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ASIA or Shoenfeld's syndrome: a novel autoimmune syndrome?

Could it be that Gulf War Syndrome (GWS), which debilitated American and British veterans of operations Desert Shield and Desert Storm, and the *scleroderma-like* reactions of patients who received silicone implantations in the 1990s constitute manifestations of the same illness? What might they have in common with a rare myopathic syndrome induced by aluminum and described for the first time in France in 1998? The logical response was suggested from clinical observations and innovative research at the Tel-Hashomer Autoimmune Disease Center in Israel and it is very simple: etiopathogenesis.[1]

These distinct and enigmatic autoimmune conditions, separated by time and geographic distance, have been classified as one syndrome: the autoimmune/inflammatory syndrome induced by adjuvants, or ASIA. An article on ASIA was recently published in a prestigious and high-impact journal in the field, namely the *Journal of* Autoimmunity.[1] ASIA is an appropriate acronym, since Asia is the largest and most populous continent on the planet, whose cultures are mysterious to those who have not opened their eyes and mind to its diversity.

Adjuvants include environment compounds that have been recognized for decades as autoimmunity inducers in different animal models and that are used in the pharmaceutical industry to develop antigenicity and to decrease the cost of vaccine production. Adjuvants, as it is already known, can trigger the development of inflammatory or autoimmune illnesses in genetically susceptible humans.[2,3] Among this large group, which includes infectious fragments, hormones, aluminum, silicone, squalene has recently been highlighted. It is a natural oil obtained from shark tissue and constitutes one of the principal adjuvants used in the anti-influenza vaccine.[4]

GWS was first described in 1998[5] in war veterans who did not suffer from classic rheumatic illnesses, but presented with symptoms characteristic of these disorders, such as arthralgia, myalgia, lymphadenopathy, chronic fatigue, facial flushing and autoimmune thyroid disease.

A double-blind cohort study completed about 10 years ago by a New Orleans group[6] presented a surprising outcome with respect to GWS. This study compared dosages of anti-squalene antibody serum in 114 Gulf War veterans and non-combat military employees (some healthy and some ill) with a control group comprised of 48 blood donors, 40 asymptomatic patients with systematic lupus erythematosis, 34 patients with silicone breast implants and 30 patients with chronic fatigue syndrome. None of the patients from the control group, even those with active autoimmune disease, presented detectable anti-squalene antibodies in their serum, whereas 95% of the military group presented positive antibodies. Among the latter, 100% of those patients who presented with symptoms of Gulf War syndrome, independent of their combat status, presented with anti-squalene antibodies. On the other hand, this antibody was not detected in any of the veterans who did not present with symptoms. The authors suggested then that GWS was not the result of exposure to chemical or biological weapons or post-traumatic stress but to immune disequilibrium caused by an intense vaccine regimen which, whether they were combatants or not, all military individuals received during the conflict preparation period. This also clarifies other findings[4] of hypergammaglobulinemia and abnormal levels of acute phase proteins found in 45% of patients with GWS.

It should be highlighted that the real health concerns of the anti-Iraqi troops in this conflict were not infectious disease epidemics such as trench illness (a fever related to ticks) or those similar to the sudden outbreak of the Spanish flu that occurred during the first and between the two World

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Wars. The concerns did not even include trauma from firearm and explosives as in the second war or the consequences of stimulant abuse and other substances in the Vietnam War. In the gulf, the greatest enemy was the desert heat and thirst. Maintaining the quality of available drinking water was as essential as good military strategy to ensure a low number of casualties for the Western contingent.

It is ironic that more soldiers have become ill due to an oily adjuvant injected as part of a complex immunoprotector than from braving the hostile environment and fighting against armed enemies who disputed the local petroleum reserves.

Siliconosis, as the fibrosing tissue reaction similar to a limited form of scleroderma became known, with its general systemic symptoms associated with cosmetic implantations, challenged the international scientific community to unravel its pathophysiological mechanisms. In the beginning of the 1990s, silicone was considered to be an inert material, and therefore incapable of triggering immune phenomena. Recent meta-analyses estimate the prevalence of developing connective tissue disease after silicone implantation at only 0.8%, very close to that of the general population. However, these studies only admitted patients who met criteria for known autoimmune diseases. They did not consider patients with less specific manifestations that did not fit the profile of a known condition, such as arthralgia, myalgia, or even neurological manifestations.

Macrophagic myofascitis, the post-vaccine muscular disease described by the French researchers, Gehard *et al*., in 1998[7] is interesting for its well documented histopathological changes. In macrophagic myofascitis, there are cytoplasmic inclusions of aluminum, which is used as an adjuvant in various vaccines. It has systemic manifestations that includes marked asthenia, chronic fatigue, myalgia, arthralgia, fever and, in some cases, demyelinating polyradiculoneuropathy, which is clinically similar to Guillain-Barré disease with documented electromyography changes. The patients presented with elevated acute phase proteins and creatine kinase (CK) levels. This research group[8] also garnered support for the theory that the rarity of complications was due to genetic susceptibility, as only patients with a HLA DRB1*01 profile developed the illness. Moreover, in 2002[8] the persistence of aluminum adjuvant deposits in the site of application for up to 10 years post-immunization was verified, which could explain the persistence of the muscular illness in patients.

Some patients with autoimmune disease and allergic profiles showed trigger reactions with the reactivation of the base illness when they were vaccinated with the common anti-influenza H1N1 vaccine, which is rich in squalene and aluminum as adjuvants. However, those who received the vaccine without adjuvants, such as pregnant patients, did not present with such alterations. These findings also give rise to debate regarding the creation of specific vaccine security recommendations for patients with rheumatic illnesses. Finally, the work of Shoenfeld[1] has led to the suggested ASIA diagnosis criteria (Table 1), which are as yet invalid but can assist immediately in the recognition of the disorder and guide future studies on it.

Table 1. Criteria suggested by Shoenfeld for ASIA diagnosis

Major criteria:
• Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations. • Appearance of one of the clinical manifestations listed below: - Myalgia, myositis, or muscular weakness; - Arthralgia and/or arthritis; - Chronic fatigue, non-restful sleep, or sleep disturbances; - Neurological manifestations (especially those associated with demyelization); - Cognitive alterations, loss of memory; - Fever, dry mouth; • Removal of the initiating agent induces improvement. • Typical biopsy of the involved organs.
Minor criteria:
• Appearance of autoantibodies directed against the suspected adjuvant. • Other clinical manifestations (e.g., irritable bowl syndrome). • Specific HLA (e.g., HLA DRB1, HLA DQB1). • Initiation of an autoimmune illness (e.g., multiple sclerosis, systemic sclerosis).

For the diagnosis of ASIA, there must be the presence of at least 2 major or 1 major and 2 minor criteria.

This editorial intends to propose a new name for ASIA, Shoenfeld syndrome, in reference to the author who studied and described in an unprecedented form the nature of these events, which were previously distinguished from one another and recognized as heterogeneous. Moreover, Shoenfeld acknowledged the important relations of the disease with environmental influence studies in the etiopathogenesis and prognosis of autoimmune diseases. The authors also propose that the diagnostic criteria for this syndrome are henceforth referred to as the Shoenfeld criteria.

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