RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS – ANTINUCLEAR ANTIBODIES, IMMUNOLOGICAL PROFILE AND RISK OF DEVELOPING THE DISEASE


1Internal Medicine Department, Sv. Anna University Hospital – Sofia, Bulgaria
2Laboratory of Clinical Immunology, Sv. I. Rilski University Hospital – Sofia, Bulgaria
3Rheumatology Department, Sv. I. Rilski University Hospital – Sofia, Bulgaria

Abstract. Systemic lupus erythematosus is a systemic autoimmune disease that begins years before its clinical onset with the appearance of antinuclear antibodies and immunological signs of dysregulation in the serum. At the same time, due to the tendency towards familial aggregation, the risk of developing the disease in the relatives of the patients is tens of times higher. In multiple studies, relatives of patients have high titers of antinuclear antibodies significantly more often than the general population, and a combination of increased pro-inflammatory and decreased regulatory cytokines may be predictive of at-risk individuals who should be protected from risk factors or even take prophylactic medication. This literature review offers a summary of current literature on the subject.

Key words: systemic lupus erythematosus, antinuclear antibodies, immunological profile, relatives of patients with systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune rheumatic disease of unclear etiology featuring systemic immune dysregulation, pathological autoreactivity, autoantibody formation, and multiorgan involvement. Autoantibodies in SLE attack various autoantigens, and those directed against nuclear structures – antinuclear antibodies (ANA), have been identified as the most characteristic of SLE and are present in 95% of cases. Some are associated with certain organ manifestations, e.g., anti-dsDNA, anti-Sm, anti-Ro and anti-La, and others [1, 2, 3]. Thus, given that women of childbearing age are most affected, SLE is the cause of significant disability of working-age people, determining the disease’s socio-economic significance.

RISK FACTORS (RF) FOR THE DEVELOPMENT OF SLE

In addition to race and age (most often an onset between 15 and 45 years), hormonal and reproductive factors related to gender stand out as RF for SLE development. Given the lack of another explanation for gender distribution, the hormonal profile of patients has been the subject of research for years. In women with SLE, testosterone and dehydroepiandrosterone levels are significantly lower than in healthy individuals, and estradiol and prolactin levels are significantly higher [9]. However, there is no evidence of the direction of the causal link. According to a study of nearly 240,000 predominantly white women followed for 22 years, oral contraceptive use and postmenopausal hormone replacement therapy correlate with an increased risk of SLE [10]. The results of this study, together with those from another large-scale study in the United Kingdom, suggest that current hormone therapy may have an acute effect on a small group of susceptible women [11].

Many epidemiological studies and a meta-analysis indicate that current smoking, unlike past smoking, is associated with an increased risk of SLE [12]. Concerning vitamin D, its levels are lower in patients with SLE. Decreased vitamin concentrations were also found in patients with SLE before and after diagnosis [13, 14], but in a prospective study, the external intake of the vitamin and other antioxidants did not associate with a reduced risk of disease [15].

INCIDENCE AND DEMOGRAPHICS

SLE is a relatively rare disease. According to various studies, the incidence in the United States (considered one of the highest) varies from 5.5 to 23.5 per 100 thousand, and prevalence – between 73 and 143 per 100 thousand [4, 5, 6, 7]. In different countries in Europe, the incidence ranges between 1.0 and 4.9 per 100 thousand people, and prevalence – between 22.2 and 97 per 100 thousand [8]. In terms of gender distribution, SLE is significantly more common in women, ranging from 2:1 in prepubertal and menopausal ages to 12:1 in childbearing age.
The Epstein-Barr virus (EBV) seropositivity is significantly higher in adults and children with SLE than in healthy age-matched controls [16, 17]. Several possible immunopathogenic mechanisms are discussed such as molecular mimicry and subsequent cross-reactivity, B-cell dysregulation, and others. However, so far, there is no clear link between the presence of antibodies against EBV, infectious mononucleosis (severe cases included), on the one hand, and the risk of developing SLE, on the other [18].

Occupational exposure to silica (for which there seems to be convincing evidence) [19, 20], various vaccinations, and other external factors are among the other risk factors considered.

**Familial aggregation and genetic model of inheritance in SLE**

SLE is a polygenic disease and shows a tendency towards familial aggregation. Studies of small cohorts and families [21, 22, 23, 24] have been conducted. The most extensive familial aggregation study (FA, λ) of SLE occurred in Latin America within the GLADEL cohort. In 1997, GLADEL (Grupo Latinoamericano de Estudio del Lupus Eritematoso), composed of 34 centers in 9 Latin American countries, created a representative cohort of SLE patients in the region [25]. By standardized questionnaire, researchers interviewed 1,177 of all 1,214 patients about the presence of SLE, RA, and other autoimmune diseases (AID) in their relatives. The ill relatives were interviewed in person, their medical records reviewed, and some were examined when necessary. The FA (λ) calculation is by the formula λ = K_{relative} / K, where K_{relative} is the disease in relatives and K is the total disease. Due to lack of data about SLE incidence in Latin America, the incidence in the relatives of the subjects was compared with the highest reported in the world (in African Americans, 0.005), and with an average between the highest and lowest in Arctic Norway, 0.0005-0.001). Out of 1,177 patients, 166 had at least one relative with AID, a total of 238 ill relatives, 116 with SLE, 79 with RA, 23 with autoimmune thyroiditis, one with another AID. Forty-two of the patients with SLE have more than one relative with AID. Thus, according to Risch’s formula [26], the type of inheritance was determined based on the different prevalence in different degree relatives: λ_{cousin} = ¼(λ_{offspring} + 3). Based on these calculations, SLE’s inheritance model is considered a polygenic additive but not a polygenic multiplicative one. The described study unequivocally proves the existence of familial aggregation of AID in SLE – to the greatest extent for SLE, to a lesser extent for RA and other AID. The authors discuss that the observed phenomenon may be due either to the presence in the given families of certain gene(s) that increase the susceptibility to the development of AID in general or gene(s) associated with the development of specific diseases.

**Antinuclear autoantibody formation in SLE**

Antinuclear antibodies are a heterogeneous group of autoantibodies (AAb), part of a group of antibodies (Ab) directed against intracellular antigens. The most common nuclear structures targeted by the humoral immune response in SLE may be dsDNA, ssDNA, Nuc, histones, DFS-70, Ro60, Ro52, La, Ku, U1RNP, Sm, PCNA. ANA can be from all three immunoglobulin classes in systemic lupus, but those from IgG are the most important in pathogenic, clinical, and diagnostic terms [27]. Intracellular antigens, including nuclear structures, are hidden in the cell and, in order to become “visible” to immunocompetent cells, need to be externalized through apoptotic or necrotic cell death. Under normal conditions, externalized intracellular antigens (EIAs) are a subject of phagocytosis under “immunological silence” conditions, which do not initiate an effector immune response but induce immune tolerance. Due to acquired or congenital disorders

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**Table 1. Prevalence of different degree relatives from the GLADEL cohort compared with the general prevalence in different regions**

<table>
<thead>
<tr>
<th>Relatives</th>
<th>Prevalence, %</th>
</tr>
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<tbody>
<tr>
<td>SLE relatives</td>
<td></td>
</tr>
<tr>
<td>First degree</td>
<td></td>
</tr>
<tr>
<td>parents/offsetspring</td>
<td>2.7</td>
</tr>
<tr>
<td>siblings</td>
<td>2.9</td>
</tr>
<tr>
<td>second degree (aunts, uncles, nephews, nieces)</td>
<td>1.95</td>
</tr>
<tr>
<td>Third degree (cousins)</td>
<td>1.1</td>
</tr>
<tr>
<td>Populations</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>0.010-0.080</td>
</tr>
<tr>
<td>Afro-Carribean</td>
<td>0.11-0.25</td>
</tr>
<tr>
<td>Afro-American</td>
<td>0.38</td>
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of mechanisms at different levels (defects in apoptosis, defects in the mechanisms of clearance and opsonization, as well as in excessive cell death, e.g., in infectious or neoplastic diseases, because of various drugs), EIA may be subject to humoral immunity and cause the formation of AAb. The latter can occur when EIAs are presented by professional antigen-presenting cells (APCs) in a milieu of costimulatory molecules (B7) and pro-inflammatory cytokines. They are then recognized by autoreactive T lymphocytes, which communicate with autoreactive B differentiating cells, which turn into plasmatic ones and start secreting ANA. Factors favoring this process are all forms of dysregulation, leading to „delayed” clearance of apoptotic or necrotic matter; the high immunogenicity of nuclear antigens (dsDNA, Nuc, histones, HSP60, HMGB1, and others) is additionally enhancing the process. The latter leads to increased synthesis of pro-inflammatory cytokines such as interferon-alpha (IFN-α), interleukins 6 and 12 (IL-6 and IL-12), tumor necrosis factor-alpha (TNF-α), and others [28, 29]. IFN-α production is associated with suppression of regulatory T-helper lymphocytes, increased secretion of BAFF (B-cell activating factor), activation of NK cells and IFN-γ production, and upregulation of IFN-α-associated transcription genes (known as „interferon signature”) [30, 31]. An additional mechanism is the so-called process of secondary necrosis that may further increase the immunogenicity of externalized nuclear complexes. Their recognition by macrophages and plasmacytoid dendritic cells leads to the production of the B-cell preserving cytokine BAFF (Blys) [32, 33]. BAFF is a powerful stimulus for the survival of autoreactive B cells, necessary for the secretion of ANA and its increased levels – a major mechanism favoring the breakdown of B-cell tolerance in the peripheral lymph organs [34]. Autoreactive B cells that recognize their autoantigen (histones, dsDNA, ribonucleoprotein complexes, and others) after internalizing it increase their antigen-presenting ability but at the same time become susceptible to apoptosis by CD95-dependent mechanism or cytokine depletion. Surviving autoreactive B cells may subsequently take the differentiation pathway into short-lived antibody-producing plasmablasts or long-lived antibody-producing plasma cells or memory cells.

**ANA and immunological changes in the preclinical phase of SLE**

Research over the years has shown that ANAs are not only associated with various organ lesions in SLE and are its diagnostic „herald” but are present in the sera of patients up to several years before clinical onset. Several studies have demonstrated the latter [35, 36, 36], but the most central among them is that of Arbuckle et al. [38]. Sera from 130 veterans with a proven SLE diagnosis were obtained by the US Department of Defense serum repository (DoDSR), where they were collected and stored annually during their military service (when subjects were clinically healthy). The study found that 115 patients (88%) had elevated ANA titers in the asymptomatic period. ANAs detected by immunofluorescence of HEp-2 cell substrate, with a cut-off value of > 1:120, were found in 78% of all ANA-positive individuals. Specific antibodies displayed different prevalence: against dsDNA – in 55% of individuals, anti-Ro60 – 47%, anti-La – 34%, anti-Sm – 32%, and anti-RNP – 26%. The average span between the appearance of antibodies in serum and diagnosis was 3.3 years (ranging from 1 to 9), about 2.2 years for anti-dsDNA, and about 1.2 years for anti-Sm and anti-RNP. Thus, there was a characteristic profile with „early” and „late” autoantibodies: anti-Ro60 and anti-La appear early, while anti-Sm were as „harbinger” of the onset of the disease, appearing about a year before first symptoms and a little over a year before the diagnosis. Another characteristic feature is the increase in the number of antibody specificities as the disease approaches. According to the same data – patients and serum bank (DoDSR), in 2007, Heinlen et al. [39] found that 104 of the 130 examined had at least one clinical ACR criterion available before diagnosis.

Subsequent studies have further clarified the immunological changes in the preclinical phase of SLE [40, 41, 42, 43]. In 55 sera of DoDSR, levels of type II interferon-linked soluble mediators were found to increase as clinical onset approached. A study showed that after ANA appearance in the serum and before the clinical onset, the activity of IFN-α was increased. Furthermore, in 20% of these subjects, this IFN-α activity was increased about four years before diagnosis. Thus, the pathogenesis of early SLE involves dysregulation of the type II IFN pathway, which enhances autoantibody production, and the increase in IFN-α occurs almost immediately before diagnosis. In another study, Lu et al. examined 84 sera of „future patients” again from DoDSR and compared them with healthy relevant controls [44]. Elevated levels of T-helper mediators were found in the sera of „future patients” about 3.5 years before diagnosis, and IFN-α, IL-4, IL-5, and IL-6 preceded the appearance of ANAs. Thus, IFN type I associated chemokines (MCP-1) and
ANAs are positive in up to 17% of individuals in the general population, but in elevated titers above 1:160 (approximately because different studies use different methods), they occur in about 2.5 to 5% [45, 46, 47, 48]. Here we will briefly present two studies – one significant in its range and the other – in its in-depth immunological studies.

In 2006 in Dallas, Texas, USA, Amy E. Wandstrat et al. [49] conducted a study of ANA and Ab against extractable nuclear antigens (ENA) among three groups – patients with SLE and incomplete lupus erythematosus (ISLE), first-degree relatives (FDRs) and a large cohort of people (over 3000), a population sample for the study of cardiovascular diseases, with a significant proportion of African Americans and Latinos. The study aimed to compare the amount and profile of autoantibodies from the whole spectrum of lupus disease (from fully developed SLE through ISLE to FDRs of patients) with those in the general population. There are a total of 176 patients, incl. 32 FDRs and 28 healthy controls; the general population cohort numbers 3470 people. ANAs were detected using ELISA-based assay, and in order to equate the results to the ANA titer, several control studies on the IFA (HEp) were performed at the local laboratory, with 10 EU ELISA equivalent to approximately 1:20 IFA, and 20 EU = 1:40. In the group of patients (SLE and ISLE), ANAs were markedly elevated, significantly less in the FDRs and controls. Of the specific antibodies in SLE, anti-dsDNA, anti-SSA, anti-SSB, anti-SM, and anti-RNP predominated, in ISLE – anti-SSA, anti-SSB, and anti-RNP; those against dsDNA, Sm, and chromatin were found almost exclusively in SLE patients. The article does not provide data on the specific Ab in FDRs. In the population sample, ANAs of 20 EU (i.e., approx. 1:40) were detected in 971 people, i.e., 27.12%, and above 118 EU, i.e., greater than two standard deviations above the group’s mean – 90 people, i.e., approx. 2.5%. ANAs were higher in women, African Americans, and Latinos; in younger individuals as well. Sera of those with ANAs > 65 EU, i.e., greater than one standard deviation above the mean in the group (171 people, approx. 5%), were tested for anti-ENa (but not for anti-dsDNA due to lack of serum). One or more anti-ENAs present in the group of patients (SLE and ISLE) were found in 59 people (i.e., 1.7% of the whole group) with no correlations with sex or age, except for anti-SSA, which was more common in women, African Americans, and Latinos. The authors emphasize that in terms of the presence of ANAs in the general population, their results are strikingly harmonized with studies from different parts of the world [45, 46, 47, 48] given the racial and ethnic differences in the manifestation of SLE and suggest that this points to broad common genetic characteristics and environmental factors predisposing to autoreactivity. The presence of ANAs in higher titers in about 2.5% of the general population may be attributed to (1) other AIDs (e.g., autoimmune thyroiditis) or (2) preclinical condition of CTD. The latter might be particularly valid for the 1.7% with ENa, who are likely to be in a state of increased autoreactivity, „in need“ of expression of additional genes to develop into a disease.

In 2016, Slight-Webb S. et al. [50] investigated 790 healthy individuals, 57 of which (7%) were ANA-positive; they were compared with 31 age- and sex-matched ANA-negative and 29 lupus patients. In healthy individuals with ANAs, the number of monocytes and memory B-cells was increased compared to ANA-negative, and B-cells from ANA-positive showed an excessive response to stimulation with IFN-α. These changes may correspond to enhanced upregulated antigen-presenting cellular function in ANA-positives. In addition, some soluble inflammatory factors such as IFN-α, TNF-α, IL-17, and granulocyte colony-stimulating factor (G-CSF) increased with the transition across the three groups: from ANA-negative healthy, through ANA-positive healthy to patients with SLE. However, only SLE patients had elevated IFN-α, IFN-β, IL-12p40, and stem cell factor (SCF). Interestingly, the levels of BAFF were elevated in patients but decreased in healthy carriers of ANAs (compared to ANA-negatives). In addition, the anti-inflammatory cytokine IL-1RA (interleukin-1 receptor antagonist) concentrations were higher in ANA-positive healthy than in patients. A possible explanation is that in asymptomatic ANA carriers, intact immunoregulatory mechanisms prevent them from developing the disease.

ANA AND IMMUNOLOGICAL ALTERATIONS IN RELATIVES OF SLE PATIENTS

Studies on the presence of antinuclear antibodies in relatives of patients with SLE are many, began...
in the 60s of last century and continue to this day. Although not always directly comparable for methodological reasons, they all prove the higher frequency of serum ANAs in this group [51, 52, 53, 54]. Here we briefly present some of the recent ones.

In a study of almost 200 families with 659 lupus patients and 544 healthy relatives, Latisha D et al. investigated the distribution of anti-Ro and anti-nRNP [55]. Logistic regression analysis shows that correlation between the presence of Ab in sick and healthy relatives exists only for anti-nRNP, but not for anti-Ro; gender is not a significant factor. This is in line with studies on identical twins, where anti-nRNP is present in both, in contrast to anti-Ro [56]. The authors refer to the fact that the appearance of antibodies in the subclinical stage of SLE is different in time, with anti-nRNPs appearing almost immediately before diagnosis, as opposed to anti-Ro, which can be found up to 8 years before. Of note, half of the “healthy” with anti-Ro had symptoms and were diagnosed with Sjögren’s syndrome. The study confirms the higher incidence of ANAs in relatives of patients and, on the other hand, is in favor of the assumption that different genetic factors determine different specific ANAs.

In 2001 in Denmark, Laustrup et al. conducted a study on ANAs’ presence in FDRs and spouses on a population level [57]. The populational representativeness of the sample was determined by the fact that subjects were recruited in 4 independent ways, mainly from national clinical and immunological registers, one of which only for SLE patients. A large percentage of all FDRs and spouses took part – the patients were 86, the FDRs – 226, the spouses – 49, and 100 blood donation sera were used as controls. The results confirm the pattern – among FDRs 23 (10%) were positive at 1:160, 55 (24%) at 1:80, and 69 (31%) at 1:40. Among spouses results were 0 (0%), 2 (4%) and 5 (10%) respectively, and among healthy controls – 5 (2.5%), 10 (5%) and 20 (10%). These data suggest that environmental factors acting on the adult organism are not essential, but rather the underlying genetic terrain is important to ANA-positivity. The clinical part of the study (conducted through questionnaires) found that FDRs had a significantly higher percentage of clinical complaints than the spouses, especially those related to ischemic heart disease. However, there was no statistical link with the ANA-positivity in the FDRs. Three facts make an additional impression. First, there is no familial aggregation of SLE in the families in question. Second, more women than men among the healthy controls were ANA-positive in all three titers, e.g., 5% versus < 1% at 1:160 (which is not the case in FDRs). Third, in patients with a higher SLICC Damage Index (≥ 4), more FDRs had ANA titer of 1:80; such a trend is present in other titers, but without reaching statistically significant values. The described study is informative mainly with the representativeness of the sample of patients and the extensive coverage of their families. However, the control group could poorly represent the general population since blood donors are usually age-limited and almost completely healthy.

The continuation of the study above in Denmark is of particular interest. Almost the same authors followed up a significant part of the initial participants after 12 years by the same method – ANA-IFA on HEp cells in dilutions 1:160, 1:80, and 1:40 [58]. Of the initial 226 participants, 33 died (29 had their medical documents reviewed), and 143 of the living agreed to participate; controls were 200 blood donors. There was no significant difference between those who agreed and those who refused to participate in gender, age, or ANA-positivity. Questions on smoking, oral contraception (OC), and hormone replacement therapy (HRT) were added to the standard questionnaire. ANA-positives increased from 9% (13 FDRs) to 24% (34), while those with a titer of 1:80 and 1:40 decreased. Multiple regression analysis revealed that ANA-positivity at follow-up depended only on ANA-positivity at baseline, regardless of age, gender, clinical complaints, smoking, OK, or HRT. Two of the participants reported developing SLE (one of which was ANA negative), 6 reported „another connective tissue disease,“ 6 reported rheumatoid arthritis (RA) (except 4 with RA at baseline); one of the deceased was diagnosed with polymyalgia rheumatica, one with granulomatosis with polyangitis and one with retroperitoneal fibrosis. The authors point out that the diagnoses described in the follow-up were patient-reported only but not verified. In summary, the results of the 12-year follow-up are that (1) FDRs of SLE patients are prone to ANA production compared to healthy controls, and (2) ANA-positive ones usually remain so over the years; (3) rheumatic diseases, incl. SLE and RA have a greater incidence than in the general population. The authors consider the two limitations of the study – the relatively small number of FDRs studied and the reliance on self-reported diagnoses by follow-up participants instead of medical examinations. Besides, the incidence of SLE in Denmark is low (1 in 100,000), and it appears that there is no familial SLE aggregation there. The authors discuss the low predictive value of the presence of
ANA to the development of AID: only 6 out of 51 (12%) ANA-positives develop AID (SLE, RA or „other CTD”) compared to 8 out of 92 (9%) ANA-negatives in that developed AID. It is essential to add that, according to the data from the above-cited pivotal study of Arbuckle et al., ANAs appear at the earliest approx. 8-9 years before the clinical manifestation of SLE. The 12-year follow-up period of the current study exceeds the period of „subclinical ANA,” which means that most likely, those who have ended up with an AID and had been ANA-negative initially, have become ANA-positive later. Another conclusion from the study is that smoking is not statistically associated with antibody production or the development of AIDs.

The most current, large-scale, and complex demographic, clinical, and immunological features study is that of Munroe M. et al. [59]. A total of 409 relatives (of various degrees) of lupus patients with less than 4 ACR criteria participating in the Lupus Family Registry and Repository (LFRR) were included. In LFRR, sera were initially collected, and clinical data were reported. The study was a follow-up, and subjects completed the SLE section of the Connective Tissue Disease Screening Questionnaire (CTDSQ); sera were collected again and compared with the initial ones from the Repository. Researchers investigated anti-dsDNA (IFA), aCL, antibodies against dsDNA, chromatin, Ro, La, Sm, RNP/Sm, and RNP by ELISA and 50 innate and adaptive cytokines and chemokines, and molecules of the TNF superfamily. In order to distinguish the predictors for transitioning to SLE as accurately as possible, two statistical models were used. First, all who transitioned to SLE were compared with all who did not regarding the type of family relationship. Second, each patient who transitioned was compared with those who did not but matched by age, race, sex, and ANA positivity/negativity to distinguish the predictors. Among the 409 subjects followed-up, 45 (11%) transitioned to SLE within an average of 6.4 years. At baseline, they have elevated levels of inflammatory mediators, incl. BAFF, SCF, and cytokines associated with IFN, as well as lower levels of regulatory mediators such as TGF-β and IL-10. Thus, independent predictors of SLE development in healthy relatives are clinical symptoms, elevated SCF levels, and decreased TGF-β levels. The study reinforces the understanding that SLE immunopathogenesis combines enhanced pro-inflammatory mechanisms with insufficient regulatory ones.

Is SLE prevention possible?

In the article „Predicting and preventing autoimmunity, myth or reality?” [60], Harel and Shoenfeld formulate the concept of „autoimmune-prone individual” (AIPI) and propose general measures to prevent the development of AIDs in such individuals. The profile of an AIPI includes female gender, having a relative with AID, a particular HLA affiliation (varying with the disease), or the presence of specific genetic polymorphisms. According to the authors, such an individual is in danger of developing the disease when exposed to certain environmental factors. Such risk factors include infections (EBV, CMV, HCV, and others), ultraviolet light, hormones, certain medications, toxins (quartz, aromatic hydrocarbons, etc.), silicone implants, smoking, stress, some vaccines. Avoidance of UV radiation, avoidance of oral contraceptives, vitamin D intake, unsaturated fatty acid intake, smoking cessation are recommended as preventive factors for SLE after screening. Moreover, several studies have shown that taking hydroxychloroquine and/or a corticosteroid slows down the accumulation of antibodies, delays the disease’s clinical onset, and reduces future organ damage [61, 62].

Conclusion

From all of the above, several facts are clear. 1. Systemic lupus erythematosus is an autoimmune disease caused by complex immunological alterations, which products might be detected up to 9 years before clinical manifestation. ANAs are subject to routine testing in clinical practice, while others are well-established immune system markers but used in research only. Changes in some of these precede the formation of ANAs, while others correlate with a transition to SLE and are candidate-predictors of disease development. Also, in „future patients,” specific ANAs display specific dynamics, both in terms of quality (some appear early, others almost immediately before the disease onset) and in terms of quantity (the number of specific ANAs increases with approaching the clinical onset).

2. The current understanding of the SLE pathogenesis is that external factors contribute to the „triggering” of genetically determined immune dysregulation. External factors include changes in estrogen/testosterone levels (including iatrogenic), decreased vitamin D levels, current smoking, quartz exposure, and Epstein-Barr virus infection. That is sketched on the following diagram.
3. Systemic lupus erythematosus has a polygenic type of inheritance and tends to have familial aggregation, and a relative of a patient is 10 to 50 times more likely to develop SLE than a random individual.

4. ANAs are found both in relatives of patients and in the general population and, for the most part, are not a sign or harbinger of disease. However, in relatives, the incidence of ANA titer of 1:160 or more is higher – about 10%, compared to only 2.5% general population. The immunological profile of relatives differs significantly from that of ANA-positives from the general population. There is enough evidence that some of these differences associate with a future transition to SLE. This is especially valid for the pro-inflammatory cytokines SCF and MCP and the regulatory cytokines TGF-β and IL-10.

There is still no data to bring together and look for interrelationships between all of the above, particularly to bring together environmental factors with clinical and immunological changes in one study. Concerning the data on immunological alterations associated with the transition in ANA-positive relatives, additional studies are needed, including prospective ones, to confirm or rule out, refine, validate, and perhaps even standardize the parameters.

The author declares that this manuscript has not been published so far. It was presented at the annual rheumatology conference.

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Fig. 1. SLE development over time due to risk factors acting upon altered immunity terrain


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