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А.А. Заяева, С.И. Р. Юнси*, А.И. Заусалина, Г.Н. Кошукова, А.В. Климчук, Г.А. Юнси

Федеральное государственное автономное образовательное учреждение высшего образования Крымский федеральный университет имени В.И. Вернадского, Симферополь, Россия

АУТОИММУННЫЙ/ВОСПАЛИТЕЛЬНЫЙ СИНДРОМ, ИНДУЦИРОВАННЫЙ АДЪЮВАНТАМИ

A.A. Zayaeva, S.I. R. Younsi*, A.I. Zausalina, G.N. Koshukova, A.V. Klimchuk, G.A. Younsi

V.I. Vernadsky Crimean Federal University, Simferopol, Russia

Autoimmune/Inflammatory Syndrome Induced by Adjuvants

Резюме

ASIA-синдром (autoimmune/inflammatory syndrome induced by adjuvants –аутоиммунный/воспалительный синдром, обусловленный адъювантами, синдром Шонфельда (Shoenfeld's syndrome)) представляет собой группу аутоиммунных заболеваний, вызванных адъювантами, обладающими способностью индуцировать иммунные реакции. Синдром включает пять иммуноопосредованных состояний, которые связаны с предшествующим воздействием различных триггерных факторов, такие как силиконоз, синдром макрофагального миофасцита, синдром Персидского залива, синдром «больных» зданий и поствакцинальные аутоиммунные явления. Развитие ASIA-синдрома связано с индивидуальной генетической предрасположенностью и возникает в результате сочетанного воздействия экзогенных и эндогенных факторов, запускающих аутоиммунный ответ. При этом, реакция иммунной системы может быть непредсказуемой. В статье приведены диагностические критерии синдрома, а также его клинико-лабораторные и морфологические проявления. Спектр клинических проявлений аутоиммунного/воспалительного синдрома, индуцированного адъювантами, обширен и затрагивает практически все системы организма человека. При этом, его характерным признаком является регресс клинических, лабораторных и морфологических проявлений после удаления адъюванта. Нет сомнений в том, что ASIA-синдром прояснил роль адъювантов в развитии аутоиммунных процессов. Это должно учитываться при создании безопасных вакцин, силиконовых имплантов, филлеров и других медицинских изделий с минимальными побочными эффектами. Кроме того, медицинские работники должны повышать уровень осведомленности пациентов о побочных эффектах применения некоторых косметологических процедур и использования силиконовых имплантов, для чего необходимо включить в учебно — методические пособия для студентов, ординаторов и врачей различных специальностей описание этиологии, патогенеза, диагностики и лечения ASIA — синдрома, как отдельной нозологической единицы.

Ключевые слова: **аутоиммунный/воспалительный синдром, индуцированный адъювантами, ASIA — синдром, синдром Шонфельда, адьювант**

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*Контакты: София Ибн Ридха Юнси, e-mail: younsisofia@mail.ru
*Contacts: Sofia Ibn Ridha Younsi, e-mail: younsisofia@mail.ru
ORCID ID: https://orcid.org/0000-0002-2361-8730

Abstract

ASIA syndrome (autoimmune/inflammatory syndrome induced by adjuvants) is a group of autoimmune diseases caused by adjuvants that have the ability to induce immune responses. The syndrome includes five immune-mediated conditions that are associated with prior exposure to various trigger factors, such as siliconosis, macrophage myofasciitis syndrome, Persian Gulf syndrome, sick building syndrome, and post-vaccination autoimmune events. The development of ASIA syndrome is associated with an individual genetic predisposition and occurs as a result of the combined effect of exogenous and endogenous factors that trigger an autoimmune response. In this case, the reaction of the immune system can be unpredictable. The article presents the diagnostic criteria for the syndrome, as well as its clinical, laboratory and morphological manifestations. The spectrum of clinical manifestations of the autoimmune/inflammatory syndrome induced by adjuvants is extensive and affects almost all systems of the human body. At the same time, its characteristic feature is the regression of clinical, laboratory and morphological manifestations after removal of the adjuvant. There is no doubt that ASIA syndrome has clarified the role of adjuvants in the development of autoimmune processes. This should be taken into account when creating safe vaccines, silicone implants, fillers and other medical devices with minimal side effects. In addition, medical professionals should raise patients' awareness of the side effects of using certain cosmetic procedures and the use of silicone implants, for which it is necessary to include a description of the etiology, pathogenesis, diagnosis and treatment of ASIA syndrome in teaching aids for students, residents and doctors of various specialties as a separate nosological unit.

Key words: *autoimmune/inflammatory syndrome induced by adjuvants, ASIA syndrome, Schoenfeld's syndrome, adjuvant*

Conflict of interests

The authors declare no conflict of interests

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ASIA-syndrome — autoimmune/inflammatory syndrome induced by adjuvants; MHC — Major Histocompatibility Complex; HLA DRB1 — Human Leukocyte Antigens, class II, beta chain; HBV — Hepatis B virus; HPV – Human papillomavirus; HAV — Hepatis A virus; HLA-B27 — Human Leukocyte Antigens, class I, beta chain; PTPN22 — Protein tyrosine phosphatase non-receptor type 22.

Introduction

ASIA-syndrome (autoimmune/inflammatory syndrome induced by adjuvants, Shoenfeld's syndrome) is a group of autoimmune diseases, such as silicosis, macrophage myofascitis syndrome, Persian Gulf syndrome, sick building syndrome and post-vaccination autoimme conditions induced by adjuvants (Figure 1). Identification of ASIA-syndrome made it possible for the first time to group specific conditions caused by hyperergic immune reaction to various adjuvants.

Adjuvants are substances that boost immune response when administered together with an immunogen [1]. They have immunomodulating action [2]. Usually adjuvants can be found in drugs, vaccines, silicone breast implants, mineral oils and cosmetics. Despite the fact that adjuvants are predominantly safe, sometimes administration of adjuvants can induce immune response in genetically susceptible and predisposed persons [1].

The scientific theory underlying Shoenfeld's syndrome is based on paradigms widely recognised in published studies. First of all, it is noted that genetic predisposition has a leading role in autoimmune process development. Numerous studies demonstrated the correlation between a certain genetic profile and autoimmune processes. Of all genetic loci defining predisposition to autoimmune reactions, most significant are

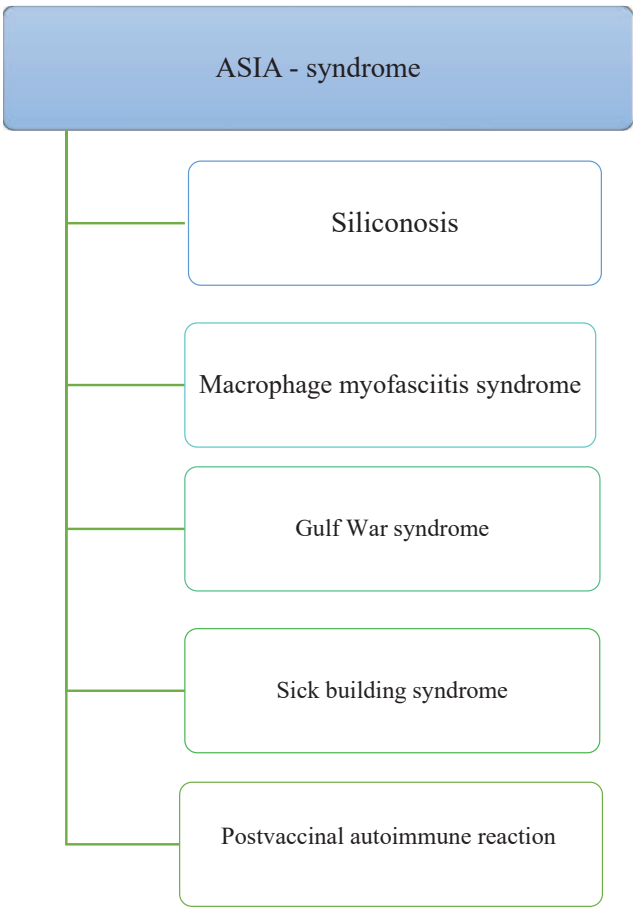

Figure 1. *Immune — mediated cjnditions ASIA syndrome*

the loci that encode type II MHC (major histocompatibility complex), responsible for antigen presentation to immune cells. However, the mechanism of MHC II involvement into autoimmune process has been understudied. It is likely that aberrant antigen presentation is a result of allele variants of the major histocompatibility complex, such as HLA DRB1 autologous-reactive T-lymphocytes [3]. It is assumed that genetic predisposition to an autoimmune process is associated with certain MHC alleles [3].

The other underlying paradigm of ASIA-syndrome is due to the role of adjuvants in immune stimulation. Over decades, adjuvants have been an essential component of experimental studies of the immune system due to their ability to activate various immune cells, thus boosting and speeding up immune response [4]. Also, adjuvants have been widely used beyond immunology laboratories. Taking into account immunostimulatory properties of adjuvants, it is no surprise that a majority of these substances that were considered safe cause autoimmune reactions [5].

Background

Before Professor Yehuda Shoenfeld proposed the term "ASIA-syndrome", the incidence of post-vaccination autoimmune diseases had not been studied properly. Similar conditions were also reported after tattooing, breast implantants surgery, Persian Gulf syndrome (a condition including such symptoms as arthralgia, muscular weakness, joint pain, fatigue, headache, memory disorders, cognitive disorders and higher susceptibility to infections, which were reported by American military men after the Gulf War in 1991) and other pathologies [4]. Cases of optic neuritis and myelitis were observed after tetanus toxoid vaccination [6]. As for flu vaccine, episodes of vasculitis, Reiter disease and Gullian-Barre syndrome were reported [4, 6]. There were cases of immune thrombocytopenic purpura and diabetes mellitus after vaccination against measles, mumps and rubella [6]. Virus hepatitis B vaccine is highly associated with such autoimmune disorders as nodal fever, polyarthritis, immune thrombocytopenia, severe myasthenia, uveitis, Reiter's syndrome, systemic lupus erythematosus, and Evan syndrome. Scientific literature sources describe development of chronic fatigue syndrome in females with silicone breast implants after hepatitis B vaccination. Thus, it can be assumed that the immune response to vaccination could have been enhanced by silicone as an adjuvant [7, 8].

Available information led to the conviction that adjuvants are a predisposing factor for development of post-vaccination autoimmune reactions [9]. This information was updated by Doctor Ye. Shoenfeld. In his papers, the scientist argues that the immune system discriminates Toll-like receptors on WBCs and triggers adjuvant-induced immune response [9].

Several adjuvants, such as virosomes for HBV, HPV and HAV, MF59 in some viral vaccines, against viral and parasitosis and cholera toxin for cholera, have been described. Some adjuvants were mentioned as factors predisposing to autoimmune disorders. For instance, mineral oil adjuvants were believed to be a cause of sclerogenic lipogranulomas [6]. However, the two principal adjuvants causing autoimmune reactions were and are aluminum and silicone [4]. It was found out that aluminum in hepatitis A and hepatitis B vaccines, tetanus toxoid vaccines, flu vaccines and pneumococcus vaccine contribute to the development of multiple sclerosis, chronic fatigue syndrome and polymyalgia rheumatica [10].

Table 1. *The diagnostic criteria for ASIA syndrome*

Major Criteria	Minor Criteria
1. Exposure to external stimuli (infection, vaccine, silicone, adjuvant) before the onset of clinical symptoms 2. The appearance of typical clinical manifestations: а. Myalgia, myositis, or muscle weakness б. Arthralgia and/or arthritis в. Chronic fatigue, un-refreshing sleep, or sleep disturbances г. Neurological manifestations (especially associated with demyelination) д. Cognitive impairment, memory loss е. Fever, dry mouth 3. Typical histological findings after biopsy of offending organs 4. Removal of offending agent results in improvement of symptomatology	1. Appearance of antibodies directed against the adjuvant suspected to be involved 2. Secondary clinical manifestations (irritable bowel syndrome, interstitial cystitis, Raynaud's syndrome, etc.) 3. Evolvement of an autoimmune disease (multiple sclerosis, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis) 4. Antigens specific for human leukocytes (HLA DRB1, HLA DQB1)

Besides, there were reports on Persian Gulf syndrome which developed as a result of Toll-like receptors exposure to WBCs after an injection containing aluminium hydroxide [11]. As for silicone, literature sources describe cases of connective tissue disorders, such as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis after silicone enters the body [6].

There is information on development of autoimmune disorders after injections of filler adjuvants or tattoos. However, it was noted that an autoimmune process after tattooing can be induced by several therapies. For instance, granulomatous reaction to tattooing was observed after intense light pulse procedure for face skin rejuvenation [12]. In some cases, authors were unable to determine the exact cause of granulomatous reaction, which can be triggered by any of numerous various pigments, especially red and black, and excipients injected into skin. Besides, there are reports on sarcoid granuloma which developed after alpha interferon therapy for head melanoma [13].

These studies, among others, were the basis for the study by Doctor Ye. Shoenfeld et al., which was a momentum for the introduction in 2011 of ASIA-syndrome as a nosologic entity and formation of diagnostic criteria (Table 1). Currently, Shoenfeld's syndrome is suspected in the presence of two major criteria or one major and two minor criteria [4].

Etiology and Pathogenesis

ASIA-syndrome is a multi-factor pathology triggered by a complex combination of exogenous and endogenous (genetic) factors. Environmental factors are a key criterion for ASIA-syndrome and are responsible for traditional signs of Shoenfeld's syndrome. After exposure to external environmental triggers, patients more often have symptoms of chronic fatigue and general weakness [14, 15]. The most well-studied triggers — silicone and aluminium — can irritate immune system and induce autoantibody production [16]. Silicone is known to cause autoimmune processes; however, initially it was considered inert and non-immunogenic. Silicone breast disease is a classic example of Shoenfeld's syndrome [17]. Numerous studies demonstrated that silicone can trigger an autoimmune inflammatory process in two possible ways: by boosting immune response and by molecular mimicry [18]. Once in the body, silicone causes an acute inflammatory process and enhances cytokine production [19]. A connective tissue capsule is formed in the area of silicone implantation, which is infiltrated with CD4+ lymphocytes, macrophages and multinucleated giant cells, surrounds the implant and forms a so-called siliconoma [20]. Also, the body can experience a cross-reaction between silicone and natural structures in human connective tissue, such as glycosaminoglycans [21].

Genetic factors are considered secondary diagnostic criteria effecting predisposition to Shoenfeld's syndrome [22]. Genetic association is mediated by HLA antigens involved in autoimmune disorders. Human leukocytal antigen system is a genomic locus of the major histocompatibility complex, the most polymorphous gene cluster of mammal genome [23]. The presence of HLA-DRB1, HLA-B27 and PTPN22 is the most common genetic background of ASIA-syndrome [15].

Epidemiology

The information on the epidemiology of the disease is scarce. Over a period from 2011 to 2016, there were more than 4000 documented ASIA-syndrome cases with various clinical severity and a various history of adjuvant exposure, a majority of which were associated with silicone implants and the use of cosmetic fillers containing mineral oils; by 2021, the number of cases doubled [24]. The mean age on onset was 37 years old, the majority of patients were women (89 %), and the average period between adjuvant stimuli and autoimmune conditions development was 16.8 months (range: 3 days to 5 years) [24].

ASIA-Syndrome in Connective Tissue Disorders:

Undifferentiated connective tissue disease

Undifferentiated connective tissue disease is an autoimmune disease and has non-specific signs and symptoms, the manifestation of which is associated with exposure to adjuvants. Undifferentiated connective tissue disease is the most common in patients who were vaccinated against hepatitis B virus [22, 25]. Studies of the effects of various adjuvants on patients with undifferentiated connective tissue disease vs. controls demonstrated that patients who had been exposed to adjuvants (vaccines or silicone) suffered from autoimmune complications or had a higher rate of typical symptoms of Shoenfeld's syndrome (general weakness, irritable bowel syndrome and fatigue) [14].

Systemic lupus erythematosus

Systemic lupus erythematosus is characterised by the presence of a wide array of autoantibodies in patients

with multisystemic involvement [26]. The possible pathogenesis mechanism is associated with mitochondrial DNA which is an autoimmune antigen and which can be targeted by autoantibodies [27]. A systemic review of selected studies and case control studies demonstrated that vaccines, specially hepatitis B and HPV vaccines, were associated with a higher risk of systemic lupus erythematosus [28]. Another study describes several various cases of disease after DTwP vaccination. The article demonstrates that aluminum adjuvant can initiate systemic lupus erythematosus by stimulating cell death, thus allowing free movement of nuclear antigens and potential activation of Toll-like receptors. Besides, aluminum-induced production of interleukin-6 can cause a cascade of reactions that eventually trigger autoantibody synthesis facilitating further disease progression [29].

Systemic sclerosis

Systemic sclerosis is a rare connective tissue disease associated with vasculomotor disorders, fibrosis and affected organ atrophy [30]. The main cause of disease is still unknown; however, it is assumed that this pathology is a result of environmental, autoimmune and genetic factors [31]. Certain HLA types were identified in systemic sclerosis [32], including HLA-DRB1, which was associated with ASIA-syndrome [22]. Various agents causing systemic sclerosis, such as CMV, Epstein-Barr virus and B19 parvovirus, as well as non-organic pathogens (quartz powder) or organic solvents, toluene, xylene, trichlorethylene and PVC [33], have been studied.

ASIA-Syndrome in Endocrine Disorders:

Primary adrenal insufficiency

Primary autoimmune adrenal insufficiency, or Addison disease, is a disease where adrenal cortex is unable to efficiently produce glucocorticoids and mineralocorticoids [33]. Clinical manifestations of this disease are fatigue, nausea, dizziness, tendency to consumer larger amounts of salt and skin and mucous hyperpigmentation [34]. Patients with Addison disease have anti-ferment-21-hydroxylase autoantibodies, a ferment participating in synthesis of adrenal hormones [35].

Literature sources describe association between adrenal insufficiency and exposure to adjuvants. A 9-year-old patient had adrenal insufficiency after hepatitis B vaccination [21]. There is a report on a 21-year-old patient who had adrenal crisis one week after flu + DTwP vaccination [36]. Since the patient did not have a history of adrenal insufficiency, but his blood draw showed a higher level of anti-ferment-21-hydroxylase autoantibodies, the patients was diagnosed with autoimmune Addison disease.

Type 1 diabetes mellitus

Type 1 diabetes mellitus is a disease associated with hyperglycemia resulting from immune-mediated destruction of insulin-secreting pancreatic β-cells by autoantibodies to Langerhans islet cells, insulin, glutamic acid decarboxylase and protein tyrosine phosphatase [37, 38].

In their paper, Ruhrman-Shahar N. et al. (2017) reported a case of a 14-year-old girl who had severe polydipsia, polyuria and weakness 3 weeks after DTwP vaccination [28]. The patient had autoantibodies to glutamic acid decarboxylase and islet cells and was diagnosed with type 1 diabetes mellitus. Of note, this case was one of the four other cases of patients who were vaccinated against DTwP and had autoimmune diseases. Also, in 1990s there were high rates of type 1 diabetes mellitus in children who were vaccinated with four doses of Hib vaccine at the age of 3, 4, 6, and 14 months, as compared to children who were vaccinated once at the age of 14 months [1].

ASIA-Syndrome in Neurological Disorders:

Myalgic encephalomyelitis/chronic fatigue syndrome

Fatigue of unknown origin lasting for over 6 months is a primary sign of myalgic encephalomyelitis and is associated with such symptoms as myalgia, arthralgia, impaired memory or attention concentration, headache, disturbing dreams, painfull lymph nodes and weakness after physical activity [39]. Idiopathic chronic fatigue syndrome is similar to post-infection fatigue; however, patients did not have pathogens, thus an idea of various pathogens and toxic compounds appeared [40]. For instance, vaccines which contain several components can induce chronic fatigue syndrome [40]. Currently, aluminum adjuvants in vaccines are believed to cause chronic fatigue syndrome [41].

Guillian-Barre syndrome

Guillian-Barre syndrome is an acute autoimmune neuromuscular disease that causes muscle weakness and palsy which can result in respiratory distress and death [41]. The cause-and-effect relationship between vaccines and Guillian-Barre syndrome was established back in 1970s during H1N1 vaccination in US army men.

According to the report, for every 100,000 vaccinated persons there was 1 case of Guillian-Barre syndrome, and the vaccination program was closed [5].

Multiple sclerosis

Multiple sclerosis is an autoimmune CNS disorder associated with amyelination and progressive palsy [42]. In 1994, France had a mass hepatitis B vaccination campaign as recommended by the World Health Organisation in early 1990s. Following the campaign, there were reports on onset or relapse of multiple sclerosis, and a hypothesis appeared that hepatitis B vaccine triggered cases of multiple sclerosis in vaccinated persons [43]. Recently, there have been discussions of multiple sclerosis progression in persons with risk factors after COVID-19 vaccination, requiring further studies [44].

Other Manifestations of ASIA-Syndrome

In addition to connective tissue, endocrine and neurological disorders, scientific literature describes non-Hodgkin lymphomas, sarcoidosis, orthostatic tachycardia, myositis, pulmonary fibrosis and Crohn's disease. Chronic immune system stimulation, exposure to silicone breast implants, hepatitis B vaccination, flu and DTwP vaccination were associated with the mentioned conditions [21, 45].

Prolonged immune system activation is considered the primary mechanism facilitating inflammatory reaction. Adjuvant-induced chronic stimulation is associated with a high risk of lymphoma. Following silicone implantation, chronic B-cell stimulation can result in pseudolymphoma progressing to well-defined non-Hodgkin lymphoma [45]. Besides, high non-Hodgkin lymphoma morbidity is observed in other autoimmune diseases, especially in Sjorgen's syndrome [46].

Thus, numerous autoimmune reactions associated with ASIA-syndrome develop after adjuvant entering into the body. Although the benefit of vaccines outweighs the risk of side effects, the role of adjuvants in autoimmune disease development should not be underestimated.

Conclusion

The article discusses the causes of development and a wide array of manifestations of ASIA-syndrome; it describes pathologies developing almost in any systems of a human body and demonstrates their correlation with autoimmune processes. Long before the term "Shoenfeld's syndrome" was introduced, clinical presentations of this condition were mentioned in literature; however, an approach for pathology diagnosis was not formulated in detail, and emerging symptoms were described as non-specific. ASIA-syndrome has definitely clarified the role of adjuvants in the development of autoimmune processes. It should be taken into account in the development of safe vaccines, silicone implants and other medical devices with minimal side effects. Also, healthcare professionals should raise patients' awareness of side effects of some cosmetic procedures and silicone implants. It is advisable and well-timed to include aetiology, pathogenesis, diagnosis and management of ASIA-syndrome as a separate nosological entity to academic and reference guides for students, registrars, postgraduates and various medical professionals.

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Заяева А.А. (ORCID ID: https://orcid.org/0000-0001-9147-8461): научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

Юнси С.И. Р. (ORCID ID: https://orcid.org/0000-0002-2361-8730): разработка дизайна и написание рукописи, редактирование статьи, поиск литературных источников, утверждение финального варианта рукописи

Заусалина А.И. (ORCID ID: https://orcid.org/0000-0003-3197-8055): разработка концепции, поиск литературных источников, редактирование статьи

Кошукова Г.Н. (ORCID ID: https://orcid.org/0000-0002-7467-7191): научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

Климчук А.В. (ORCID ID: https://orcid.org/0000-0003-1577-7077): научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

Юнси Г.А. (ORCID ID: https://orcid.org/0000-0003-2965-4975): научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Zayaeva A.A. (ORCID ID: https://orcid.org/0000-0001-9147-8461): scientific advice, editing the article, approval of the final version of the manuscript

Younsi S.I. R. (ORCID ID: https://orcid.org/0000-0002-2361-8730): development of the design and writing of the manuscript, editing the article, search for literary sources, approval of the final version of the manuscript

Zausalina A.I. (ORCID ID: https://orcid.org/0000-0003-3197-8055): development of the concept, search for literary sources, editing the article

Koshukova G.N. (ORCID ID: https://orcid.org/0000-0002-7467-7191): scientific advice, editing the article, approval of the final version of the manuscript

Klimchuk A.V. (ORCID ID: https://orcid.org/0000-0003-1577-7077): scientific advice, editing the article, approval of the final version of the manuscript

Younsi G.A. (ORCID ID: https://orcid.org/0000-0003-2965-4975): scientific advice, editing the article, approval of the final version of the manuscript

Список литературы / References:

1. Guimarães L.E., Baker B., Perricone C. et. al. Vaccines, adjuvants and autoimmunity. Pharmacol Res. 2015; 100: 190-209. doi: 10.1016/j.phrs.2015.08.003.
2. Tregoning J.S., Russell R.F., Kinnear E. Adjuvanted influenza vaccines. Hum Vaccin Immunother. 2018; 14(3): 550-564. doi: 10.1080/21645515.2017.1415684.
3. Segal Y., Dahan S., Sharif K. et. al. The value of Autoimmune Syndrome Induced by Adjuvant (ASIA) — Shedding light on orphan diseases in autoimmunity. Autoimmun Rev. 2018; 17(5): 440-448. doi: 10.1016/j.autrev.2017.11.037.
4. Watad A., Sharif K., Shoenfeld Y. The ASIA syndrome: basic concepts. Mediterr J Rheumatol. 2017; 28(2): 64-69. doi: 10.31138/mjr.28.2.64.
5. Sisti A., Huayllani M.T., Restrepo D.J. et. al. Oil injection for cosmetic enhancement of the upper extremities: a case report and review of literature. Acta Biomed. 2020; 91(3): e2020082. doi: 10.23750/abm.v91i3.8533.
6. Seida I., Seida R., Elsalti A. et. al. Vaccines and Autoimmunity-From Side Effects to ASIA Syndrome. Medicina (Kaunas). 2023; 59(2): 364. doi: 10.3390/medicina59020364.
7. Jara L.J., García-Collinot G., Medina G., et. al. Severe manifestations of autoimmune syndrome induced by adjuvants (Shoenfeld's syndrome). Immunol Res. 2017; 65(1): 8-16. doi: 10.1007/s12026-016-8811-0.
8. Blomberg J., Gottfries C.G., Elfaitouri A. et. al. Infection Elicited Autoimmunity and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: An Explanatory Model. Front Immunol. 2018; 9: 229. doi: 10.3389/fimmu.2018.00229.
9. Guo M., Liu X., Chen X., et. al. Insights into new-onset autoimmune diseases after COVID-19 vaccination. Autoimmun Rev. 2023; 22(7): 103340. doi: 10.1016/j.autrev.2023.103340.
10. Golomb B.A., Nguyen E., Dinkeloo E. Radiation Exposure Predicts Reported Vaccine Adverse Effects in Veterans with Gulf War Illness. Int J Environ Res Public Health. 2020; 17(19): 7136. doi: 11.3390/ijerph17197136. PMID: 33003502;
11. Nkiliza A., Joshi U., Evans J.E. et. al. Adaptive Immune Responses Associated with the Central Nervous System Pathology of Gulf War Illness. Neurosci Insights. 2021; 16: 26331055211018458. doi: 10.1177/26331055211018458.
12. Muñoz-Ortiz J., Gómez-López M.T., Echeverry-Hernández P. et. al. Dermatological and Ophthalmological Inflammatory, Infectious, and Tumoral Tattoo-Related Reactions: A Systematic Review. Perm J. 2021; 25: 20.225. doi: 10.7812/TPP/20.225.
13. Beutler B.D., Cohen P.R. Sarcoidosis in Melanoma Patients: Case Report and Literature Review. Cancers (Basel). 2015; 7(2): 1005-21. doi: 10.3390/cancers7020821.
14. Scanzi F., Andreoli L., Martinelli M., et. al. Are the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and the undifferentiated connective tissue disease (UCTD) related to each other? A case-control study of environmental exposures. Immunol Res. 2017; 65(1): 150-156. doi: 10.1007/s12026-017-8912-4.
15. Borba V., Malkova A., Basantsova N. et. al. Classical Examples of the Concept of the ASIA Syndrome. Biomolecules. 2020; 10(10): 1436. doi: 10.3390/biom10101436.
16. Perricone C., Colafrancesco S., Mazor R.D. et. al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects. J Autoimmun. 2013; 47: 1-16. doi: 10.1016/j.jaut.2013.10.004.
17. Halpert G., Amital H., Shoenfeld Y. Silicone Breast Illness as a Classical Example of Autoimmune/Inflammatory Syndrome Induced by Adjuvant (ASIA). Isr Med Assoc J. 2022; 24(6): 357-359.
18. Mahroum N., Elsalti A., Alwani A. et. al. The mosaic of autoimmunity — Finally discussing in person. The 13th international congress on autoimmunity 2022 (AUTO13) Athens. Autoimmun Rev. 2022; 21(10): 103166. doi: 10.1016/j.autrev.2022.103166.
19. Cohen Tervaert J.W., Kappel R.M. Silicone implant incompatibility syndrome (SIIS): a frequent cause of ASIA (Shoenfeld's syndrome). Immunol Res. 2013; 56(2-3): 293-8. doi: 10.1007/s12026-013-8401-3.
20. Oh J.H., Song S.Y., Lew D.H. et. al. Distant Migration of Multiple Siliconomas in Lower Extremities following Breast Implant Rupture: Case Report. Plast Reconstr Surg Glob Open. 2016; 4(10): e1011. doi: 10.1097/GOX.0000000000001011.
21. Watad A., Bragazzi N.L., Amital H., et. al. Hyperstimulation of Adaptive Immunity as the Common Pathway for Silicone Breast Implants, Autoimmunity, and Lymphoma of the Breast. Isr Med Assoc J. 2019; 21(8): 517-519.
22. Watad A., Quaresma M., Bragazzi N.L. et. al. The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry. Clin Rheumatol. 2018; 37(2): 483-493. doi: 10.1007/s10067-017-3748-9.
23. Trowsdale J., Knight J.C. Major histocompatibility complex genomics and human disease. Annu Rev Genomics

Hum Genet. 2013; 14: 301-23. doi: 10.1146/annurev-genom-091212-153455.
24. Cohen Tervaert J.W., Martinez-Lavin M., Jara L.J. et. al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) in 2023. Autoimmun Rev. 2023; 22(5):103287. doi: 10.1016/j.autrev.2023.103287.
25. Pepmueller P.H. Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology. Mo Med. 2016; 113(2): 136-40.
26. Xiao Z.X., Miller J.S., Zheng S.G. An updated advance of autoantibodies in autoimmune diseases. Autoimmun Rev. 2021; 20(2): 102743. doi: 10.1016/j.autrev.2020.102743.
27. Chen P.M., Tsokos G.C. Mitochondria in the Pathogenesis of Systemic Lupus Erythematosus. Curr Rheumatol Rep. 2022; 24(4): 88-95. doi: 10.1007/s11926-022-01063-9.
28. Wang B., Shao X., Wang D. et. al. Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: A systematic review and meta-analysis. Autoimmun Rev. 2017; 16(7): 756-765. doi: 10.1016/j.autrev.2017.05.012.
29. Ruhrman-Shahar N., Torres-Ruiz J., Rotman-Pikielny P. Autoimmune reaction after anti-tetanus vaccination-description of four cases and review of the literature. Immunol Res. 2017; 65(1): 157-163. doi: 10.1007/s12026-016-8822-x.
30. Denton C.P., Khanna D. Systemic sclerosis. Lancet. 2017; 390(10103): 1685-1699. doi: 10.1016/S0140-6736(17)30933-9.
31. Rubio-Rivas M., Moreno R., Corbella X. et. al. Occupational and environmental scleroderma. Systematic review and meta-analysis. Clin Rheumatol. 2017; 36(3): 569-582. doi: 10.1007/s10067-016-3533-1.
32. Silva I.S., Ferreira B.H., Almeida C.R. Molecular Mechanisms Behind the Role of Plasmacytoid Dendritic Cells in Systemic Sclerosis. Biology (Basel). 2023; 12(2): 285. doi: 10.3390/biology12020285.
33. Barthel A., Benker G., Berens K., An Update on Addison's Disease. Exp Clin Endocrinol Diabetes. 2019; 127(2-03): 165-175. doi: 10.1055/a-0804-2715.
34. Betterle C., Presotto F., Furmaniak J. Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. J Endocrinol Invest. 2019; 42(12): 1407-1433. doi: 10.1007/s40618-019-01079-6.
35. Saverino S., Falorni A. Autoimmune Addison's disease. Best Pract Res Clin Endocrinol Metab. 2020; 34(1): 101379. doi: 10.1016/j.beem.2020.101379.
36. Kamath S., Khabra J.K., Desai P. et. al. Adrenal Crisis Secondary to Influenza and Tetanus Vaccination in an Adult Without Known Adrenal Insufficiency: A Case of Autoimmune Adrenalitis. Cureus. 2021; 13(7): e16312. doi: 10.7759/cureus.16312.
37. Liu J., Zhang B., Zhu G. et. al. Discovering genetic linkage between periodontitis and type 1 diabetes: A bioinformatics study. Front Genet. 2023; 14: 1147819. doi: 10.3389/fgene.2023.1147819.
38. Rai U., Senapati D., Arora M.K. Insights on the role of anti-inflammatory and immunosuppressive agents in the amelioration of diabetes. Diabetol Int. 2022; 14(2): 134-144. doi: 10.1007/s13340-022-00607-9.
39. Tschopp R., König R.S., Rejmer P. et. al. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A preliminary survey among patients in Switzerland. Heliyon. 2023; 9(5): e15595. doi: 10.1016/j.heliyon.2023.e15595.
40. Gherardi R.K., Crépeaux G., Authier F.J. Myalgia and chronic fatigue syndrome following immunization: macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system. Autoimmun Rev. 2019; 18(7): 691-705. doi: 10.1016/j.autrev.2019.05.006.
41. Rigolet M., Aouizerate J., Couette M., et. al. Clinical features in patients with long-lasting macrophagic myofasciitis. Front Neurol. 2014; 5: 230. doi: 10.3389/fneur.2014.00230.
42. Dobson R., Giovannoni G. Multiple sclerosis — a review. Eur J Neurol. 2019;26(1):27-40. doi: 10.1111/ene.13819.
43. Stowe J., Andrews N., Miller E. Do Vaccines Trigger Neurological Diseases? Epidemiological Evaluation of Vaccination and Neurological Diseases Using Examples of Multiple Sclerosis, Guillain-Barré Syndrome and Narcolepsy. CNS Drugs. 2020; 34(1): 1-8. doi: 10.1007/s40263-019-00670-y.
44. Alluqmani M. New Onset Multiple Sclerosis Post–COVID-19 Vaccination and Correlation With Possible Predictors in a Case-Control Study. Cureus. 2023;15(3):e36323. doi:10.7759/cureus.36323.
45. Butnaru D., Shoenfeld Y. Adjuvants and lymphoma risk as part of the ASIA spectrum. Immunol Res. 2015; 61(1-2): 79-89. doi: 10.1007/s12026-014-8622-0.
46. Colafrancesco S, Perricone C, Shoenfeld Y. Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Sjögren's Syndrome. Isr Med Assoc J. 2016; 18(3-4): 150-3.