Antinuclear antibodies in autoimmune and allergic diseases

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Abstract

Antinuclear antibodies (ANA) are primarily significant in the diagnosis of systemic connective tissue diseases. The relationship between their occurrence in allergic diseases is poorly documented. However, the mechanism of allergic and autoimmune diseases has a common thread. In both cases, an increased production of IgE antibodies and presence of ANA in selected disease entities is observed. Equally important is the activation of basophils secreting proinflammatory factors and affecting the differentiation of TH17 lymphocytes. Both autoimmune and allergic diseases have complex multi-pathogenesis and often occur in genetically predisposed individuals. The presence of antinuclear antibodies was confirmed in many systemic connective tissue diseases and some allergic diseases. Examples include atopic dermatitis, non-allergic asthma, and pollen allergy. Co-occurring allergic and autoimmune disorders induce further search for mechanisms involved in the aetiopathogenesis of both groups of diseases.

Key words: autoimmune diseases, allergy, antinuclear antibodies, molecular background.

Introduction

Due to the autoimmune aetiology of allergic diseases, common mechanisms in etiopathogenesis of allergic diseases and connective tissue diseases are suspected [1–4]. Firstly, the importance of characteristic markers of allergic diseases, mainly immunoglobulin E (IgE), in the course of connective tissue diseases is highlighted [5, 6]. An example may be an increased production of these antibodies in systemic lupus erythematosus (SLE). This disease is also characterised by strong polyclonal synthesis of ANA and circulating immune complexes [5]. It is believed that not only increased IgE synthesis, but also the involvement of dependent Th2 response, may be one of the many components of the allergic response in systemic lupus [5, 6].

Also, the role of basophils is important in the triggering of allergic and autoimmune reactions. Basophils, when activated by various allergens, release specific inflammatory modulators (cytokines and chemokines) [7, 8]. It was proven that basophils may activate B cells and indirectly influence antibody synthesis by B lymphocytes [9]. In addition, they are thought to be involved in the differentiation of Th17 lymphocytes contributing to the inflammatory process [10, 11].

An increased histamine release from basophils coexisting with ANA presence in some patients with non-allergic asthma probably suggests an autoimmune cause of this disease. Higher prevalence of ANA was demonstrated in non-allergic asthma than in healthy subjects in the general population (6–15%) [3]. This fact may suggest an effect of immune system regulation disorders, mainly impaired activation of regulatory T cells, which are involved in the immune response against individual antigens [12]. In addition, non-allergic asthma and many autoimmune diseases of connective tissue predominate in the female, suggesting a common contribution of oestrogens (natural and synthetic) in antibody induction [1, 2].

Co-occurring allergic and autoimmune background of connective tissue and allergic diseases is poorly documented [1–4], which leads to further search for mechanisms involved in aetiopathogenesis in both groups of diseases.

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Characteristics of antinuclear antibodies and their importance for the diagnosis of connective tissue diseases

In addition to clinical features, the presence of autoantibodies in blood serum is of diagnostic significance in the diagnosis of rheumatic diseases. In clinical practice, tests for the presence of antinuclear antibodies that react with solid and dissolved antigens of cell nucleus (ENA) are often used [13]. They involve an indirect immunofluorescence assay that can be used to determine the ANA level and the type of lighting. The most commonly used source antigen is the Hep-2 (Human Epithelial cell) cell line, which originates from human epithelial larynx cancer. The Hep-2 cell has a large nucleus and a relatively small cytoplasm. Due to an intensive proliferation of the cell line, the presence of numerous antibodies that react with antigens is noted during cell proliferation [14]. Using the HEp-2 cell line, five basic types of cell nucleus lightning can be distinguished: homogenous, membrane, nucleic, spotted, and centromeric type. In patients with systemic lupus erythematosus, homogeneous fluorescence is observed, while the nucleic one is seen in patients with systemic sclerosis [13]. The most common type of fluorescence is the spotted "glow" of cell nuclei, but it is not specific for any systemic connective tissue disease. Additionally, immunofluorescence may indicate the presence of antibodies against histones [15]. Low level of positive ANA is also reported in healthy individuals with viral or bacterial infections. When the ANA value exceeds 1/160 and clinical signs of illness are presented, systemic connective tissue disease may be suspected [14]. False negative reactions in IIF tests are the reason for an abnormality in activities that may lead to the closing of antigenic orders. In the case of abnormalities regarding adsorption and several related antigens about what epitopes. Automation of the IIF name can significantly improve the standardisation of markings and help in reducing the variability of intra-laboratory collaboration [16].

Antinuclear antibodies in the healthy population

Antinuclear antibodies are one of the most venerable tests in immunology and are considered as screening biomarkers in many connective tissue diseases (CTD). Measuring ANA should be related not only to the use of adequate tests allowing the early and reliable diagnosis of CTD, but also with the analysis of personal and family history, as well as social lifestyle including dietary habits [17]. ANA are commonly found in the general population in up to 20% of healthy subjects, but significantly elevated levels are observed in 2.5% [18]. Such prevalence is comparable between populations of different ethnicity and race [19]. In comparison, the prevalence of all autoimmune disorders ranges from 5 to 7% [20].

Positive ANA are more often detected in women and thus female gender is a risk factor for significant ANA positivity [18]. This fact is in accordance with the study of a Brazilian healthy population, which showed nearly two-fold higher prevalence of ANA in females as in males [21]. Similar data were reported by Semchuk et al. [22], who revealed that ANA levels were higher in Canadian females from rural regions. Moreover, during normal pregnancy there is an extensive exposure to nuclear antigens and inflammatory activity escalates, which is related to elevated ANA titres [23]. Interestingly, administration of oestrogen in the form of oral contraceptives or postmenopausal replacement therapy might induce high ANA levels in healthy individuals [24].

Age usually positively correlates with increased ANA level in healthy individuals due to decreased self-regulatory mechanisms [25]. In the 1999–2004 population-representative National Health and Nutrition Examination Survey (NHANES), the prevalence of ANA at ages ≥ 70 years was nearly double that at ages 12–19 years [26]. However, some data do not confirm this hypothesis [19]. The presence of thyroglobulin can be one of the reason for elevated ANA, which is observed in thyroid autoimmune diseases [27]. Besides, autoantibodies to cartilage proteoglycan can be one of the reasons of high ANA level, which might be observed before clinical symptoms of connective tissue diseases are present, e.g. in the course of Sjögren's syndrome or systemic lupus erythematosus [28]. Moreover, an upregulation of some genes such as *MX-1* gene or type I interferon (IFN) can be associated with increased ANA level in the healthy population [19].

In conclusion, high prevalence of ANA (usually in small titres) suggests that these antibodies may be an important component of the normal immune response. From clinical experience, these facts explain why in many situations of elevated ANA positivity seen in rheumatology practice is not related with any connective tissue disease or other particular pathology. This fact gives the background for the practical advice of ANA measurements only when the clinical evidence allows suspicion of rheumatic disease.

Food and drug allergens and adjuvants that affect autoimmune disease development

Adjuvants are the substances that stimulate the immune system for an immune response. They are used, for example, in vaccines, chemically linked to the anti-

gen of which they enhance the immunisation process. They are also found in mineral oils and medicines. Exposure to adjuvants in genetically predisposed individuals may lead to the development of autoimmune diseases [17]. The most common adjuvants in vaccines are aluminium hydroxide and phosphate. Inducing cytokines, these compounds cause an inflammation and affect the regulation of the function of lymphocytes and antigen presenting cells. By slow release of antigen in the area of administration, inflammation may develop at the injection site [29].

Based on an analysis by Shoenfeld et al., it was confirmed that the most frequently diagnosed autoimmune disease induced by food adjuvants, drugs, or environmental factors is the autoimmune inflammatory syndrome induced by adjuvants (ASIA syndrome). It can coexist with undiagnosed connective tissue disease and is accompanied by ANA presence [30]. It was also demonstrated that this syndrome is present in genetically predisposed individuals after exposure to an adjuvant and is associated with HLA class II alleles such as DRB1. The development of specific antibodies determined by DRB1 is a result of abnormal immune response [31]. The group of drugs leading to autoimmunisation (drug-induced autoimmunity, DIA) include procainamide, which can cause drug-induced lupus erythematosus. Despite the proven effect of some adjuvants and drugs, the unambiguous cause of autoimmune diseases is difficult due to the multifocal involvement of pro-inflammatory factors and increased antibody synthesis in its course [32].

Aetiopathogenesis of allergic diseases

The incidence of allergic diseases in the world is increasing, both in developed and developing countries. According to the World Health Organisation (WHO), allergic rhinitis caused by IgE-dependent mucositis affects 400 million people. It is also estimated that about 235 million people suffer from bronchial asthma, which significantly affects the quality of life of patients and their families and their socio-economic situation. Sensitisation of exogenous allergens occurs in 40% of the population. In addition, allergies not only cause a long-term dysfunction of the immune system, but also contribute to systemic inflammation as a primary developmental factor for other non-infectious diseases [33, 34].

Hypersensitivity of an allergic nature is initiated by immunological mechanisms dependent on antibodies that belong to IgE class immunoglobulins. The inherent tendency for an excessive production of IgE is called atopy. IgE-dependent mechanisms observed in asthma, allergic rhinitis, atopic dermatitis, and some forms of urticaria and angioedema are important in atopic allergy

[35]. In addition to genetic factors, also environmental factors that are associated with the presence of allergens that cause immune hypersensitivity affect atopic disease development [34]. The same allergens may also affect and condition the development of autoimmune diseases [35]. Due to the main route of penetration, the allergens are divided into inhalation, food, contact, insect venoms, drugs, and latex. The presence of allergens in the environment leads to immune system stimulation and the development of atopic disease [36].

Aetiopathogenesis of connective tissue diseases

Systemic connective tissue diseases are a classic example of autoimmune diseases that develop as a result of immune tolerance disorders. Autoimmune tolerance means no reactivity to specific antigens – foreign or own (autotolerance) [37]. The maintenance of suitable autotolerance is possible due to the proper functioning of mechanisms involved in the maturation of immunocytes in central lymphoid organs. The most important of these mechanisms are antigen sequestration, anergy, and clonal deletion as well as regulation of Th1/Th2 cell balance [38]. Antigen sequestration consists of its separation from the immune system by an anatomical barrier. The autoantigen can be treated by T lymphocytes as an exogenous antigen, if it has not been in contact with its cells during immune maturation, which is dictated by anatomical conditions. As a result, no tolerance to this autoantigen was formed. As a result of, for example, a traumatic event, autoantigen sequestration may be aborted, which starts an autoimmune response [39].

Clonal deletion, which is associated with apoptosis of lymphocytes capable of recognising their own autoantigens, occurs in the thymus. If this mechanism is ineffective, autoreactive cells may emerge from the thymus to the periphery, leading to an autoimmune response [40]. The phenomenon of clonal anergy involves functional inactivation of autoreactive lymphocytes that were not subject to clonal deletion. Reaching the state of anergy, lymphocytes are capable of recognising autoantigens without producing a response against them [41].

The regulation of Th1/Th2 cell balance is also an important issue in autoimmune diseases because it affects the functional status of subpopulation of T cells and determines their interrelationships [42]. Factors leading to dysfunction of the immune system, the consequences of which are the loss of autotolerance and development of autoimmunisation, include, inter alia, bacterial and viral infections and hormonal disorders. Sex hormones (especially oestrogens) play a significant role in the development of autoimmune diseases and predispose

women to more frequent occurrence of these diseases [42]. Oestrogens stimulate the immune response by acting on T-helper 2 lymphocytes and interact through the receptors present on many immune cells. Their effect depends on local concentration and inflammation [42, 43]. Genetic factors also play an important role. Gene products on partially deactivated X chromosome may avoid presentation in thymus and cause immune tolerance suppression [43].

The high level of ANA in CTD (e.g. systemic lupus erythematosus) can be associated with the activity of microRNA-155 (miR-155), which is involved in regulation of T helper cell differentiation [44]. The microRNA-155 controls the synthesis of T cell-dependent antibody response, partially by regulating cytokine production [44, 45]. In animal studies miR-155 in part modulates the expression level of the SH2 domain-containing inositol 5′-phosphatase 1 (SHIP-1) after colligation of the B-cell receptor and the low-affinity IgG inhibitory receptor Fcγ–RIIB (Fc γ receptor IIB, FcγRIIB) by immune complexes. SHIP-1 acts downstream of inhibitory cell-surface receptors [46] including FcγRIIB [44]. FcγRIIB is crucial in opposing B-cell activation signals in mice and humans [45]. Mice harbouring B-cell-specific FcγRIIB or SHIP-1 deletion develop severe lupus-like disease [47]. Moreover, in animals, high concentrations of serum antinuclear and anti-kidney autoantibodies are detected, and they are associated with lymphadenopathy, splenomegaly, and renal pathologies [48].

Antinuclear antibodies in allergic disease development

The functioning of the immune system is impaired in cases of allergic and autoimmune disease occurrence [49]. The presence of selected antibodies in some allergic disorders suggests their autoimmune origin [50, 51]. Recent scientific evidence confirms the presence of antinuclear antibodies (ANA) in patients with allergic diseases [51]. However, a small amount of data does not allow for a clear definition of the relationship between autoimmunisation and allergic diseases. Therefore, the coexistence of allergy with the presence of antinuclear antibodies synthesis remains a matter of further research.

High ANA levels are not always associated with connective tissue disease. Examples are anti-DFS70 antibodies. Their presence was confirmed, inter alia, in patients with atopic dermatitis [52]. Western blot analysis showed a positive correlation between the signal of IgG and IgE antibodies against anti-DFSF0 in patients with atopic dermatitis [9]. The mechanism of ANA action and its association with allergic diseases is not well understood. There is some evidence that inflammation results

from an increased cellular apoptosis and the resulting products induce the autoimmunisation process [53].

The relationship between ANA and atopic dermatitis (AD), which is a chronic, genetically predisposed skin disease of type I immediate mechanism related to IgE antibodies, has been confirmed to date. Elevated IgE levels are reported in about 60–70% of patients [54]. Severe apoptosis occurring in the keratinocytes of patients with atopic dermatitis contributes to the induction of ANA. The study by Higashi et al. [55] demonstrated that 19% of patients with this disease had positive ANA at a level of 1 : 40 to 1 : 640. In addition, it was demonstrated in the same study that in patients with AD and ANA presence, the concentration of IgE specific to cedar pollen was higher than in patients with negative level of antinuclear antibodies [55]. This fact may be due to the presence of self-reactivity of IgE against a wide spectrum of human proteins. During exacerbation of skin symptoms, the level of IgE antibodies increases in AD patients [56]. This is partly due to the presence of antibodies induced during an enhanced apoptosis in keratinocytes. Therefore, chronic allergic inflammation can be observed in patients without exposure to environmental allergens [57].

In addition, antibodies against human Hom s 1–5 (*Homo sapiens allergen* 1–5) and DFS70 are present in the serum of most patients with AD [52, 58]. Antibodies of this type are not present in patients with systemic lupus erythematosus (SLE) or chronic urticaria and usually form intracellular complexes. In patients with AD, they are present in serum in the form of IgE immune complexes and are released from damaged tissues [58]. Patients with SLE may exhibit elevated levels of IgE and antinuclear antibodies in the IgE class without the occurrence of characteristic clinical signs of allergy. At the same time, antibody synthesis in the IgE class may occur, with the exception of possible linkages between SLE and allergy [48]. In addition, it is supposed that basophils are involved in Th17 lymphocyte differentiation in SLE [10, 11], although activation and differentiation of Th17 lymphocytes requires synergistic action of other inflammatory signals such as interleukin (IL)-23, IL-1β, IL-6, and TGF-β [59]. Studies in animal models demonstrated that under certain conditions murine basophiles may exhibit an increased IL-6 expression [60].

The allergic response to external antigens was recognised as an important mechanism in the development of air-derived inflammation in asthmatic patients [61]. Asthma is an inflammatory disease of the respiratory tract, in which chronic inflammation causes bronchial hyper-responsiveness, leading to wheezing, shortness of breath, chest tightness, and coughing, particularly at night and in the morning. The nature of the disease is chronic bronchitis, especially eosinophil, mastocytes,

and T-lymphocyte infiltrates [56]. An allergic type of asthma is the most common form of the disease. The course of the disease is mild or acute. Compared to the non-allergic form, a mild form with concomitant rhinitis and conjunctivitis or AD and elevated IgE levels is observed considerably more frequently [50].

Antinuclear antibodies share was mainly observed in the development of atopic asthma, aspirin-dependent, and typical asthma with good aspirin tolerance. Positive ANA at a level ≥ 1 : 40 was found in 39% of patients with atopic asthma, which resulted from complement activation [1] IgE specific diseases with ANA presence was presented in Table I. The relationship between the development of autoimmunisation and pathomechanism of asthma was also confirmed by other researchers. The

study conducted by Agache et al. [62] in a group of 100 patients with asthma demonstrated the association of occurrence of antinuclear antibodies in patients with particularly severe disease course. After a year of follow-up, five deaths and 28 severe exacerbations requiring hospitalisation were reported, 24 patients had a need for inhaled corticosteroids use, while 19 had a rapid fall in FEV1. All of these cases showed positive antinuclear antibodies. Moreover, positive antinuclear antibodies were more common in the patients with asthma (22%) compared to the control (3.3%), irrespective of the diagnosis of atopic (20.59%) and non-atopic (22.73%) asthma. The presence of ANA in patients with asthma may be used as a prognostic factor to predict higher incidence of exacerbations and a faster decline in lung function [62].

Table I. Presence of ANA and IgE in specific diseases

	Aetiology	Specific diseases		Aetiology	Specific diseases
Antinuclear antibodies related mechanism	infections	– viral or bacterial	Immunoglobulin E related mechanism	infections	– parasitic – viral or bacterial
	lung diseases	– primary pulmonary fibrosis – pulmonary hypertension		anaphylactic reactions	– food – drugs – venoms of insects and snakes
	gastrointestinal diseases	– ulcerative colitis – Crohn's disease – primary biliary cirrhosis		allergic diseases	– allergic rhinitis – skin allergies – allergic conjunctivitis – asthma
	endocrinological diseases	– Hashimoto's autoimmune thyroiditis – Grave's disease		immune shortages	– primary – secondary (HIV)
	hematologic diseases	– idiopathic – thrombocytopenic purpura – haemolytic anaemia		inflammatory diseases	– colitis ulcerosa – juvenile idiopathic arthritis
	cancers	– melanoma – breast – lung – kidney – ovarian		cancers	– Hodgkin – myeloma – lung
	dermatologic diseases	– psoriasis – pemphigus		dermatologic diseases	– psoriasis – pemphigus
	specific population	– elderly		others	– coeliac disease
		– relatives with a family history of rheumatic diseases			
	drug induced	– procainamide – phenytoin			
Both mechanism involved					
ANA and IgE-mediated diseases					– non-allergic asthma – chronic urticaria – systemic lupus erythematosus – atopic dermatitis

Conclusions

Antinuclear antibodies are not only characteristic for autoimmune diseases but can also be produced in patients with various diseases or might be induced by specific medications. The specific diseases causing elevated ANA and IgE-mediated diseases or both mechanisms are summarised in Table I.

Although recent findings concerning the relationship of positive ANA and allergy are very encouraging, further studies are needed to confirm the pathomechanism of their interdependence. The description of this mechanism can provide valuable tools for better diagnostics of allergic diseases and provide the possibility of targeted therapies in patients with coexisting allergic diseases and present ANA antibodies.

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