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## THE LATEST STATISTICAL ANALYSIS AND ETIOPATHOGENESIS OF ASIA-SYNDROME

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Annotation: ASIA-syndrome (autoimmune syndrome caused by adjuvants) was first described by the Israeli immunologist I. Schoenfeld in 2011. The second, eponymous name of the pathology is Schonfeld's syndrome. The disease is the subject of ongoing discussions in the scientific community. To date, no clear criteria have been developed and no indisputable evidence of its existence has been presented, and nosology itself is not included in ICD-10. Schonfeld and his followers are accused of anti-vaccination propaganda. At the same time, more than 4 thousand clinical cases of ASIA syndrome have already been described, dozens of articles and discussions at international congresses have been devoted to it.

**Key words:** ASIA syndrome, immunomodulatory, acrylic hydrogels caused.

The development of ASIA syndrome is associated with the ingestion of adjuvants and the appearance of a hyperergic immune response. Adjuvants are chemicals that can enhance and prolong the antigen-specific immune response, but do not have to have their own immunoreactivity. As such compounds in the modern pharmaceutical industry, aluminum, silicon, squalene, silicone, and many other components that are part of vaccines, implants, and fillers are most often used.

According to modern concepts, ASIA syndrome develops as a result of the presence of an individual genetic predisposition due to the carrier of certain mutations of HLA genes (HLA-DRB1, HLA-DRB4, HLA-DQA1, HLA-DQB1, etc.). The direct causes of ASIA-syndrome are::

- Immunization. The question of whether vaccine adjuvants can cause autoimmune disorders is highly controversial. On the one hand, there are studies that reliably refute the association of vaccination with SLE, multiple sclerosis, diabetes, and other autoimmune pathologies. Meanwhile, proponents of ASIA-syndrome point to the existing relationship between vaccination against HPV, hepatitis B, influenza and other infections and the development of autoimmune reactions.
- Implantation of silicone prostheses. Silicone implants used for breast augmentation, buttocks, and lower legs have a certain immunogenicity, causing an increase in the level of CRP, RF, pro-inflammatory factors, and autoantibodies. Local reactions are represented by rejection of the implant or the formation of a fibrous capsule. In recent years, people are increasingly talking about breast implant disease, although not all experts recognize the fact of its existence.
- Injections of hyaluronic acid. Clinical observations are described when subcutaneous administration of hyaluronic acid alone or in combination with acrylic hydrogels caused the development of collagenosis, autoimmune thyropathies.
- Tattooing. Some pigments contained in permanent makeup dyes can cause systemic reactions such as vasculitis, nephrotic syndrome, and granulomatous lung damage.

The mechanism of occurrence of ASIA-syndrome is insufficiently studied. It is assumed that adjuvants cause immunological reactions in several ways. Being non-immunogenic in nature, these excipients contribute to the deposition of antigens with which they are associated at the injection site and prolonged antibody synthesis. Some adjuvants stimulate the production of pro-inflammatory factors: cytokines, chemokines, interleukins (IL-1b, IL-4, IL-6, IL-12, IL-18), which support the chronic inflammatory response.

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In addition, adjuvants can induce humoral immunity by stimulating Th2-lymphocytes. Finally, adjuvants can directly activate the major histocompatibility complex in genetically predisposed individuals.

Classification

The term "ASIA-syndrome" combines a group of independent syndromes that have their own causes and clinical manifestations. A common criterion for them is the supposed connection with the introduction of adjuvant substances into the body that provoke an autoimmune reaction. There are 5 forms of ASIA-syndrome.

- 1. Siliconosis. Occurs in less than 1% of patients within 6-15 years after implant placement. Implant ruptures and gel migration increase the risk of autoimmune diseases. Silicon compounds present in silicone prostheses can contribute to the development of skin and lung sarcoidosis, rheumatoid arthritis, Shagreen disease, and systemic vasculitis.
- 2. Post-vaccination phenomenon. It is associated with the presence of adjuvants such as aluminum hydroxide in vaccine preparations. The manifestations of ASIA include:
- Guillain-Barre syndrome that develops after the introduction of an anti-influenza and anti-hepatitis vaccine;
- rheumatoid arthritis on the background of immunization against tick-borne encephalitis, influenza;
- SLE associated with immunization against HPV, rubella, measles, tuberculosis, and hepatitis B.
- 3. Macrophage myofascial syndrome. It is believed that the surge in the incidence of macrophage myofasciitis is associated with the transition to mass administration of vaccines to the deltoid muscle and quadriceps of the thigh. This explains the typical localization of local inflammation, specific histological findings (deposits of aluminum hydroxide nanocrystals). It is noted in patients after vaccination for hepatitis A, B, tetanus.
- 4. "sick building" syndrome. This phenomenon is mentioned if at least 20% of people experience similar pathological symptoms when they are in the same room. It occurs more often in office workers, sometimes in residents of the same building. Among the most common complaints are lacrimation, nasal congestion, itchy and dry skin, and drowsiness. It is assumed that this variant of ASIA syndrome is associated with chemicals used in air conditioning systems, possibly mold antigens, phthalates.
- 5. Gulf War syndrome. It was first recorded in military personnel who took part in combat operations in this region in 1991. The cause of this syndrome, which was accompanied by muscle and joint pain, ataxia, cephalgia, fever, skin rashes, gastrointestinal disorders, and sleep disorders, is considered to be multiple vaccinations of the military in combination with psychological stress and increased physical exertion.

**Symptoms** 

Signs of ASIA-syndrome can develop in a wide time frame-from 2 days to 20 or more years after the intended exposure (immunization, augmentation mammoplasty, administration of hyaluronic acid, tutuage). Early complaints are non-specific, including unexplained weakness, persistent subfebrility, arthralgia of various localization or polyarthritis, pain in the muscles and spine. In the future, asthenia increases, insomnia, shortness of breath may bother.

Some patients with various variants of ASIA-syndrome complain of the appearance of hemorrhagic rash on the skin, dry mouth, hair loss, brittle nails. Sometimes there is a Raynaud's phenomenon. Irritable bowel syndrome may occur. At a later stage, there may be amnesia, cognitive decline, as a result of demyelination.

A distinctive feature of ASIA-syndrome is the regression of most clinical and laboratory manifestations after removal of the provoking agent (silicone, pigment, etc.).

Complications

Россия - Узбекистан, 2024

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From the moment the first signs of Schonfeld syndrome appear to its diagnosis, years and decades pass. All this time, patients receive inadequate treatment, endure frequent hospitalizations, and suffer from a decrease in the quality of life. ASIA-syndrome can lead to the manifestation of various autoimmune pathologies: systemic vasculitis, rheumatoid arthritis, SLE, Sjogren's disease, multiple sclerosis. The prolonged presence of adjuvants in the body (for example, silicone implants) is accompanied by constant stimulation of immune responses, which is a risk factor for the occurrence of pseudolymphoma, as well as non-Hodgkin's lymphoma.

## Diagnostics

Immunologists and rheumatologists are involved in the examination and observation of patients with manifestations of ASIA syndrome. Currently, special criteria are proposed for the diagnosis of this pathology. Mandatory criteria include:

- association of symptoms with external influences (infection, immunization, silicone injection);
- muscle syndrome (myalgia, myositis, paresis);
- joint syndrome (arthralgia, arthritis);
- asthenia (fatigue, weakness, sleep disorders);
- psychopathological manifestations (memory disorder, cognitive deficits);
- pyrexia;
- xerostomia.

Small criteria for ASIA-syndrome include detection of At to the intended adjuvant, specific HLA halotypes, signs of systemic diseases, and other manifestations (IBS).

- 1. Study of blood parameters. ESR is increased in the blood, positive CRP is detected, the level of fibrinogen, LDH, ALP is increased. Markers of autoimmune diseases (anti-CCP, antinuclear factor, At to dsDNA, RF, At to Sm antigen, etc.) are often detected.
- 2. Tissue biopsy. Biopsies of the skin, muscles, blood vessels, lymph nodes, and sometimes internal organs are examined. In the focus of adjuvant administration, a characteristic histological picture of immune inflammation develops: lymphohistiocytic tissue infiltration, scleroid and granulomatous changes.
- 3. Instrumental research. To assess the integrity of breast implants, ultrasound of the mammary glands is performed, and if necessary, MRI monitoring is performed. If the internal organs are affected, ultrasound of the kidneys and CT of the lungs are prescribed. In Raynaud's syndrome, capillaroscopy is performed.

## Treatment of ASIA-syndrome

To eliminate pathological symptoms, it is necessary to eliminate the provoking factor (remove implants and fillers, abandon the use of air conditioning, change the place of work/residence). NSAIDs (nimesulide, etoricoxib, ibuprofen) are used to relieve symptoms. If necessary, pulse therapy with methylprednisolone, penicillamine, and antimetabolites (methotrexate) are added to the basic anti-inflammatory therapy scheme.

# Prognosis and prevention

The correlation between ASIA syndrome and adjuvant administration needs to be further studied and recognized by the medical community. To date, the effect of adjuvants on the development of systemic diseases remains unproven. The ASIA syndrome clinic often disappears after the trigger is eliminated. However, the FDA recommends that plastic surgeons opt out of silicone gel breast implants due to their high immunogenicity in favor of saline-based implants. Before medical manipulations involving the introduction of foreign substances, it is necessary to conduct a thorough immunological examination of patients.

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