

Determination of antibodies in everyday rheumatological practice

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Abstract

Antibody determination is routinely used in everyday rheumatological practice. Its result repeatedly determines the diagnosis or exclusion of a particular disease. Antibodies are immunoglobulins, i.e. some of the most important proteins in the immune system, and have specific properties that we should know. In addition, there are a number of factors that can affect their concentration, including drugs commonly used in the treatment of rheumatic diseases. There are definite indications, when the total concentrations of individual classes of immunoglobulins should be initially determined and it should be evaluated whether the patient produces them at all or their production is impaired. In some cases, we should evaluate the levels of specific antibodies along with the total protein concentration and the γ -globulin fraction, in which the antibodies are contained. The article presents information on the most common mistakes made when performing these tests.

Key words: rheumatic diseases, immunoglobulins, antibodies.

Introduction

Antibodies are immunoglobulins and, like other molecules secreted by the human body, have specific properties. There are numerous factors that can affect the concentration of antibodies, and these are mainly some groups of drugs, as well as many congenital or acquired diseases.

Specific antibodies or autoantibodies are most often determined in people with infections or suspicion of an autoimmune disease. At the same time, these diseases are an indication for determination of total concentra-

tions of major classes of immunoglobulins, because in patients with these disorders, more often than in the general population, there is a defect in the production of antibodies, and some drugs additionally exacerbate this defect. That is why it is so important to determine these concentrations before the beginning of treatment. It enables, among other things, the diagnosis of a pre-existing immunodeficiency and appropriate dosage adjustment of an immunosuppressive drug and reduces the risk of complications. Although humoral immunodeficiencies seem to be rare, it is not true. Obviously, secondary deficiencies are much more common; however,

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for example, selective IgA deficiency in the Caucasian population occurs with a frequency of 1 : 500 to 1 : 700. In about 50% of people affected by this deficiency, the course is asymptomatic and it is often detected accidentally. Other patients with this disease suffer much more often, especially from respiratory infections, and more frequently develop autoimmune diseases [1].

Determination of IgA class antibodies in these patients, e.g. for *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*, has a limited diagnostic value.

The importance of knowledge of antibody properties is demonstrated by the example of patients who have received or are chronically receiving an immunoglobulin G preparation. Positive results for specific diseases in the IgG class may be (or are) due to the presence of the donor antibodies. Therefore, when we want to determine specific IgG in these patients, we need to do it either before starting drug treatment, or after a minimum of 6 weeks, when there are no antibodies in the blood derived from immunoglobulin donors (it must be remembered that immunoglobulin preparations are obtained from plasma from at least 1000 healthy donors) [2].

Another example is the use of drugs that affect the production of antibodies. The flagship example is rituximab – an anti-CD20 antibody that causes depletion of B lymphocytes responsible for antibody production [3]. Determination of antibodies after application of the drug that destroys antibody producing cells, first of all, does not make much sense, and secondly, generates unnecessary costs. Obviously, in the initial stage of treatment we still have antibodies produced before starting the drug therapy, but when we know the average half-life of immunoglobulins in the serum, we may conclude that after this period, the obtained results of concentration or antibody titers will also be non-diagnostic. There are really a lot of drugs that disrupt the production of antibodies and they will be discussed later in the article.

These few examples show how important it is to know the properties that immunoglobulins are characterized by. The article presents the most important information about these proteins from a rheumatologist's point of view.

Characteristics and biological significance of antibodies

Immunoglobulins are secreted by plasma cells that come into being as a result of B lymphocytes stimulation and are the only cells capable of producing antibodies) and along with blood or lymph reach the most distant parts of the body. They are glycoproteins that are commonly found in plasma and body fluids, or are found on the cell membrane of B lymphocytes. Immunoglobulins

have twofold effects. B-cells present on the surface play the role of receptors for specific antigens (BCR, B-cell receptor). In the free form as antibodies, they circulate in the blood or are found in tissues or mucous membranes, where they perform effector functions appropriate for their class. They are proteins that are able to specifically bind to the antigen. Although most often a particular immunoglobulin binds to one specific antigen, some of the antibodies are called multispecific (polyreactive) antibodies, which bind to more than one antigen.

In humans, there are five classes of immunoglobulins, IgA, IgD, IgG, IgE and IgM, which show functional differences [4, 5].

Immunoglobulin A

The human body produces two types of class A immunoglobulins: serum and secretory (sIgA). In the serum, IgA makes up only one fifth of the IgG concentration, because this protein in people constitutes the main class of immunoglobulins in mucous-serous secretions such as colostrum, saliva, tears, sweat, secretions of glands of the alimentary tract, the respiratory tract and genitourinary tract. The secretory IgA is the main element of the defense of serous and mucous membranes against the invasion of microorganisms, and these membranes are the largest portals of entry. The importance of class A immunoglobulins in the serum remains unclear. It is postulated that IgA plays a complementary role in neutralizing these antigens which have overcome the mucosal barrier and entered the bloodstream and in activating phagocytes, followed by the removal of immune complexes forming with the involvement of this isotype.

The immune response in the IgA class is caused by many pathogens. This response is induced mainly locally, in mucous membranes, but also systemically, where, apart from IgA, antigen-specific IgG and IgM antibodies appear. It must be remembered that IgA antibodies are used not only in the diagnosis of infections, but also in celiac disease and in the diagnosis of rheumatoid arthritis (RF IgA), although, of course, it is known that this factor is most common in the IgM class [4–8]. IgA deficiency is associated with an increased risk of developing infectious and autoimmune diseases. A deficiency of IgG subclasses (IgG2 and/or IgG4) may also coexist with IgA deficiency. Therefore, before we start determining expensive specific IgA antibodies, it is worth determining first their total concentration (these recommendations also apply to IgM and IgG) to avoid diagnostic errors.

Immunoglobulin D

There is not much free IgD in the serum and body fluids because this immunoglobulin acts only as a sur-

face receptor. The function of this protein is still not well known. It is difficult to assign an important role to free IgD in body fluids due to its low concentration. This immunoglobulin exists mostly as a transmembrane monomeric mIgD form, which is an antigen specific receptor of mature B cells [4, 5].

Immunoglobulin E

Immunoglobulins E (IgE) antibodies are present in a small amount in the serum. They are located mainly on the surface of basophils and mast cells, which are equipped with high affinity IgE receptors, which results in their constant saturation with this immunoglobulin. Unlike other immunoglobulins, it is not an opsonin and does not activate complement by the classical pathway. The average serum half-life of IgE is short and only lasts 2.5 days. The concentration of IgE, low at birth, gradually increases, reaching a peak around 10–15 years of age [9].

In people with a predisposition to atopy, it usually shows an earlier gradual increase. From the second to the eighth decade of life its concentration gradually decreases. However, the concentration of circulating IgE does not reflect its true activity. It is believed that approximately 50% of the total IgE pool is found in the extravascular space [4, 5, 9].

It must be remembered that in the case of acute allergic reactions (IgE-mediated), the serum IgE levels may not be determinable due to the migration of IgE to the target organs, i.e. those affected by the allergic reaction. Therefore, the diagnostics of this group of diseases should be performed after a minimum of 2 weeks.

Immunoglobulin G

Immunoglobulin G (IgG) constitutes about 75% of antibodies in the human serum and is the most common type of antibody in circulation. IgG is the essential antibody for the secondary immune response. Immunoglobulins of this class exist in balance in the intravascular and extravascular space, determining adequate general protection. They also bind to monocytes and macrophages, providing a better immune response. Due to the specific structure (their chain exists in four isotypic variations), immunoglobulins G (IgG) are divided into four types (subclasses): IgG1, IgG2, IgG3, IgG4.

Particular subclasses also differ in terms of the ability to recognize and form complexes with various antigens and allergens. Immunoglobulins of this class are the only ones that are able to cross the placenta, providing the newborn with passive immunity. Therefore, if an autoimmune disease in a newborn baby is suspected, it must be remembered that the presence of pathological antibodies in this class may be of maternal origin.

IgGs are practically the only immunoglobulins whose deficiency can be effectively supplemented in an intravenous or subcutaneous form.

These preparations are also used in rheumatology. It is particularly important to determine the total concentration of this immunoglobulin before starting immunosuppressive therapy and immunoglobulin substitution. An autoimmune disease may be the first and only symptom of congenital immunodeficiency, including a deficiency with decreased IgG concentration (e.g. common variable immunodeficiency). Implementation of immunosuppressive therapy may aggravate the previously existing defect and increase the risk of serious infections and their complications (IgG concentration < 500 mg/dl significantly increases this risk). It should also be remembered that for patients who have received or are chronically receiving an immunoglobulin G preparation, positive results for specific diseases in this class may be due to the presence of donor antibodies. In such cases, possible diagnostics based on determination of antibodies in this class should be performed before the beginning or after the end of supplementation, taking into account the period of persistence of these immunoglobulins in the blood.

In conclusion, the evaluation of the total concentration of IgG and specific IgG allows the recognition of pre-existing immune deficiency, for which a particular disease may be a symptom or complication, and which may require additional or completely different treatment. It enables the adjustment of an appropriate dose of the immunomodulatory drug, reducing the possible risk of complications, and above all, allows us to assess whether the conducted diagnostics using antibody determinations is reliable. Initiation of treatment before performing these tests interferes with the diagnostic process and the possibility of determining whether the deficiency is primary or secondary, which is often of great importance in the subsequent diagnostic and therapeutic process. IgG antibodies important for a rheumatologist include antinuclear antibodies, anti-cytoplasmic antibodies (MPO, PR3), anti-cyclic citrullinated peptide (ACPA) antibodies and anti-DFS70 antibodies [4, 5, 10–13].

Immunoglobulin M

Antibodies of this class constitute about 10% of serum immunoglobulins and are produced in the initial phase of the immune response. They are the first antibodies produced in the primary immune response. They occur mainly in the intravascular space. Their titer also increases in the case of reactivation of chronic or latent infection. IgM antibodies activate complement 100–400 times more efficiently than IgG. IgMs are mainly produced by plasma

Table I. Fundamental properties of different immunoglobulin classes in humans [4, 5]

Feature	IgA	IgD	IgE	IgG				IgM	
Properties									
Form	Monomer, dimer	Monomer	Monomer	Monomer				Pentamer	
Percentage among serum immunoglobulins	15–20	< 1	< 1	70–80				10	
Average half-life period (days)	5.8	2,8	2,5	23				5.1	
Synthesis (mg/kg body mass/day)	66	0.4	0.016	34				7.9	
Molecular weight ($\times 10^3$)	160 (monomer)	185	190	150				970	
Subclass	IgA1	IgA2	–	–	IgG1	IgG2	IgG3	IgG4	–
Functions									
Neutralization	++	–	–	++	++	++	++	+	+
Opsonisation	+	–	–	+++	*	++	+	+	+
Susceptibility for destruction by NK cells	–	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+++	+	–	+	–	–	–
Complement system activation	+	–	–	++	+	+++	–	+++	+
Distribution									
Presence on the surface of B cells	–	+	–	–	–	–	–	–	+
Transport through the epithelium	+++ (dimer)	–	–	–	–	–	–	–	+
Transport through the placenta	–	–	–	+++	+	++	+/-	–	–
Transport to breast milk	+	+	+	+	+	+	+	+	+
Diffusion to the extravascular space	++ (monomer)	–	+	+++	+++	+++	+++	+++	+/-

*IgG2 in the presence of a receptor for Fc fragment of a particular allotype plays the role of an opsonin.

cells in the spleen and lymph nodes and are secreted into the serum. The intramembrane monomeric form (mIgM) occurs, similarly to mIgD, as an antigen-specific receptor on mature B lymphocytes [4, 5].

Each class and subclass of immunoglobulins has different properties. The main differences between them are presented in Table I. Immunoglobulins are mainly found in the γ -globulin fraction (all immunoglobulin classes) and, to a small extent, in the β -globulin fraction (IgA and IgM). Therefore, in questionable cases, especially when we obtain negative results, despite the suspicion of a particular disease, their concentration should be evaluated together with the total protein concentration and the abovementioned fractions (determined in the proteinogram). This particularly concerns patients with secondary immunodeficiencies. We should also determine the concentrations of major classes of immunoglobulins and assess whether the patient produces them or whether their production is not disturbed. This is the situation which we have in primary immunodeficiencies with disruption of antibody production and secondary deficiencies, e.g. resulting from treatment.

When assessing immunoglobulin concentrations, the age of the subject must be taken into account, as their concentrations differ depending on the age group. Despite the development of a humoral immune response in the fetal period, infants show a natural impairment of antibody synthesis. Significantly reduced IgM concentration and almost undetectable levels of IgE and IgA and IgG are observed. In this period, the protective function is ensured by maternal IgG. The immune system of a newborn responds to emerging antigens, producing mainly low affinity class M immunoglobulins. Around the age of 4–6 months, the antibody titer reaches the lowest values. It results from the predominance of maternal IgG catabolism over the synthesis of their own antibodies. The level of immunoglobulin synthesis comparable to an adult organism in the IgM class is reached at around 12 months of age, in the IgG class at school age, and in the IgA class only about 12 years of age [4, 5, 7].

It should be remembered that there are specific clinical situations when we should determine the total levels

of immunoglobulins (IgA, IgM, IgG, optionally IgE). They are as follows:

- suspicion of autoimmune diseases,
- taking medicines that affect the level of immunoglobulins (especially before the beginning of treatment),
- severe, persistent, opportunistic or recurrent infections and chronic inflammatory conditions,
- neoplasms, in particular of hematopoietic system,
- liver and spleen diseases,

- other secondary immunodeficiencies (discussed later in this article),
- allergies (especially those difficult to treat).

Attention should be paid to a certain paradox. The abovementioned conditions are indications for determining total immunoglobulin concentrations, as they occur more frequently in patients with primarily dysfunctional antibody production. Some of these states secondarily impair their synthesis. At the same time, it

Table II. Detailed indications for the determination of major antibody classes significant from the rheumatologist's point of view [14–20]

Interstitial lung diseases, unexplained bronchiectases, obstructive pulmonary disease difficult to treat	
Organ and skin granulomas	
Atypical diseases/symptoms of autoimmunity and/or lymphoproliferation (including relatives)	
Family history of primary immunodeficiency, unexplained infant deaths, parental consanguinity	
Lymphopenia, neutropenia and/or thrombocytopenia, unexplained eosinophilia	
GvH reactions after a transfusion of blood or its preparations	
Infections with atypical clinical picture, severe course, chronic or not responding to treatment	
Bacterial infections (especially sinuses, ears, lungs, bronchi)	
The necessity of intravenous antibiotic therapy to control the infection	
Recurrent infections caused by the same pathogen	
Infections that are difficult to treat (no remission between episodes of infection)	
Recurrent infections caused by capsular bacteria (<i>H. influenzae</i> , <i>S. pneumoniae</i> , <i>S. aureus</i>)	
Enteroviral infections	
Persistent thrush or skin fungal infections or in other locations	
Opportunistic infections (<i>Candida</i> , <i>P. jiroveci</i> , CMV) or caused by "unexpected" microorganisms	
Deviations in physical examination such as:	
<ul style="list-style-type: none"> • sunlight sensitivity • discoid lupus erythematosus (DLE) • Gottron sign • dry eyes, mouth, vagina • mouth ulcers • lymphadenopathy • fever of unknown origin • erythroderma • telangiectasias, café au lait spots • lack of lymph nodes or tonsils • inflammation of the gums, mouth ulcers and aphthae • improper wound healing • dysmorphic features (especially facial) and microcephaly 	<ul style="list-style-type: none"> • butterfly erythema • heliotrope erythema • sclerodactyly, sclerostomy • Raynaud syndrome • vasculopathies • hepatosplenomegaly • vrases of unknown etiology • eczema, dermatitis (severe) • clubbed fingers, nail dystrophy • partial albinism • stunted growth in children, cachexia in adults • baldness, abnormal hair structure
Symptoms suggestive of secondary immunodeficiency:	
<ul style="list-style-type: none"> • congenital defects of protein synthesis • disorders of absorption and digestion (intestinal inflammation) • increased protein loss in the urine (kidney diseases), in body cavities (effusion), blood, and in the course of burns 	<ul style="list-style-type: none"> • liver diseases (impaired immunoglobulin synthesis) • malnutrition, starvation

is in these patients that specific antibodies are most often determined.

Detailed indications for the determination of major antibody classes significant from the rheumatologist's point of view are presented in Table II [14–20].

Although some of the abovementioned symptoms are characteristic of other types of immunodeficiency, such as cellular immunodeficiencies or phagocytosis disorders, also in these cases the levels of concentration of main classes of immunoglobulins should be measured, as different types of deficiency may co-exist. Some of the symptoms are characteristic of autoimmune diseases, for example, systemic lupus erythematosus or dermatomyositis. However, as mentioned before, in any person with suspected or already diagnosed autoimmune disease, the total concentrations of major classes of immunoglobulins should be measured. It should be routine, not just accidental and occasional determination. Therefore, these symptoms have been mentioned.

Factors affecting the decrease in antibody concentration

In everyday practice, it is important to know the conditions that affect both the decrease and increase in the concentration of antibodies. There is no practical guide in the literature that would elaborate on the differen-

Table III. Primary immune deficiencies occurring with agammaglobulinemia or hypogammaglobulinemia according to (ESID) [20]

Agammaglobulinemia
Bloom syndrome
CSR defects (defects of class-switch recombination and HIGM syndromes)
Common variable immunodeficiency disorders (CVID)
HLA class II deficiency (MHC2)
IgA with IgG subclass deficiency
Immunodeficiency centromeric instability facial anomalies syndrome (ICF)
Isolated IgG subclass deficiency
Nijmegen breakage syndrome
Selective IgA deficiency
Selective IgM deficiency
Thymoma with immunodeficiency
Transient hypogammaglobulinaemia of infancy
Wart, hypogammaglobulinemia infections and myelokathexis (WHIM)
X-linked lymphoproliferative syndrome (XLP)
Unclassified antibody deficiency

tial diagnosis in this area. The following are primary and secondary causes that lead to changes in antibody concentrations (immunoglobulins).

The primary causes of decreased antibody concentration are primary immunodeficiencies, which are shown in Table III. Detailed characteristics of these conditions and their diagnostic criteria are available on the website of the European Society for Immunodeficiencies [20].

Much more often we deal with conditions that cause secondary antibody deficiency (see Table IV). Nowadays, the use of biological drugs is becoming of particular importance. Every year, new biological medicines are registered, used in many diseases, including rheumatology. That is why it is so important to know in particular those that cause a decrease in concentration or lead to a total absence of antibodies. Due to the rapid progress of knowledge and therapeutic methods in this area, Table IV presents the drugs used currently. Since not all mechanisms of action of biological drugs are thoroughly known, especially in terms of causing disturbances in the production of antibodies, the authors insist on getting familiar with the side effects of each new drug and determining the concentrations of major classes of immunoglobulins before and after starting the drug therapy [21–29].

Decreased serum IgD and IgE concentrations have little clinical significance. However, it should be remembered that correct concentrations of both total IgE and specific IgE do not entitle us to exclude allergies, and in this case it is advisable to deepen the diagnostics and use other available testing methods.

Factors that cause elevated levels of antibodies

Analyzing the reasons for elevated antibody concentrations, we must pay attention to whether they are the result of the presence of monoclonal or polyclonal antibodies. We meet the latter more often. This is the situation in medical conditions such as acute and chronic inflammation, chronic liver diseases – cirrhosis (alcoholic – increase mainly in IgA, primary biliary cirrhosis increase mainly in IgM), autoimmune diseases (especially in the early stages), parasitic diseases, sarcoidosis and AIDS. It should be remembered that polyclonal antibodies are more likely to cross-react with other antigens of similar structure. In contrast, monoclonal antibodies appear, among other conditions, in the course of lymphomas, chronic lymphocytic leukemias, plasma cell neoplasms and monoclonal gammopathies.

The issue of monoclonal gammopathy, which should be differentiated from hematological diseases, is also important. It is worth remembering that monoclonal gammopathies may also accompany other diseases such as

Table IV. Causes of secondary hypogammaglobulinemia [21–29]

Medications	Medications with immunomodulating and immunosuppressive properties: glucocorticosteroids, sulfasalazine, gold salts, penicillamine, mycophenolate mofetil, methotrexate, cyclosporine, cyclophosphamide, hydroxychloroquine, leflunomide, some biological drugs Biological drugs: abatacept, alemtuzumab, atacicept, belimumab, bortezomib, dasatinib, epratuzumab, ibrutinib, imatinib, inotuzumab, milatuzumab, obinutuzumab, ocrelizumab, ofatumumab, rituximab, tabalumab, veltuzumab Antiepileptics: carbamazepine, phenytoin, sodium valproate, lamotrigine Antipsychotics: chlorpromazine Other: captopril, diclofenac
Immunosuppression	Induced by medications – see above Radiotherapy
Hereditary diseases	Some metabolic diseases (e.g. trans-cobalamin II deficiency with hypogammaglobulinemia) Chromosomal aberrations (monosomy 22, trisomy 8 and 21, chromosome 18q- syndrome)
Infections	Viral infections (infections with CMV, EBV, HIV, parvovirus B19, rubella, measles, HSV) Bacterial infections (e.g. mycobacterial infection) Parasitic infections (e.g. toxoplasmosis – including hereditary, malaria)
Proliferative diseases	Chronic lymphocytic leukemia, multiple myeloma, thymoma, non-Hodgkin lymphoma, other B cell lymphomas, monoclonal gammopathy, solid organ neoplasms
Systemic diseases	Kidney diseases, e.g. nephrotic syndrome Digestive tract diseases, e.g. Crohn's disease, enteropathy, severe diarrhea Autoimmunological diseases, e.g. systemic lupus erythematosus, rheumatoid arthritis, Felty's syndrome Protein deficiencies, e.g. starvation, cachexia Intensive immunoglobulin catabolism, e.g. neoplasms, hyperthyroidism, sepsis Liver diseases (decrease in synthesis of proteins including immunoglobulins)
Trauma and surgical procedures	Multiorgan trauma, burns, extensive surgical procedures, splenectomy
Environmental factors	Chemical compounds
Other	Asplenia or impairment of its function Plasma exchange transfusion

neoplastic diseases, connective tissue systemic diseases (rheumatoid arthritis, systemic lupus erythematosus, polymyositis, systemic sclerosis, Sjögren's syndrome), nervous system diseases (multiple sclerosis, myasthenia, Gaucher disease), bacterial infections (e.g. bacterial endocarditis) and viral infections (CMV, HCV, HBV, HIV). They may also occur after the transplantation of an organ or hematopoietic cells. Monoclonal gammopathy should be differentiated from reactive polyclonal plasmacytosis, which may occur in the course of infections (e.g. rubella, infectious mononucleosis), chronic inflammation or liver diseases. In the case of polyclonal plasmacytosis, the percentage of plasmacytosis in the bone marrow usually does not exceed 10% and there is no M protein. Differentiation is facilitated by immunofixation, which allows confirmation of the presence of monoclonal protein in the serum. In justified cases bone marrow punch biopsy should be performed [30, 31].

Hyperproteinemia, and thus hypergammaglobulinemia, can also be noticed in dehydration.

Other causes of elevated concentrations of particular immunoglobulin classes are presented below [20, 32–35]:

- IgA – in bronchial asthma and bronchiectasis, alcoholic cirrhosis, primary immunodeficiencies, such as deficiency of FOXP3 (IPEX) and IPEX-like disease, in which we also observe elevated IgE levels.
- IgD – in the course of the hyper-IgD syndrome, also known as the mevalonate kinase associated periodic fever syndrome (MAPS), belonging to auto-inflammatory diseases (80% of patients with this syndrome also have elevated IgA).
- IgE – due to numerous conditions that may occur with elevated levels of these immunoglobulins, they are presented separately below (Table V).
- IgG and subclasses – IgG substitution, IgG4-related disease (IgG4-RD).
- IgM – in immunoglobulin class-switch recombination defects (CSR defects) and hyper-IgM syndrome (HIGM) – mentioned in Table IV, in primary biliary cirrhosis.

Table V. Causes of increased serum IgE concentration [9, 36–44]

Allergic diseases	Allergic diseases of the skin and gastrointestinal tract, allergic rhinitis, allergic conjunctivitis, asthma Anaphylactic reactions caused by: food components (e.g. peanuts), drugs (e.g. antibiotics, aspirin, NSAIDs), immunizations, venom of insects, snake etc., hormones, polysaccharides, human and animal proteins, dyes (e.g. carmine), physical activity
Parasitic infections	Schistosomiasis, malaria, filariasis, ascariidosis, enterobiasis, giardiasis, amebiasis, toxocarosis, cysticercosis, trichinosis, infection with liver fluke, cutaneous larva migrans
Bacterial and viral infections	Epstein-Barr virus, <i>Helicobacter pylori</i> , <i>Mycobacterium tuberculosis</i>
Skin diseases	Pemphigus vulgaris, ichthyosis, psoriasis, alopecia areata, vitiligo
Neoplasms	Hodgkin disease, IgE myeloma, Sezary syndrome, lung and bronchial cancer, neoplasms of ears and throat
Immunological deficiencies	Primary (Wiskott-Aldrich syndrome, hyper-IgE syndrome, (DiGeorge syndrome, Nezelof syndrome, Omenn syndrome, Comel-Netherton syndrome, FOXP3 (IPEX) deficiency and disease similar to IPEX (IPEX-like disease) Secondary (HIV)
Autoimmunological diseases	Kimura's disease, ulcerative colitis, celiac disease, autoimmune pancreatitis, chronic juvenile arthritis, vasculitis (e.g. Behçet's disease, Churg-Strauss syndrome, granulomatosis with polyangiitis, Kawasaki disease, polyarteritis nodosa)
Other	Allergic bronchopulmonary aspergillosis, cystic fibrosis, nephrotic syndrome, ischemic heart disease, drug-induced interstitial nephritis, alcoholic liver cirrhosis, idiopathic thrombocytopenia

Conclusions

Antibody determination is an important tool in the daily work of rheumatology specialists. Each newly discovered antibody attracts a lot of interest. That is why it is so important to know the basic properties of antibodies, which are often forgotten, and factors that affect their concentration. The authors hope that the article will be very helpful in everyday practice, will dispel a lot of doubts and, above all, will improve the quality of the diagnostic and therapeutic process of patients with rheumatic diseases, especially when there is a discrepancy between clinical symptoms and the results of additional medical tests.

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