred to adult practice at 18 years old. The average period of diagnosis for CVID was 12.6 years with the longest period of diagnosis being 28 years, for the other cases - up to 4 years.

Manifestations of infectious syndrome with lung injury in our patients were repeated pneumonia as well as bronchiectasis. The history of repeated pneumonias was found in patients with all four nosological forms of PAD *(Table 2*).

Thus, repeated pneumonia is the most characteristic sign of the onset and course of AGG, CVID; it occurs in some cases in other DA and necessarily requires consultation with an immunologist and an immunological examination. The repeated pneumonias were different localization, bilateral lesions. In one case, a patient with CVID was treated for different episodes of pneumonia 8 times within one year. Antimicrobial therapy for pneumonia in patients with PID was carried out according to clinical recommendations [22]. The average age of patients with AGG, who had clinical manifestations in the form of repeated pneumonia at the onset, was 3.2 years (Q1-Q3: 1.9-4.8), patients with CVID - 18.8 years (Q1-Q3: 11.7-27.8), with SD IgA - 5.6 years (Q1-Q3: 3.8-19.1). In patients with AGG and CVID, there was a decrease in the frequency of pneumonia after the diagnosis of PID, which was due to the replacement therapy with intravenous immunoglobulins to these patients.

Another common clinical manifestation of lung lesions in patients with defects in antibody production as part of an infectious syndrome is bronchiectasis and its exacerbations (*Table 3*).

Most often, the presence of bronchiectasis occurred in our patients with AGG and CVID, which may be associated not only with the infectious syndrome, but also with combined genetic defects leading to disturbances in the structure of the bronchi [23]. The average age of patients in whom bronchiectasis was first diagnosed was 21.5 years (Q1-Q3: 13.4–28.2) for CVID, 8.0 years (Q1-Q3: 5.3–9.6) for AGG. In case of SD IgA, bronchiectasis was

Table 2. The repeated pneumonias before predominantly antibody deficiencies diagnosis and during the course of the illness

Таблица 2. Неоднократные пневмонии в дебюте и в течение заболевания у больных с дефектами антителообразования

Nosological entity of antibody production defects	Onset of PID		During the course of the illness	
	Number of patients, n	% of the total number of patients with this disease	Number of patients, n	% of the total number of patients with this disease
AGG	11	100	9	81.8
CVID	37	100	26	70.3
PIK3 kinase deficiency	0	0	1	33.3
SD IgA	23	25	16	17.4

AGG – agammaglobulinemia, CVID – common variable immune deficiency, SD IgA – selective IgA deficiency.

Table 3. Exacerbations of bronchiectasis before predominantly antibody deficiencies diagnosis and during the course of the illness

Таблица 3. Обострения бронхоэктатической болезни в дебюте (до установления диагноза первичного иммунодефицита) и в течение заболевания у пациентов с дефектами антителообразования

Nosological entity of antibody production defects	Onset of PID		During the course of the disease	
	Number of patients, n	% of the total number of patients with this nosology	Number of patients, n	% of the total number of patients with this nosology
AGG	2	18.8	4	36.4
CVID	6	16.2	14	37.8
PIK3 kinase deficiency	0	0	0	0
SD IgA	3	3.3	8	8.7

AGG – agammaglobulinemia, CVID – common variable immune deficiency, SD IgA – selective IgA deficiency.

detected at the onset of DA in patients who also had concomitant diseases: cystic fibrosis, type I diabetes mellitus, scleroderma. The average age of the patients was 6.1 years (Q1-Q3: 3.7–8.5). Bronchiectasis was not detected in patients with PIK3 kinase deficiency. Localization of bronchiectasis: unilateral lesions were observed in 19 patients (13.3% of all patients with DA), bilateral lesions in 5 patients (3.5% of all patients with DA). Mostly, the middle lobe of the right lung was affected (n = 17, 11.9% of patients with DA), which was also noted by other researchers [24, 25]. In patients with AGG and CVID, there was an increase in the frequency of exacerbations of bronchiectasis after the diagnosis of PID, which, in our opinion, is due to the improvement in the diagnosis of bronchiectasis during the follow-up of patients with PID. The best method for diagnosing

bronchiectasis is spiral computed tomography of the lungs (SCT of the lungs) [13, 24]. The described characteristic signs of bronchiectasis during SCT of the lungs (bronchial dilatation, thickening of the bronchial wall, lack of narrowing and bronchi visible closer than 2 cm to the surface of the pleura [13, 25]) were also found in our patients. In addition, pulmonary CT can be used to monitor the progression of bronchiectasis. Lobectomy for bronchiectasis was performed in 2 patients with CVID. Obstructive disorders during spirography were identified in all patients with bronchiectasis. Such patients were prescribed bronchodilator therapy and postural drainage.

Chronic obstructive pulmonary disease (COPD) does not fit into the framework of a standard infectious syndrome, however, manifestations of this disease are present in our patients, including as a consequence (or possibly as a cause) of the above-mentioned repeated pneumonia and bronchiectasis. The development of COPD was typical for patients with AGG and CVID (*Table 4*).

Clinical and functional manifestations of COPD were observed in patients only with AGG and CVID (n = 33).

All patients with COPD and DA (even with moderate bronchial obstruction) had severe clinical symptoms: CAT ≥ 10, mMRC ≥ 2, frequent exacerbations requiring antibiotic therapy, bronchodilators, a short course of systemic glucocorticoids, respiratory support, oxygen therapy and repeated hospitalizations. The administration of standard basic therapy for COPD, in accordance with clinical recommendations [26], in patients with DA had small effect on the improvement of clinical symptoms, improvement in respiratory function, quality of life and course of the disease, which distinguishes patients with COPD in combination with DA from patients with COPD without DA. Also, a distinctive feature in patients with COPD in combination with DA was the early onset of the disease (average age of onset 27.6 years (Q1-Q3: 15.8–37.9)), as well as the absence of a history of smoking (average pack-year index 0.9 years (Q1-Q3: 0.3–1.2)). The severity of COPD in patients with DA causes deaths, including during the COVID-19 pandemic, as noted by other researchers [27].

According to modern concepts, granulomatous-lymphatic interstitial lung disease (GLILD) is a distinct interstitial pulmonary disease in patients with CVID, associated with lymphatic infiltration and/or granuloma formation in the lungs when other causes have been excluded [28–30]. It is also important to note that granulomatous-lymphatic inflammation in these patients is multisystem and may involve damage to other organs. The main diagnostic methods are CT scan of the lungs, spirography, gas transport indicators, bronchoscopy and lung biopsy, as well as confirmation of the genetic defect CVID [28–30]. We will consider interstitial lesions within the framework of the proliferative syndrome.

In our registry, five patients with CVID had interstitial lung lesions (3.5% of all patients with DA). These lesions were not detected at the onset of the disease. In all five patients, lesions of the interstitial lung tissue were accompanied by lymphadenopathy of the intrathoracic lymph nodes. Patients did not undergo invasive studies with histological confirmation due to the high risk of infections because of a deep defect in antibody production. These patients took systemic glucocorticoids (initial dose of prednisolone up to 40 mg per day, maintenance doses up to 15 mg per day). Our information is similar to that of other centers [17, 18, 20].

Manifestations of allergic syndrome with lung damage were bronchial asthma in patients with DA. Symptoms of asthma were noted by 22 patients with SD IgA (15.4% of all patients with DA). In these patients, asthma was mild with a rare need for short-acting bronchodilators and did not require basic therapy. The average age of onset was 9.7 years (Q1-Q3: 6.3–13.3). In 14 (63.6%) patients, the age of onset of bronchial asthma and DA (in this case, SD IgA) coincided. This fact indicates the importance of determining the level of immunoglobulins during the initial diagnosis of asthma.

The absence of lung lesions was noted only at the onset of the disease in 1 patient with AGG and 6 patients with CVID (0.01% and 0.06%, respectively, of all patients with DA). Almost a quarter of patients with SDIgA (n = 18, 19.1% of all patients with DA) did not have lung lesions either at the onset or during the course of the disease.

Table 4. Chronic obstructive pulmonary disease in patients with defects in antibody production

Таблица 4. Хроническая обструктивная болезнь легких у пациентов с дефектами антителообразования

Nosological entity of antibody production defects	Number of patients, n	% of the total number of patients with this nosology
AGG	7	63.6
CVID	26	70.3
Deficiency of PIK3 kinase	0	0
SD IgA	0	0

AGG – agammaglobulinemia, CVID – common variable immune deficiency, SD IgA – selective IgA deficiency.

DISCUSSION

Lung damage is typical for patients with DA. However, such patients are often seen by a pulmonologist, are not examined for PID, and do not receive intravenous immunoglobulin replacement therapy. Our patients demonstrated repeated pneumonia, the presence of bronchiectasis, interstitial lung diseases, COPD and asthma. In some patients, the time to diagnosis of DA took several decades. At the same time, testing the level of immunoglobulins A, G, M, E in the blood is a simple, fast and inexpensive diagnostic method [6]. It is necessary to include determination of the level of immunoglobulins in the examination plan for patients with repeated pneumonia, bronchiectasis and interstitial lung disease, bronchial asthma and COPD, diagnosed before 40 years of age and without smoking status, as well as referral of these patients to an immunologist.

Clinical case

Male, 30 years old. In childhood, he was observed for hypoplasia of the right kidney; is currently removed from the nephrologist's register. He suffered 30 episodes of pneumonia of different localization (up to 3 times a year). The family history is noteworthy: the father died at the age of 36 years old; he had frequent bronchopulmonary infections, bronchiectasis, and liver cirrhosis. The patient's grandparents (on his father's side) had oncological diseases.

The patient underwent an immunological examination: a decrease in CD19 cells to 0.01 x 10^9 per liter and a decrease in the level of immunoglobulins of all classes (IgA 0.01 g/l, IgM 0.14 g/l, IgG 3.03 g/l) were revealed. Blood test for HIV PCR, hepatitis B and C – negative. CT scan of the lungs – without pathology. CT scan of the paranasal sinuses – catarrhal changes in the paranasal sinuses (at the time of the study there was acute sinusitis).

Initially, agammaglobulinemia was suspected in the patient, and therefore a study was carried out on the *BTK* gene. No pathogenic variants were identified. The patient then underwent genetic testing for the CVID genes. A heterozygous mutation (c.487C > T) in the *IKZF1* gene was detected. Heterozygous mutations in this gene are associated with CVID, type 13, with an autosomal dominant mode of inheritance (possible transmission from the father). The gene encodes the Ikaros transcription factor, which is a key regulator of lymphoid cells at the earliest stages of lymphopoiesis, promotes their differentiation and maturation, and is involved in the organization of chromatin structure. Impaired Ikaros function, resulting from intragenic deletions and point mutations, leads to a block in the differentiation of lymphoid cells [31–33].

This clinical example is typical for patients with CVID and emphasizes the role of lung diseases as a marker of primary immunodeficiencies with impaired antibody synthesis.

CONCLUSION

Lung diseases are common clinical manifestations in patients with antibody production defects, which may remain unrecognized for a long time due to the lack of alertness of doctors regarding this pathology. A study of immunoglobulin levels and referral to an immunologist are necessary in patients with repeated pneumonia, bronchiectasis, interstitial lung disease, bronchial asthma and early onset of COPD without smoking status. Given the insufficient amount of data on the incidence of lung diseases in patients with primary immunodeficiencies in other areas of the world, in particular in Central Asia, screening of blood immunoglobulins is necessary to identify primary immunodeficiencies and subsequent diagnosis of pulmonary lesions.

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