



Autoimmune or auto-inflammatory syndrome induced by adjuvants (ASIA): Old truths and a new syndrome?

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ABSTRACT

There has been considerable interest in the role of environmental factors and the induction of autoimmunity and the ways by which they facilitate loss of tolerance. Clearly both genetic and environmental factors are incriminated, as evidenced by the lack of concordance in identical twins and the relatively recent identification of the shared epitope in rheumatoid arthritis. In this issue a new syndrome called 'Asia'-autoimmune/auto-inflammatory syndrome induced by adjuvants has been proposed. It is an intriguing issue and one that is likely to be provocative and lead to further biologic and molecular investigations.

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A syndrome defines a collection of signs and symptoms that often occur together in the same individuals. Its characteristics may share a common etio-pathogenesis or may be induced by a number of different primary causes that give rise to the same clinical manifestations. Once a syndrome has been delineated the presence of one feature alerts the physician to the presence of another, thus enabling early diagnosis and in some cases early administration of the appropriate treatment. In the current journal Shoenfeld and Agmon-Levin [1] describe a new syndrome termed 'ASIA'- autoimmune/auto-inflammatory syndrome induced by adjuvants. This new syndrome takes in four well known medical conditions namely post-vaccination adverse events, exposure to silicone implants, the Gulf war syndrome and macrophagic myofasciitis, all of which share similar clinical manifestations as well as previous exposure to immune adjuvants.

In the last decade the plausible association between vaccines, silicone and other environmental factors with immune mediated conditions has raised concerns addressed both by the medical and legal communities [2–4]. Although numerous studies, case reports and case series described such associations it has remained difficult if not impossible to prove a cause and effect relationship between those plausible triggers and autoimmune or auto-inflammatory diseases [2,5–7]. In the aim of proving a causal association large epidemiological studies have been performed, and in several cases such as the link between the "swine flu" vaccine and Guillain-Barré

syndrome, a causal association was accepted [2,8]. However the rarity of events as well as the search for defined autoimmune diseases has yielded conflicting results [9].

In contrast to the controversy regarding defined diseases, a relationship between certain environmental factors and a particular set of symptoms, which do not fulfill diagnostic criteria of a specific disease, has been reported. For instance, although the interaction between silicone breast implants and defined autoimmune diseases remained controversial [7], a statistical significant link between breast implantation and a constellation of symptoms was documented leading to the definition of "siliconosis" as a silicone-implant related disease [10–12].

Another epidemiological impediment is the time period between exposure to a plausible trigger and the appearance or diagnosis of a medical condition. Previously only a latency period of several weeks was accepted, resulting from the known classical association between streptococcal infection and rheumatic fever [13]. However, both infectious agents and other environmental factors were found to be linked with autoimmunity months and even years following exposure [13–15]. In their manuscript Shoenfeld and Agmon-Levin [1] review cases of MMF and post-vaccination adverse events diagnosed 3–8 years subsequent to exposure. Thus, the question raised by authors is whether epidemiological studies addressing these interactions do need longer follow up periods.

Immune mechanisms are activated by various environmental triggers. Exposure to adjuvants set in motion both the innate and adaptive immune responses [16–18]. In most cases these are desirable ones (i.e. immune response to vaccination) but dangerous responses may also be observed. Such adjuvant "side-effects" can be

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found in animal models too as reviewed by Shoenfeld and Agmon-Levin [1,19,20]. In the four medical conditions included under the new syndrome 'ASIA', past exposure to adjuvants was obvious and a role for such an exposition was suggested. However, "natural adjuvants" contained in our food, indoor and outdoor substances (i.e. plastic, air pollution) as well as following an infection are hard to trace [17,21–24]. So, the other point raised by the paper is whether we should look at other conditions displaying comparable clinical manifestations fitting with the picture of ASIA in order to put them under the umbrella of this newly born syndrome.

The mechanisms by which ASIA-related symptoms are triggered (i.e. cognitive impairment, joint pain) are unknown, yet for several of them an adjuvant effect was put forward. This may be the case of aluminum. Aluminum is in fact the most widely distributed metal in our environment and it is the most common adjuvant used in human vaccine. Chronic exposure of animals to aluminum is associated with behavioral, neuropathological and neurochemical changes [25]. Several epidemiological studies have also shown poor performance in cognitive tests and a higher abundance of neurological symptoms for workers occupationally exposed to aluminum [26].

Adjuvants may apparently play a major role in inducing the ASIA manifestations. However, we do not know whether the concomitant exposure to adjuvants and to other environmental agents (infectious?) is the real trigger mechanism.

The rarity of the events does suggest a role for an individual susceptibility. So, while the risk of these side effects does not overcome the beneficial effects of adjuvants in vaccines, unrevealing environmental factors and their mechanisms of adjuvancy may enable the identification of individuals at risk (e.g. genetic risk factors). This implies preventive measurements and development of specific therapies such as extraction of silicone implants or future modulation of immune mediated pathways (i.e. TLR).

The clinical and epidemiological observation by Shoenfeld and Agmon-Levin [1] is bright and provocative. It should be noted that the recent Congress of Autoimmunity in Slovenia was devoted to environmental factors and autoimmunity and led to a dedicated issue that focused on this theme, including not only the role of environmental factors, but also the genetic interactions with those factors [27–67].

We need now to support it from a biological point of view by investigating the molecular mechanisms that are behind and the possible biomarkers of ASIA as well as their correlation with the symptoms.

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