



## Review

## Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects



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## ABSTRACT

In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves both in animal models and in humans: for instance, silicone was associated with siliconosis, aluminum hydroxide with post-vaccination phenomena and macrophagic myofasciitis syndrome. Several mechanisms have been hypothesized to be involved in the onset of adjuvant-induced autoimmunity; a genetic favorable background plays a key role in the appearance on such vaccine-related diseases and also justifies the rarity of these phenomena. This paper will focus on protean facets which are part of ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to the autoimmune/inflammatory response. The data herein illustrate the critical role of environmental factors in the induction of autoimmunity. Indeed, it is the interplay of genetic susceptibility and environment that is the major player for the initiation of breach of tolerance.

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### 1. Introduction

Shoenfeld and Agmon-Levin recently coined the term "ASIA—Autoimmune/inflammatory Syndrome Induced by Adjuvants" [1] to describe an "umbrella" for clinical conditions namely siliconosis, Gulf War Syndrome (GWS), Macrophage Myofasciitis Syndrome (MMF), sick building syndrome (SBS) and post-vaccination phenomena which share similar signs or symptoms [2–6]. The most frequently reported symptoms include myalgia, myositis, arthralgia, neurological manifestations, fever, dry mouth and cognitive alterations. Moreover, really common is the presence of chronic fatigue syndrome (CFS) [7], often associated with sleep disturbances or non-restful sleep. These shared symptoms suggested the presence of a common denominator which has been subsequently identified in the adjuvant. The adjuvant is defined as

"any substance that acts to accelerate, prolong, or enhance antigen-specific immune response" [8]. It is an agent that may stimulate the immune system and increase the response to a vaccine, without having any specific antigenic effect in itself. The abovementioned syndromes, are immune mediated conditions that appear following a chronic stimulation of the immune system by agents with adjuvant characteristics. The prevalence of immune mediated conditions is rising in different geographical areas and these geo-epidemiological changes may be explained by a complex of genetic and environmental factors [9,10]. While specific genetic compositions may predispose to the emergence of an autoimmune or an auto-inflammatory syndrome, the presence of an external or endogenous environmental factor, recently called "exosome" [11], is essential for triggering the immune response itself. The presence of a favorable genetic background as a prerequisite for the development of such conditions explains why they are so rare [12]. It also clarifies why physicians should be aware of the possible complications that may occur post vaccination, in these specific individuals [13]. Silicone, alum, pristane and infectious components are some of the environmental factors that comprise an immune

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