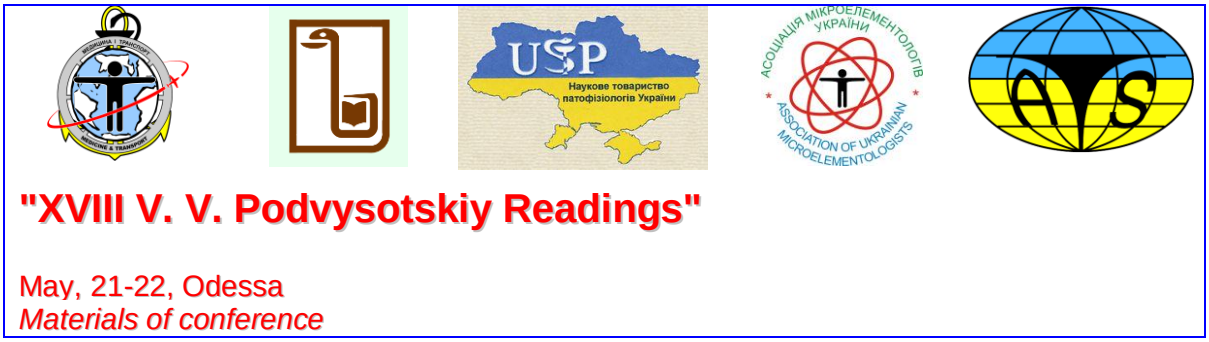
**Yakimenko Dmitro. The role of autoimmune reactions in formation and progressing of Sjogren's syndrome as systemic damage of organism. Journal of Education, Health and Sport. 2019;9(5):556-563. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3238637**
**http://ojs.ukw.edu.pl/index.php/johs/article/view/6998**

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.04.2019. Revised: 15.05.2019. Accepted: 24.05.2019.




# The role of autoimmune reactions in formation and progressing of Sjogren's syndrome as systemic damage of organism

**Dmitro Yakimenko**

**Odessa National Medical University, Odessa, Ukraine**

## Abstract

The purpose of the research was the identification of association of organs and systems damage in Sjogren's syndrome with the presence of organ-specific and organ-nonspecific autoantibodies.

On the basis of complex examination of 21 patients with Sjogren's syndrome (women age 53,5 ± 0,9 years old) and content determination of wide spectrum of organ-specific and organ-nonspecific autoantibodies we estimated the existence of association between presence of these autoantibodies and clinical manifestations of Sjogren's syndrome. The received results demonstrate the relationship between the expressiveness of inflammatory manifestations and the content of antibodies to DNA. The expressiveness of salivary glands injuries is associated with content of autoantibodies to salivary glands. The presence of

associated diseases is also associated with existence of particular autoantibodies. As in all examined patients with Sjogren's syndrome was present the digestive tract pathology, it can be assumed that changes in digestive tract wall lead to damage of immune system structures and polyclonal uncontrollable activation of antibodies production.

**Key words: Sjogren's syndrome, organ-specific autoantibodies, organ-nonspecific autoantibodies, clinical features**

In modern medicine there is a rather extensive group of diseases where the presence of autobodies is considered as a pathogenetic sign or diagnostic criterion. The development of autoimmune processes in these diseases is associated with features of organs' damage as the list of autoantibodies is rather limited for each disease. The presence of organ-specific anti-nuclear antibodies (ANA) is characteristic of system lupus erythematous, the presence of rheumatoid factor (RF) – an antibody to Fc-fragment of IgG, antibodies to cyclic citrullinated peptide (CCP) and vimentin - are characteristic of rheumatoid arthritis. The presence of organ-specific antibodies to mitochondria is characteristic of Hashimoto thyreoiditis and primary biliary cirrhosis, and the first one is also characteristic of presence of antibodies to thyroid gland antigens (thyroglobulin, microsomes, thyroperoxydase) [5, 15, 16, 22].

Primary Sjogren's syndrome (SjS) holds a special place among autoimmune diseases. Primary SjS is an organ-specific disease of external secretion organs (salivary, lacrimal, digestive tract glands). Clinical manifestations of external secretion glands damage are the dryness of eyes, mouth, nose, throat, airways, vagina [18, 19]. Development of these clinical manifestations is connected with the activation of immune system cells, firstly of B-lymphocytes and increasing in autoantibodies production by several clones of antibody-producers [8].

In different countries the prevalence of SjS is from 4 to 250 cases on 100 thousand population, mainly women suffer over the age of 40 [1, 7, 20].

Numerous researchers of SjS note the presence in blood of ANA (SS A/Ro and SS B/La), RF, organ-specific autoantibodies which are characteristic of systemic scleroderma and systemic lupus erythematous, autoantibodies to thyroid gland antigens. This phenomenon is connected with polyclonal activation of antibody-producer cells because of immunological tolerance disorder [10, 12, 13, 21]. In some cases it can lead to development of non-Hodgkin's lymphoma, the risk of its development in patients with SjS is 44 times higher, than in the general population [2, 6, 7, 9, 11].

The presence of organ-specific and organ-nonspecific autoantibodies in patients with SjS is accompanied by damage of different organs and systems besides glands of external secretion. However the interrelation of organ damage with a range and character of autoantibodies demands further clarification.

Based on the above the purpose of research was the identification of association of organs and systems in SjS with the presence of various organ-specific and organ-nonspecific autoantibodies in this group of patients.

**Materials and methods**

21 patients with Sjogren's syndrome were examined, all women, average age 53,5 ± 0,9 years old. The clinical and laboratory examination included the examination by stomatologist, ophthalmologist, rheumatologist, neurologist, endocrinologist, otorhinolaryngologist, Schirmer's test performing, determination of speed of non-stimulated salivation, general clinical analyses, determination of the general protein and its fractions content, glucose, bilirubin, AsAT, AlAT, GGTP, ALP, creatinine, identification of cryoglobulins, C-reactive protein (CRP), thyrotropic hormone (TSH), hormones of thyroid gland – thyroxine (T4) and triiodothyronine (T3). Also we determined the existence and content of rheumatoid factor (RF), antibodies (AB) to cyclic citrullinated peptide (CCP), antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), verification of ANA and ANCA in its existence, antibodies to gastric parietal cells and antigens of thyroid gland (microsomes, thyroperoxedase, thyreoglobulin), antibodies to salivary glands (using tissue sections of monkey's salivary gland) and to alpha- fodrin Ig A and Ig G. As a control group for studying of antibodies prevalence to tissue of salivary glands and to α-fodrin were serums of 21 women with rheumatoid arthritis, with the ANA negative test – screening, and with a normal speed of salivation. Sjogren's syndrome was diagnosed on the basis of SICCA criteria (Sjogren's International Collaborative Clinical Alliance, 2012) [10].

The received results were processed with methods of mathematical statistics using the Microsoft Exel software package.

**Results and their discussion**

The clinical examination of the patients included in this research revealed that 100% of patients complained of dryness in a mouth, difficulty of swallowing of dry food, 95% of patients complained of dryness of eyes, feeling of sand in eyes. On objective examination we revealed parenchymatous sialadenitis, keratoconjunctivitis, cheilitis. Speed of salivation decreased to less than 0,2 ± 0,01 ml/min. At the same time in 81,1% of patients recurrent parotitises were revealed, and in 95,0% of patients - dry rhinopharyngitis, that is in all patients

the pathology of external secretion glands was revealed. On this background in 85,7% of patients was periodic arthralgia. Besides, in different patients of the examined group were the pathological processes associated with autoimmune reactions: the regional lymphadenopathy, cryoglobulin purpura, Reynaud's syndrome, serositis, autoimmune thyroiditis and others. It should be noted especially that in 80,9% of examined patients was damage of digestive tract in different clinical forms. As it is considered that 70% of structural formations of the immune system are located in digestive tract walls, it is possible to believe that long-term damages of this system create preconditions for development of polyorganic autoimmune pathologies.

More detailed examination of oral cavity revealed that all patients had cervical caries, in 95,2% - partial adentia, in 4,8% - total adentia. 100% of patients had dry, hyperemic mucous membrane of oral cavity, in 95,2% of patients were painful cracks in the mouth angles, in 90,5% of patients - erosions of oral mucous membranes, and in 9,5% of patients was severe damage – "the burning mouth". The Green-Vermillion index of oral cavity hygiene was 5,4± 0,1 (unsatisfactory hygiene of oral cavity). The average tear production in the Schirmer's test was 5,5±0,05 ml/ 5 mines (is significantly decreased). In all patients we observed the changes in protein spectrum of blood with increasing in average ESR up to 25± 0,8 mm/hour.

The determination of organ-specific and organ-nonspecific autoantibodies content in blood revealed significant changes of these indicators. Results of research are shown in Table 1. According to table data, in majority of patients was increasing in content of ANA SSA, RF, antibodies to thyroid gland antigens, to salivary glands, to α–fodrin of the classes IgA and IgG. In smaller part of examined group was increased content of autoantibodies to single- and double-helix DNA and antibodies to smooth muscles (SMA). Increasing in content of antibodies to mitochondria, microsomes, gastric parietal cells and kidney glomeruli were observed in certain patients. Generally it is possible to note the expressed activation of antibodies production in examined patients.

The used methods of determination of content of antibodies to salivary glands showed sensitivity of 95%, specificity of 90,5%; to α–fodrin Ig A -sensitivity of 90%, specificity of 85,7%; to Ig G - sensitivity of 47,6%, specificity of 71,4%. Therefore, the existence of antibodies to salivary glands and α–fodrin IgA – sensitive and specific sign of SjS and can be used as diagnostic (pathogenetic significant) criterion of SjS on early stages of disease progressing. The existence of antibodies to α–fodrin Ig G is less sensitive and specific sign of SjS that demands further researches for specification of diagnostic significant levels of these antibodies and their place in diagnostics of Sjogren's syndrome.

Table 1

The presence of autoantibodies and associated clinical features in Sjogren's syndrome

| № | Characteristic of autoantibodies | Number of patients with their presence (abs./%) | Clinical features |
|---|---|---|---|
| 1. | Antinuclear antibodies (ANA) | 20 (95,2%) | |
| 2. | SS - A | 17 (81%) | |
| 3 | SS - B | 9 (42,5%) | |
| 4. | AB to double-spiral DNA (dsDNA) | 2 (9,5%) | High activity of disease |
| 5. | AB to single-spiral DNA (ssDNA) | 4 (19,0%) | High activity of disease |
| 6. | Anti-mitochondrial AB (AMA)-M2 | 2 (9,5%) | Increased level of ALP, AsAT, AlAT |
| 7. | RF | 16 (76,2%) | Arthralgias and arthritis |
| 8. | AB to CCP | 2 (9,5%) | Arthralgias and arthritis |
| 9. | AB to gastric parietal cells | 1 (5%) | Atrophic gastritis, hemolytic anemia |
| 10. | AB to smooth muscles (SMA) | 8 (38,1%) | Arthralgias, increased level of AsAT, AlAT, GGTP |
| 11. | ANCA<br>AB to glomerular basal membrane (anti -GBM) | 1 (5%) | Transient proteinuria |
| 12. | AB to thyroid gland antigens total | 17 (80,9%) | In 8 patients – hypothyreosis |
| 13. | AB to thyroperoxedase | 13 (61,9%) | |
| 14. | AB to microsomes | 4 (19%) | |
| 15. | AB to thyroglobulin | 7 (33,3%) | |
| 16. | AB to salivary glands | 20(95,2%) | |
| 17. | AB to alpha–fodrin Ig A | 19(90,5%) | |
| 18. | AB to alpha–fodrin Ig G | 10 (47,6%) | |

In the comparative analysis of clinical features of SjS and autoantibodies spectrum certain associations were revealed. In patients with maximum activity of inflammatory process the existence of rather large number of antibodies to single- and double-helix DNA was observed. Patients complained of arthralgias, they had high level of RF, antibodies to CCP, however the morning joint stiffness did not exceed 40 minutes, and rheumatoid arthritis changes of skeletal and articular system were not revealed, so it can be assumed that patients had the autoimmune reaction without development of clinical pathology. In patients with increased activity of AlAT, AsAT, GGTP and ALP (cytolysis and cholestasis syndrome) anti-mitochondrial antibodies M2 (AMA M2) and antibodies to smooth muscles (SMA) were defined. In patients with thyroiditis the increasing in content of antibodies to thyroperoxedase, thyroglobulin and microsomes were defined. In patient with transient proteinuria was

increased content of antibodies to glomerular basal membrane, in patient with atrophic gastritis and hemolytic anemia – increased content of antibodies to gastric parietal cells. It is necessary to highlight that all above-mentioned pathological processes were in patients with Sjogren's syndrome, the disorder of antibodies production in all of them has the wide spectrum.

Thus, the obtained data testify to existence of wide spectrum of organ-specific and organ-nonspecific autoantibodies associated with polyclonal uncontrollable activation of antibodies production in patients with Sjogren's syndrome. As all examined patients had pathologies of digestive tract, it can be assumed that damage of immune system structures of digestive tract wall is present that leads to disorder of antibodies production and development of autoimmune pathology – Sjogren's syndrome. At the same time the spectrum width of antibodies production disorder defines the accession of other diseases with autoimmune component.

**Reference**

1. Vasilev V.I. Klinika, diagnostika i differentsialnaya diagnostika bolezni Shegrena [Clinic, diagnostics and differential diagnosis of Sjogren's syndrome ]. Russkiy meditsinskiy zhurnal. Revmatologiya, 2008; 10(16): 638-649. ( in Russian)

2. Lopatina I.A., Lopatkina T.N., Tanaschuk E.L., Arion E.A. Variantnaya forma porazheniya pecheni: autoimmunnyiy gepatit – pervichnyiy biliarnyiy tsirroz pecheni pri bolezni Shegrena [Alternative form of damage of a liver: autoimmune hepatitis – primary biliary cirrhosis at Sjogren's syndrome.]. Klinicheskaya meditsina, 2013; 1: 66-70. (in Russian)

3. A.V.Gordeev, E.A.Galushko, E.L.Nasonov Kontseptsiya polimorbidnosti v revmatologicheskoy praktike [The concept of a polimorbidity in rheumatologic practice]. Nauchno-prakticheskaya revmatologiya. 2014; 4: 362-365. (in Russian)

4. Selifanova E.I., Simonova M.V., Razumova S.I., Bulgakov V.S Diagnostika bolezni i sindroma Shegrena v usloviyah stomatologicheskoy polikliniki [Diagnostics of Sjogren's syndrome in the conditions of dental policlinic.]. Rossiyskiy stomatologicheskiy zhurnal, 2016; 20(4): .218-220. ( in Russian)

5. Nikitin N.M., Afanasev I.A., Rebrov A.P. Komorbidnost u bolnyih revmatoidnyim artritom [Komorbidity at patients with rheumatoid arthritis.]. Nauchno-prakticheskaya revmatologiya. 2015; 2: 149 - 154. ( in Russian)

6. Panchovska M.S., Sheytanov Y.I., Stoilov R.M., Martinova F.G., Nikolov K.G. Pervichnyiy sindrom Shegrena i bazedova bolezn (semeynyiy sluchay )[ Primary Sjogren's syndrome and bazedov disease (family case)]. Nauchno-prakticheskaya revmatologiya. 2001; 1: 71-72. ( in Russian)

7. Vasilev V.I., Simonova M.V., Safonova T.N., Logvinenko O.A. Sovremennyie podhodyi k ispolzovaniyu glyukokortikoidnyih i tsitotoksicheskih preparatov pri bolezni Shegrena [Modern approaches to use of glucocorticoid and cytotoxic medicines at Sjogren's syndrome.]. Sovremennaya revmatologiya. 2008; 2: 39-56. ( in Russian)

8. Kuvardin E.S., Grigoreva N.I., Maslyanskiy A.L., Hohlov D.S., Behtereva I.A., Krivolapov Yu.D. Cpektr kletochnyih subpopulyatsiy limfotsitarnyih fokusov maloy slyunnoy zhelezyi pri bolezni Shegrena kak dopolnitelnogo kriteriya diagnostiki [Range of cellular subpopulations of lymphocytic focuses of small salivary gland at Sjogren's syndrome as additional criterion of diagnostics]. Nauchno-prakticheskaya revmatologiya 2018; 56 (suppl. 3): 21-22. ( in Russian)

9. Shornikova N.S., Vasilev V.I., Smirnov A.V. Porazhenie sustavov pri bolezni Shegrena [Damage of joints at Sjogren's syndrome]. Nauchno-prakticheskaya revmatologiya. 2002; 1: 13( in Russian)

10. American college of rheumatology classification criteria for Sjogren's syndrome a data-driven, expert consensus approach in the SICCA cohort. Shiboski S., Shiboski C., Criswell L. et al. Arthritis Care res. 2012; 64 (4): 475-487.

11. Csepregi A., Szodaray P., Zeher M. Do antibodies predict autoimmune liver disease in primary Sjogren's syndrome? Data of 180 patients upon a 5years follow up. Scand. J. Immunol. 2002; 56: 623-629.

12. Diagnostic accuracy of anti-alpha-fodrin antibodies for primary Sjogren's syndrome Quin Q., Wang H., Huang YL, Li H, Zhang WW, Zhang LR, He LL, Zhao DB, Deng AM Mod. Rheumatol. 2014; 24(5): 793-797.

13. EULAR recommendation for the management of rheumatoid arthritis with syntetic and biologikal disease-modifying antirheumatic drugs. Smolen J.S., Landewe R., Breedveld F.C. et al. Ann. Rheum. Diseases. 2013; 73: 492 - 509.

14. Focal sialadenitis in patients with ankylosing spondylitis and spondyloarthropathy: a comparison with patients with rheumatoid arthritis or mixed connective tissiu disease. Helenius L.M., Hietanen J.H., Helenius I. et al. Ann. Rheum. Dis. 2001; 60: 744-749.

15. Goldblatt F., O'Neil S.C. Clinical aspects of autoimmune rheumatic diseases. Lancet. 2013; 382: 797-807.

16. International consensus: What else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren's syndrome)?: The unmet needs and the clinical grey zone in autoimmune disease management. Giacomelli R, Afeltra A, Alunno A et al. Autoimmune res. 2017; sept 16(9): 911- 924.

17. Jiunn-Hong Kang, Herng-Ching Lin Comorbidites in patient with primary Sjogren's syndrom a registry-based case-control study. J.Rheumatol. 2010; 37(16): 1188-1194.

18. Kassan S.S., Moutsopoulos H.M. Clinical manifestations and early diagnosis of Sjogren syndrome. Arch.Intern.Med. 2004; 164: 1275–1284.

19.Mattews S.A., Kurien B.T., Scofield R.H. Oral manifestation of Sjogren's syndrome. J.Dental Research. 2008; 87(4): 308-318.

20. Prelevance of xerostomia in population-based samples: a systematic rewiev. Orellana M.F., Lagraviere M.O., Boychuk D.G. et al. J.Public.Health.Dent. 2006; 66(2): 152-158.

21. Ramos–Casals M., Tzioufas A., Font J. Primary Sjogren's syndrome: new clinical and therapeutic concepts. Ann.Rheum.Dis. 2005; 64, 1: 347 – 354 22.Rosseir V., Bart P.A., Spertini F. Sjogren's syndrome: a new approach to treatment. Rev. Med. Sci. 2012; 18; 8(337): 843 -847.

23. Reviewing primary Sjogren's syndrome: beyond the dryness. From pathophysiology to diagnosis and treatment. Both T., Dalm V.A., van Hagen P.M. et al. Int.J.Med. Sci. 2017; 14(3): 191-200.