EXPERT REVIEWS

# Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum

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Olga Vera-Lastra[1,2], Gabriela Medina[1,2], Maria Del Pilar Cruz-Dominguez[1,2], Luis J Jara[1,2] and Yehuda Shoenfeld*[3,4]

[1]*Hospital de Especialidades Centro Médico La Raza, Instituto Mexicano del Seguro Social, Mexico City, Mexico*
[2]*Universidad Nacional Autónoma de México, Mexico City, Mexico*
[3]*Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center (affiliated to Tel-Aviv University), Tel-Hashomer, Israel*
[4]*Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Tel-Aviv University, Tel-Aviv, Israel*
**Author for correspondence: shoenfel@post.tau.ac.il*

An adjuvant is a substance that enhances the antigen-specific immune response, induces the release of inflammatory cytokines, and interacts with Toll-like receptors and the NALP3 inflammasome. The immunological consequence of these actions is to stimulate the innate and adaptive immune response. The activation of the immune system by adjuvants, a desirable effect, could trigger manifestations of autoimmunity or autoimmune disease. Recently, a new syndrome was introduced, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), that includes postvaccination phenomena, macrophagic myofasciitis, Gulf War syndrome and siliconosis. This syndrome is characterized by nonspecific and specific manifestations of autoimmune disease. The main substances associated with ASIA are squalene (Gulf War syndrome), aluminum hydroxide (postvaccination phenomena, macrophagic myofasciitis) and silicone with siliconosis. Mineral oil, guaiacol and iodine gadital are also associated with ASIA. The following review describes the wide clinical spectrum and pathogenesis of ASIA including defined autoimmune diseases and nonspecific autoimmune manifestations, as well as the outlook of future research in this field.

**Keywords:** ASIA • environmental factors • Gulf War syndrome • human adjuvant disease • macrophagic myofasciitis syndrome • mineral oil • postvaccination phenomena • silicone

Autoimmune diseases (AID) are the result of interactions between genetic and environmental factors with innate and adaptive immune activation response. In relation to environment, an important problem is to identify the criteria of patients in whom it plays a causative role [1].

Recent findings from a National Institute of Environmental Health Sciences Expert Panel Workshop concluded that crystalline silica, solvents, smoking and UV radiation exposure can contribute to the development of several AID [2]. In experimental models, chemical, physical and biological agents induce and/or exacerbate autoimmunity. Examples include mercury, pristane, silica, gold, UV radiation and infection with *Streptococcus* or Coxsackie B virus and so on [3].

Recently, a new syndrome was introduced termed autoimmune/inflammatory syndrome induced by adjuvants (ASIA). The environmental factors that participate in ASIA are squalene associated with Gulf War syndrome (GWS), aluminum hydroxide (Alum) with postvaccination phenomena and macrophagic myofasciitis syndrome (MMF) and silicone with siliconosis [4]. In addition, environmental factors that include mineral oil, guaiacol (metoxiphenol) and iodine gadital (this substance is a mix of guaifenasine, proxyphylline, maleate of clorphenamine [mucolytic, bronchodilator, antihistaminic, respectively]) plus mineral oil are associated with new models of ASIA [5]. The aim of this review is to analyze the role of environmental factors in the pathogenesis and the clinical spectrum of ASIA. In this review, the main clinical syndromes discussed are:

- Postvaccination phenomena associated with rheumatic diseases that include vasculitis, systemic lupus erythematosus (SLE), inflammatory myopathy (IM), and rheumatoid

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arthritis (RA). Neurological syndromes: Guillain-Barré syndrome (GBS), narcolepsy, multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), transverse myelitis (TM). Gastrointestinal syndrome: inflammatory bowel disease (IBD);

- MMF;
- GWS;
- Siliconosis associated with systemic sclerosis (SSc) and other AID;
- Mineral oil and other inducers of AID.

## Environmental factors in ASIA

The most widely accepted environmental conditions that trigger autoimmunity through epigenetic mechanisms are drugs, pollutants, viruses and other pathogens, sex hormones, radiation, heavy metals and stress. The development of AID after exposure to environmental factors can be mediated by a variety of mechanisms such as T-cell dysregulation, nonspecific activation of the immune system, release of cryptic antigens, altered structure or expression of autoantigens, antiapoptotic effects on autoreactive cells, molecular mimicry and immunological crossreactivity, to name a few [6,7].

The major mechanisms of epigenetic gene regulation include DNA methylation and histone modification. In these cases, gene expression is modified without involving changes in DNA sequence. Aluminum is known to have a genotoxic profile, capable of causing both DNA alterations and epigenetic effects. Several new findings about epigenetic modifications of gene expression have been reported in different AID [8,9]. In this context, ASIA emerged as a new syndrome that included four conditions: siliconosis, the GWS, the MMF and postvaccination phenomena. All these conditions are linked with previous exposure to an adjuvant. Furthermore, these four diseases share a similar complex of signs and symptoms, which further supports a common denominator [10]. Environmental factors that include mineral oil, guaiacol and iodine gadital also share a similar clinical picture, and they could be considered as new models of ASIA [5]. In relation with ASIA and epigenetics, there are no studies that support the epigenetic regulation. Therefore, it is important to analyze the immunologic mechanisms that support the link between environmental factors (adjuvants) and the clinical manifestations of ASIA.

## Immunological mechanisms of adjuvants in ASIA

Various adjuvants used in vaccines enhance a specific immune response against antigens and may produce autoimmunity and AID both in experimental models and humans.

Regarding humoral and cellular immunity, some possible mechanisms have been proposed to explain how the adjuvants interact with the immune system:

- Induction of a progressive release of the antigen (Ag) enhancing antibody production, blocking its clearance and leading to a longer exposure of it to antigen-presenting cells (APCs);
- Promotion of the translocation of Ag to lymph nodes where Ag can be recognized by T cells;
- Conversion from soluble Ag into a particulate form. which is phagocytosed by APCs, for example macrophages, dendritic cells (DCs) and B cells;
- Increase in local reactions at the site of injection by simulating danger signals;
- Induction of the release of inflammatory cytokines;
- Interaction with Toll-like receptors (TLRs) and nucleotide oligomerization domain-like receptors including the NALP3 inflammasome [11,12].

Regarding cell-mediated immunity, $CD8^+$ cytotoxic T-lymphocyte responses to polypeptide and protein Ags are poorly induced by Alum. Concerning the proliferative responses of $CD4^+$ T cells, as well as Th2 cytokine production, these are enhanced in murine and human studies suggesting that alum increases humoral immunity by providing Th2 cell help to follicular B cells. Many agents with adjuvant activity, such as bacterial endotoxin, Freund's adjuvant and others, increase immunity through induction of DCs' maturation. There is less information about how Alum-containing adjuvants can stimulate DCs' mobilization and maturation. The response of DCs is a bridge between innate and adaptive immunity [11].

## Main adjuvants in ASIA

The principal environmental factors associated to ASIA are Alum, silicone, squalene, mineral oil, guaiacol and iodine gadital, and these are analyzed in the following sections.

### *Aluminum hydroxide*

Alum is the adjuvant most often used in vaccines, but the mechanisms by which it works are complex and little known. Alum adjuvants are good humoral immune potentiators in vaccine formulations. This property has recently been attributed to NLRP3 inflammasome activation. The inflammasome is an intracellular multiprotein complex that mediates caspase-1 cleavage of the inactive precursor of the proinflammatory cytokine IL-1β, leading to the release of mature IL-1β. Inflammasome-mediated cleavage of pro-IL-1β *in vitro* depends on signals that activate both TLR and nucleotide oligomerization domain-like receptors, such as NLRP3. Activation of these innate immune system receptors is now recognized as a step for effective adaptive immunity through a combination of stimuli for naive T cells [13]. The aluminum salts induce humoral immunity via Th2 responses but have less effect on cell-mediated immunity, and therefore are not useful in vaccines directed against intracellular pathogens.

### *Oil injection & other foreign substances*

Mineral oil is considered 'nontoxic' and has been used widely for many purposes. There is some evidence that mineral oil exposure may be associated with human disease. Subcutaneous injection of mineral oil induces a chronic local inflammatory reaction

(sclerosing lipogranulomas). It has been shown that medicinal mineral oil promotes anti-chromatin/DNA autoantibody production even more efficiently than squalene or incomplete Freund adjuvant (IFA), suggesting that different types of autoantibodies could be produced in response to different hydrocarbons [14].

Adjuvants that use oil for experimental studies are IFA, which is a mix of paraffin oil and a surfactant, and complete Freund adjuvant, which is created by adding killed mycobacteria (*Mycobacterium tuberculosis*) to IFA. Both are strongly immunogenic, but only complete Freund adjuvant induces a Th1 response. Another adjuvant that uses oil is MF59, which was recently approved for use in humans, and has replaced Alum in several influenza vaccines (Inf-V) and has shown significant immunogenicity [15].

In Mexico, there is a common practice of illegal use of mineral oil for cosmetic purposes, and the authors consider that this is a human-model-like IFA. In recent times, it has been reported that the injection of oil substances induces AID [5]. The result of oil injection is chronic inflammation with granuloma formation. At the dermis level, there is thickening with accumulation of collagen fibers oriented in parallel form to the superficial epithelium with an increase of fusiform fibroblasts. It has been seen that oil injections induced the spontaneous production of interleukin-1 by active macrophages [16]. Experimental models demonstrated that adjuvant oils induced T-cell-dependent polyarthritis. Therefore, mineral oil and other synthetic types of oils can induce AID. Similar situations may have occurred in patients after injection of other illegal substances, which act as adjuvants to enhance the immune response. These patients may have antinuclear antibodies, anti-dsDNA, rheumatoid factor, anticardiolipin (aCL) antibodies and so forth [5].

### *Silicone*

The link between silicone and immune-mediated diseases has been reported in the past and is one of the cornerstones of ASIA [4]. It has been reported that modern silicone implants produce increased levels of C-reactive protein following surgery and correlate with proinflammatory and procoagulatory indices, such as IgM anticardiolipin antibody and other autoantibodies that could signal ongoing immunogenicity of silicone. However, silicone catheters cannot be termed 'inert' or 'biotolerated'. Rather, they must be regarded as 'bio-active' implants shown by histopathological analysis that revealed the development of collagenous membranes and chronic immune reactions around the catheters [17].

Silicone has been associated to the development of foreign body reaction and chronic fibrotic response, which is initially an acute inflammatory response, and subsequently a chronic fibrotic response [18].

To summarize, the adjuvants enhance a specific immune response and stimulate APCs, induce the release of inflammatory cytokines, and interact with TLRs and the NALP3 inflammasome. The immunological consequence of these actions is stimulation of the innate and adaptive immune response, with activation of DCs, macrophages, T and B cells [19].

## Genetic background of ASIA

### *Postvaccination phenomena*

The rarity of the postvaccination events suggests a role for an individual genetic susceptibility. However, at this time, there are no studies of genetic background and postvaccination syndromes except for MMS.

### *Macrophagic myofasciitis syndrome*

This syndrome, observed following the use of vaccines where the adjuvant was Alum, has been associated with the HLA class II allele *DRB1*01* [20].

### *Gulf War syndrome*

It has been demonstrated that veterans with GWS had low levels of enzyme paraoxonase-1 (PON1). The gene that regulates PON1 makes some people more sensitive to insecticides and possibly nerve agents. Of interest, the neurotoxicity effects from pesticides are similar to that described for GWS. In this regard, the polymorphism of *PON1* can be an important contributor to the genetic susceptibility to organophosphate toxicity in some soldiers who developed GWS [21].

### *Siliconosis*

Patients who developed IM following silicone implants had increased frequency of *HLA-DQA1*0102* (odds ratio [OR] = 9.8) with low frequency of the myositis-associated genetic risk factors. In contrast, other studies in Caucasian patients with scleroderma and silicone implants found no differences in allele frequencies compared with idiopatic scleroderma and anticentromere autoantibodies. Symptomatic patients with silicone implants had significant associations with the HLAs *DQ2* and *DRW53* [22].

## Clinical spectrum of ASIA

The influenza, pneumococcal and hepatitis A and B vaccines are safe among all age groups, with an acceptable immunogenicity among the older and juvenile idiopathic arthritis patients [23]. Exceptionally, healthy individuals might develop AID following vaccination, or other adjuvants, because they might have a genetic risk or an underlying disease that activates innate and adaptive immune response [24]. Therefore, there is a subset of patients who developed an immune response with a wide spectrum of clinical manifestations that include AID and neurological syndromes among others. Herein, the authors describe the main AID involved in ASIA.

### *Postvaccination phenomena*

Postvaccination phenomena are rare conditions that have been associated with protean clinical manifestations of specific AID and nonspecific autoimmune manifestations (Box 1).

#### Vasculitis

Several types of vasculitis have been associated with postvaccination reactions, postinfluenza vaccination being one of the vaccines most frequently associated with systemic vasculitis. The

**Box 1. Clinical spectrum of autoimmune/ inflammatory syndrome induced by adjuvants.**

**Postvaccination syndrome**
- Vasculitis
  - Microscopic polyangiitis
  - Leukocytoclastic vasculitis
  - Henoch–Schonlein purpura
  - Giant cell arteritis
  - Polyarteritis nodosa
- Systemic lupus erythematosus
- Inflammatory myopathy
- Rheumatoid arthritis
- Neurological syndromes
  - Guillain–Barré syndrome
  - Narcolepsy
  - Multiple sclerosis
  - Acute disseminated encephalomyelitis
  - Transverse myelitis
- Inflammatory bowel disease
- Autoimmune thrombocytopenia
- Alopecia areata
- Nonspecific autoimmune manifestations

**Macrophagic myofasciitis syndrome**
- Inflammatory myopathy
- Nonspecific autoimmune manifestations

**Gulf War syndrome**
- Chronic fatigue syndrome
- Nonspecific autoimmune manifestations

**Siliconosis and other substances such as oils**
- Systemic sclerosis
- Rheumatoid arthritis
- Still's disease
- Systemic lupus erythematosus
- Fibromyalgia
- Nonspecific autoimmune manifestations

main clinical manifestations are purpura and mononeuritis [25]. Histological findings of nerves have revealed necrotizing vasculitis involving small blood vessels [26].

### Microscopic polyangiitis

Cases of microscopic polyangiitis associated with influenza vaccination according to the Chapel Hill Consensus have been described. These patients had microscopic polyangiitis with different affected organs such as lung, kidney and skin, and a high level of myeloperoxidase antineutrophil cytoplasmic antibody. These patients were treated with steroids and cyclophosphamide and the majority of cases resolved without recurrence [27,28].

### Leukocytoclastic vasculitis

Another side effect of influenza vaccination is leukocytoclastic vasculitis. These patients present with cutaneous vasculitis and abnormal urinalysis suggestive of associated renal involvement. As influenza vaccination is increasingly used, physicians should be aware of the potential serious side effects such as leukocytoclastic vasculitis, particularly in patients who are immunocompromised due to either an underlying disorder or a treatment-related side effect [29].

### Henoch–Schonlein purpura

Henoch–Schonlein purpura (HSP) has also been associated with influenza vaccine and meningococcal vaccine. HSP is a form of systemic leukocytoclastic vasculitis characterized by the deposition of IgA-containing immune complexes in tissues. HSP is commonly preceded by symptoms of an upper respiratory tract infection. Pre-existing HSP may be exacerbated by influenza vaccination [30]. HSP is the most common type of vasculitis diagnosed in childhood and is less frequent in adults. The main clinical manifestations of HSP include palpable purpura, arthritis, abdominal pain, gastrointestinal bleeding and nephritis due to IgA deposits in vessel walls, with the increase in serum IgA concentrations, circulating immune complexes that contain IgA and IgA rheumatoid factor demonstrable in most cases [31]. There are some case reports of HSP temporally associated with the meningococcal vaccine [31,32]. However, a recent study did not find an association between meningococcal vaccine and HSP [33].

### Giant cell arteritis

Giant cell arteritis (GCA) and polymyalgia rheumatic (PMR) are inflammatory rheumatic diseases common in people over the age of 50 years, and there are other vasculitides associated with the administration of the influenza vaccine to older people [34]. Immunization with the influenza vaccine is a widely accepted recommendation and a common practice in older and high-risk individuals, as it is highly effective and well tolerated. Mild transitory side effects after vaccination are common, while systemic complications such as vasculitis and rheumatic disorders remain rare [35]. In recent times, ten cases of GCA and PMR have been reported. In this series, of 20 patients affected by GCA/PMR, ten were diagnosed following Inf-V, with a median of two post-immunization cases per year and a frequency of one out of two cases. Owing to this, all patients with recent onset of GCA/PMR should be asked about previous vaccinations. Patients at higher risk of developing GCA/PMR should be followed up for 2–6 months after Inf-V. This may allow the identification of genetic markers of high-risk individuals in order to avoid potentially dangerous immunizations or reactivation of a latent disease [36].

### Polyarteritis nodosa

The vaccines against HBV have been associated with AID. Nevertheless, a causal relationship has not been established between HBV and autoimmune neuromuscular disorders. However, some studies have suggested an association between HBVs and polyarteritis nodosa (PAN) with vasculitic neuropathy and dermatomyositis. The HBVs may trigger the onset of AID in genetically or immunologically susceptible individuals [37].

The Vaccine Adverse Event Reporting System received 25 cases of PAN over an 11-year period until 2001. Among them, only ten

individuals were diagnosed as definite or possible PAN. A modal peak of 2 weeks and a median of 2.8 weeks postvaccination were noted. All cases received at least two doses of vaccine prior to onset of symptoms. There were less than 20 reports on the development of vasculitis of small, medium and large vessels following influenza vaccination. In general, this would be considered a rare event [38]. Cutaneous PAN has also been described in children following HBV vaccination. The patients were successfully treated with colchicine [39]. In some cases, HPV vaccination may be the triggering factor for vasculitis in individuals with a genetic predisposition [40].

#### Systemic lupus erythematosus & antiphospholipid syndrome

The quadrivalent HPV (virus types 6, 11, 16 and 19) recombinant vaccine has been mainly associated not only to SLE but also to RA, mixed connective tissue disease, Sjogren's syndrome, dermatomyositis and SSc [41]. In recent times, three cases of SLE following HPV vaccination have been reported. In this study, the start or exacerbation of SLE following HPV immunization was demonstrated, which suggests adjuvant-induced autoimmunity. In addition, there are some reports that show a higher incidence of HPV infection in SLE [42]. SLE related to vaccination has shown a relatively high incidence of neuropsychiatric symptoms and low hematologic involvement with absence of lupus nephritis. Thus, clinical manifestation of SLE associated with vaccination may resemble those of drug-induced SLE. Other serious autoimmune adverse events following HBV vaccination were RA, optic neuritis, alopecia, MS and vasculitis. On the other hand, a review of reported cases of newly diagnosed SLE following vaccination showed that the HBV vaccine did not appear to be a significant risk among patients [43–47]. A recent study did not find an increase of antibodies following the use of adjuvant- and nonadjuvant-containing H1N1 vaccine in patients with SLE [48].

A transient increase in anticardiolipin antibodies was reported in SLE patients who received influenza vaccination, but not in β2-GP1. The induction of antibodies against independent β2-GP1 has been shown to act as a cofactor among aCL-positive SLE patients to increase thrombosis risk [49]. In rare cases, postvaccination-induced antiphospholipid antibodies and clinical manifestations of antiphospholipid syndrome (APS) were observed following tetanus toxoid, HBV and influenza vaccine [50].

There are case reports about vaccination with tetanus toxoids and induction of APS, suggesting that vaccination may trigger antibodies targeting tetanus toxoid and β2-GPI, due to molecular mimicry leading to APS. Therefore, the relationship between tetanus toxoid vaccination and APS reveals a novel view on ASIA. Other vaccines such as HBV and influenza are associated in rare cases with APS [51].

### *Inflammatory myopathy*

The etiology of dermatomyositis is unknown, but immune mechanisms play an important role. Vaccines such as HBV, Calmette–Guérin bacillus, tetanus, influenza, small pox, poliomyelitis and diphtheria are reported as triggers of IMs [52]. It is important to consider that hepatitis B vaccine can elicit dermatomyositis and polymyositis [53]. Nevertheless, massive vaccination campaigns with this vaccine have not shown an increase in the incidence of IMs. Although MMS has been seen following vaccination, this is attributed to the Alum used as an adjuvant. It is important to investigate the possible relationship between vaccines and dermatomyositis and polymyositis [54].

### *Rheumatoid arthritis*

Postvaccinal arthritis has been seen following hepatitis B vaccination, which may be explained by the presence of immune complexes containing viral antigen and anti-hepatitis B antibodies as observed in hepatitis B infections, or to hypersensitivity to components of the vaccine (thimerosal or yeast proteins) [55].

A study of 898 patients showed that 48 of them (5.3%) developed early inflammatory polyarthritis 6 weeks after receiving hepatitis B vaccination. In addition, genetic studies revealed that the frequencies of *HLA-DRB1*01*04* and the shared epitope in 33 patients who received the vaccine resembled 185 nonimmunized patients and 136 healthy controls [56]. Seropositive RA has been triggered by recombinant HBV vaccine in susceptible individuals. DR4-positive RA has been reported in few cases following hepatitis B vaccination. In one study, 11 patients who were previously healthy presented RA after hepatitis B vaccine, and five individuals expressed *HLA-DR4* [57]. In another, case–control epidemiological study, patients who received HBV vaccination showed an OR of 18 to develop RA [58]. In contrast, another study of 22 RA patients versus controls who received HBV vaccination showed that the vaccine was safe in 68% of patients [59]. On the other hand, pneumococcal vaccination is safe and immunogenic in patients with RA as well as SLE [60].

### *Neurological syndromes*

Neurological manifestations associated with vaccines are diverse, and include GBS, narcolepsy, MS, demyelinating syndrome and neuropathy, among others.

#### Guillain–Barré syndrome

Among the vaccines reported to be associated with the onset of GBS are the swine influenza vaccine in 1976–1977, oral poliovirus vaccines and tetanus toxoid [61]. A causal relationship between influenza vaccine and GBS was observed following administration of the swine flu vaccine in 1976. Studies of subsequent influenza vaccination in general, detected no significant increase in the overall risk for GBS [62,63].

Antiganglioside antibodies (anti-GM1)- are associated with the development of GBS, and it was suggested that the swine flu vaccine having contaminating moieties (e.g., *Campylobacter jejuni* antigens that resemble human gangliosides or other vaccine components) elicited an anti-GM1 antibody response in susceptible recipients. It was found that, although *C. jejuni* was not detected in the 1976 swine flu vaccines, these vaccines induced anti-GM1 antibodies in mice, as did vaccines from 1991–1992 and from 2004–2005 [64]. In another study, antiganglioside antibodies were not detected in human subjects infected with or vaccinated against 2009 pandemic A H1N1 influenza virus. The induction of antiganglioside antibodies by influenza viruses or vaccines was not supported [65]. Vaccination against influenza is associated

with a low risk for GBS presentation. In contrast, influenza infection may play a more important role as a triggering factor for GBS than previously assumed [66].

Recent studies found a rare incidence of GBS after contemporary H1N1-influenza vaccine. Five patients presented 'atypical' GBS variants after 4 weeks of 2010/2011 H1N1 influenza vaccine. These patients showed sensory ataxia, areflexia, extremity and oropharyngeal paresthesias, numbness, pain, weakness, sphincteric disturbances, dysautonomia and Miller Fisher syndrome [67]. On the other hand, Pandemrix® (GlaxoSmithKline, London, UK) vaccines were demonstrated to be safe, without change in the risk for GBS, MS, Type 1 diabetes or RA. Yet, relative risks were significantly increased for Bell's palsy, paraesthesia and IBD after vaccination, especially in the early phase of the vaccination campaign [68]. Patients with GBS should not receive vaccinations, since they can exacerbate the clinical manifestations; neither should those whose syndrome was triggered by the vaccination.

### Narcolepsy

Narcolepsy is a chronic sleep disorder of unknown etiology, with genetic and predisposing environmental factors producing excessive daytime sleepiness and cataplexy. An abrupt increase in childhood narcolepsy was observed in Finland soon after the 2009 influenza pandemic and vaccination with AS03-adjuvanted Pandemrix [69]. The WHO review of data from Finland's National Institute of Health and Welfare found a ninefold increased risk of narcolepsy in children and adolescents following H1N1 vaccination with Pandemrix [70]. In a few individuals, the onset of narcolepsy occurred approximately 8 weeks following these vaccinations [71]. The Swedish Medical Products Agency found that the relative risk of narcolepsy was 6.6-times higher in vaccinated children and adolescents compared with unvaccinated individuals [72]. In China, narcolepsy onset correlated with seasonal and annual patterns of upper airway infections, including H1N1 influenza, and the correlation was independent of H1N1 vaccination [73].

Although no formal link can be established, the unusual characteristic of the reported cases, and the striking temporal relationship suggests that narcolepsy may be the result.

### Multiple sclerosis

MS is an autoimmune, inflammatory, neurodegenerative, demyelinating disease of the CNS, predominantly involving myelinated neurons of the brain, spinal cord and optic nerve. Influenza vaccines should be recommended as part of treatment practice in MS because influenza infections are associated with increased risk of exacerbations of MS. Vaccines containing viable pathogens should not be used during immunosuppressive therapy [74]. Risk of developing MS remained unchanged after Calmette–Guérin bacillus, hepatitis B, influenza, MMR, polio and typhoid fever immunization, whereas diphtheria and tetanus vaccination may be associated with a decreased risk of MS. Further research is needed for the remaining vaccines [75]. Therefore, vaccinations have not been associated with a major risk of developing MS.

### Acute disseminated encephalomyelitis

ADEM is an inflammatory demyelinating disease of the CNS that is usually considered a monophasic disease. ADEM includes several categories of primary inflammatory demyelinating disorders of the CNS (e.g., MS, optic neuropathy, acute TM and neuromyelitis optica [Devic's disease]). Postinfectious and postimmunization encephalomyelitis is investigated in approximately 75% of cases; postvaccination ADEM has been associated with several vaccines (e.g., rabies, diphtheria–tetanus–polio, MMR, Japanese B encephalitis, pertussis, influenza, hepatitis B and the hog vaccine.) After a review of the literature from 1976 to 2007, only one patient was found with bilateral optic neuropathy within 3 weeks of 'inactivated' influenza vaccination followed by a delayed onset of ADEM 3 months postvaccination [76].

### Transverse myelitis

TM is a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord. The pathogenesis of TM is of an autoimmune nature predominantly, triggered by various environmental factors, including vaccination. In a systematic review from 1970 to 2009, there were 37 reported cases of TM associated with different vaccines against HBV, MMR, diphtheria–tetanus–pertussis and others. The temporal association lasted from several days to 3 months, although sometimes it has been seen for several years. Thus, TM can be triggered by the vaccines previously mentioned [77].

### Inflammatory bowel disease

IBD, such as Crohn's disease (CD) and ulcerative colitis (UC), is associated with genetic factors, environmental factors, enteric flora and immunological abnormalities. Some vaccines have been associated with IBD: vaccination against pertussis (OR: 2.08) and polio (OR: 2.3) increased the odds for IBD, whereas measles infection increased the odds for UC (OR: 3.50) [78]. However, in experimental models, the administration of the vaccine induced specific antibodies to IL-12 and IL-23, which was associated with improvement of intestinal inflammation and fibrosis. This hints at the fact that the vaccine may provide a potential approach for the long-term treatment of CD. Therefore, the administration of vaccines and the development of IBD is a controversial issue [79]. Moreover, in animal models where Alum is used as an adjuvant in vaccines, this can be a potential factor for the induction of inflammation in CD, and its immune activities share many characteristics with the immune pathology of CD. Many luminal bacterial or dietary compounds can be adsorbed to the metal surface and induce Th1 profile cytokines, sharing cytokines/chemokines, costimulatory molecules, intracellular pathways and stress-related molecular expression enhancement, affecting intestinal microbiota. The aforementioned suggests that Alum used in vaccines stimulates the innate and adaptive immune response and induces AID, which meet the diagnostic criteria of ASIA [80].

### *Macrophagic myofasciitis syndrome*

MMF is one of the entities most evaluated as a postvaccination condition, in which there is an association with Alum used as

adjuvant. Gherardi *et al.* reported that the deposition of Alum, used to adjuvant different vaccines, produced an immune-mediated muscle disease. The fact that patients developed MMF without previous exposure to Alum, except for the one contained in the vaccines against hepatitis A or B or tetanus toxoid vaccines, suggests a direct relationship between Alum and MMF [81]. Patients with MMF have shown a greater frequency of *HLA-DRB1*01* allele presence [20].

MMF affects middle-aged adults and is characterized by systemic manifestations as well as local active lesions at the site of inoculation. Systemic manifestations include myalgias, arthralgia, asthenia, muscle weakness, chronic fatigue, cognitive dysfunction, fever, and in some cases, a demyelinating disorder. In addition, elevated creatine kinase, erythrocyte sedimentation rate, autoantibodies and myopathic electromyography changes have also been documented [82,83]. The local lesion of MMF was found to be the result of persistence of Alum adjuvant at the site of inoculation months or even years following immunization. Muscle biopsy revealed a large infiltration of PAS-positive, MHC-1-positive macrophages and $CD8^+$ T cells, in the absence of muscle fiber damage. On electron microscopy, these macrophages enclose cytoplasmic crystal material representing Alum [83,84]. The stereotyped cognitive dysfunction is reminiscent of cognitive deficits described in foundry workers exposed to Alum particles. Animal experiments indicate that biopersistent nanomaterials taken up by monocyte-lineage cells in tissues, for example fluorescent Alum surrogates, can first translocate to draining lymph nodes, thereafter circulate in blood within phagocytes and reach the spleen and eventually slowly accumulate in brain. Clinical studies and experimental Alum-containing vaccines explain many systemic manifestations of MMF, especially in the CNS. Clinical manifestations associated with MMF are paradigmatic of the recently delineated ASIA [84].

### *Gulf War syndrome*

GWS is another syndrome associated with the effect of vaccines administered to soldiers who were sent to the Gulf War. Multiple vaccinations performed over a short period of time were suggested to be the cause of this syndrome. Of interest, during the Gulf War, the veterans' vaccination protocol included the anthrax vaccine, which was administered in a six-shot regimen, and the adjuvants were Alum and squalene. The etiology of GWS is unclear, but many reviews and epidemiological analyses suggest an association with other substances such as pyridostigmine bromide, a variety of possible chemical exposures, including smoke from oil-well fires or depleted uranium from shells, as well as physical and psychological stress. On the other hand, the appearance of chronic fatigue syndrome and fibromyalgia has been seen after infectious agents, pesticides and vaccines. Therefore, it was postulated that the GWS is the result of the adjuvant effect that induced a chronic immune response [85,86]. This syndrome is characterized by a spectrum of symptoms including fatigue, rash, headaches, arthralgias, myalgias, lymphadenopathy, diarrhea, memory loss, impaired cognition, depression, chronic somatic pain, paresthesias of the extremities, autoimmune thyroid disease, increased allergies and sensitivities to environmental elements and other neurological abnormalities. While GWS patients in general do not suffer from classic rheumatic diseases, the signs and symptoms are similar to those of entities such as fibromyalgia, lymphadenopathy, autoimmune thyroid disease, chronic fatigue syndrome, malar rashes, arthralgias and musculoskeletal signs and symptoms associated with various autoimmune conditions [85].

Asa *et al.* investigated if the presence of antibodies to the adjuvant squalene correlated with the diagnosis of GWS. In this study of 144 Gulf War era veterans versus controls, squalene antibody measurement was performed [87]. The majority, 95% of overtly ill deployed GWS patients, had antibodies to squalene. All 100% of GWS patients immunized for service in Desert Shield/Storm had antibodies against squalene. In contrast, none of the control groups that incorporated patients with AID, healthy controls and Persian Gulf veterans not showing signs and symptoms of GWS had antibodies to squalene. Independent of the etiology of GWS (i.e., exposure to environmental factors or chemical drugs, vaccinations or the adjuvants in them), GWS correlates well with the definition of ASIA [85]. This syndrome represents a wide spectrum of neurologic injury involving the central, peripheral and autonomic nervous system as well as skeletal muscle system among others.

## Siliconosis & other substances: oils (modelants)

Since the 1960s, silicone implants have been successfully used for breast augmentation and reconstruction. Since their appearance, breast prostheses of silicone have been associated with autoimmune rheumatic disease (ARD). However, safety issues regarding the use of silicone led to a moratorium by the US FDA between 1992 and 1996 [88]. In 1995, the American College of Rheumatology evaluated the epidemiological data and concluded that there was no association between silicone breast implants (SBI) and ARD [89]. Later, a meta-analysis documented no association between SBI and defined ARD [90]. However, in the years to follow, Hennekens *et al.* found that SBI were related to ARD with a relative risk of 1.24, and various subsequent studies documented an association between SBI and nondefined autoimmune rheumatic manifestations [91]. Thus, the interaction between SBI and defined ARD remains controversial [92]. More than 1000 patients with rheumatic disorders and SBI have been reported, especially patients with SSc, inflammatory myositis and SLE. Nevertheless, the clinical features of the most common rheumatic disorder associated with SBI are nonspecific rheumatic disease manifestations, local regional and neurologic disorders associated with silicone [93].

### *Silicone & systemic sclerosis*

Silicone is not an inert substance, and silicone compounds were found in the blood and liver of women with SBI. The development of disease related to SBI would depend on genetic factors, so that only a very few women are potentially at risk of developing ARD or manifestations that do not fulfill criteria for AID [94,95]. The ARD most commonly claimed to be associated with SBI is SSc.

Since the 1980s many cases of SSc have been described several years following cosmetic augmentation mammoplasty associated with SBI. The interval between implantation mammoplasty and

the onset of SSc ranged from 6 to 15 years. Owing to the long period of latency observed, the full impact of this association may not yet be apparent. The majority of these patients fulfilled the criteria established by the American College of Rheumatology for SSc. In some cases, particles of silicone in tissues distant from the prostheses have been demonstrated. A notable chronic inflammatory process containing lymphocytes, 'foamy' histiocytes and multinucleated giant cells with vacuoles and asteroid bodies was seen at the same sites. The silicone leakage from SBI suggests that silicone plays a role in the development of certain cases of SSc [96,97]. Morphea and other scleroderma-like skin conditions are occasionally linked to exposure to chemical compounds such as silicone [98].

Several prospective studies corroborated the lack of a significant association between SBI and the development of SSc. However, one should note that these studies lack sufficient statistical power to detect an increase in risk of a relatively rare disease, such as SSc. In addition, the follow-up period was generally not extensive enough, as SSc may develop many years postexposure and even when established, the delay in diagnosis averages an additional 6 years [99]. A report by Levy *et al.* describes four women who have developed SSc post-SBI. Disease manifestations appeared 5, 14, 15 and 20 years postsurgery manifested primarily by arthralgias, heartburns and Raynaud's phenomenon. Three of these four cases (75%) would have been missed in all studies published to date, weakening the association between SBI and SSc [100]. It has been demonstrated that there is an increase of autoantibodies in symptomatic women who had undergone a SBI compared to asymptomatic women who received the prostheses [101].

Despite the fact that there are epidemiological studies that have failed to reveal the association between SBI and ARD, several cases showing this association keep appearing in the literature. Recently, siliconosis, related to these various manifestations occurring following exposure to silicone, was incorporated into ASIA [102].

### *Silicone & other autoimmune rheumatic diseases*

RA is another ARD considered to be associated with SBI [102]. However, some studies have not found an association between SBI and RA [103]. Recently Jara *et al.*, reported the relationship of Still's disease and SBI, following implant rupture adding to six other previous case reports [104]. Other ARD, such as SLE, mixed connective tissue disease, SSc, polymyositis and microscopic polyangiitis have also been associated with SBI [104]. It has also been suggested that there is an association between extracapsular silicone from ruptured SBI and fibromyalgia; therefore, women with SBI should be informed of the potential risk of developing fibromyalgia if their breast implants rupture and the silicone gel escapes the fibrous scar capsule [105]. Sarcoidosis is another manifestation of siliconosis associated with SBI as part of ASIA [106,107].

### *Oily substances & other inducers of autoimmune rheumatic diseases*

Human adjuvant disease (HAD) is an entity initially described in the past century and is characterized by clinical and laboratory manifestations that suggest ARD such as SSc, SLE, RA, Sjogren's syndrome, among others in association with the injection of foreign substances (paraffin and silicone fluid), but the most frequent manifestations are nonspecific symptoms of ARD such as arthralgias, myalgia, cognitive impairment, malaise, fever and so on. Later, a series of ARD after cosmetic injection of paraffin and silicone was reported. These patients were classified into two groups: group I consisted of 24 patients with definite ARD (12 with SSc, six with RA, five with SLE and one with polymyositis) and group II consisted of 22 patients with HAD with some symptoms, signs and laboratory abnormalities suggestive, but not diagnostic of ARD. Prolonged exposure to the injected substance may play a role in the induction of these immunologic disorders [5].

In Mexico, HAD has also been associated with the injection of heterogeneous substances that include mineral oil, guaiacol, iodine gadital and others that can act as GWS adjuvants [16]. Recently, the group reported 50 patients of which 41 were injected with mineral oil and nine with other substances (e.g., iodine gadital, guaiacol). Thirty of them presented nonspecific autoimmune manifestations, and 20 patients fulfilled the criteria for a defined AID such as SLE, RA, SSc, overlap syndrome, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune hepatitis and UC. The authors consider that these substances act as adjuvants in humans, the same way as the IFA model, enhancing the autoimmune response, which explains the development of ARD and nonspecific rheumatic diseases [5].

Finally, the authors consider that ASIA, which is characterized by an ample variety of manifestations of autoimmunity, can be triggered by diverse environmental factors such as oil, guaiacol and so forth [4], and other substances (e.g. mercury and filler substances such as hyaluronic acid, polyacrylamide hidrogel or methacrylate) have also been associated with clinical and serological manifestations of AID as other examples of ASIA [107–110].

## Summary

- The clinical and laboratory data support an association between adjuvants and autoimmune diseases;
- Experimental models demonstrated that the concept of autoimmunity and autoimmune diseases may be induced by adjuvants;
- The literature is flooded with case reports and small case series of systemic autoimmune diseases related to vaccines or other stimuli (e.g. infection) or other adjuvants such as silicone or liquid paraffin and oil;
- The ASIA includes four conditions linked to previous exposure to an adjuvant substance: siliconosis, GWS, MMS and postvaccination phenomena;
- Other substances (e.g., mineral oil, paraffin, liquid silicone, hyaluronic acid, polyacrylamide hidrogel or methacrylate) used for cosmetic purposes can also induce autoimmune manifestations and are also another model of ASIA;

- It is noteworthy that considerable controversy surrounds the topic of siliconosis, mainly SBI, since there are many questions that remain to be answered;
- The role of adjuvants in the pathogenesis of autoimmune diseases needs to be confirmed with other studies that define the true prevalence of ASIA spectrum and the relationship between adjuvants and gene expression with epigenetic studies.

## Expert commentary

ASIA is a new syndrome in which environmental factors play a role with a wide spectrum of clinical manifestations and complex pathogenesis, representing only the tip of the iceberg. Owing to the participation of genetic susceptibility, epigenetic studies are required for a better understanding of this syndrome.

## Five-year view

In the near future, we expect to witness further refinements in the development of newer studies such as epigenetics and experimental models, that are necessary to fully understand the underlying genetic and environmental causes of ASIA and the application of this knowledge to the treatment and prevention of this syndrome. Environmental factors are numerous, and it is very difficult to prove an exact cause–effect relationship for the development of ASIA.

Regarding vaccines, they are safe for most people, in spite of the fact that they can show mild and transient side effects in the majority of cases; however, there can be rare and severe adverse effects that are life-threatening. Therefore, all individuals with risk factors for the development of postvaccination phenomena should be identified. In the future, we need safer and more effective vaccines based on the development of newer adjuvants with fewer side effects. Further progress in pharmacogenetics and pharmacogenomics will increasingly allow us to understand and predict immune response, adverse events to vaccines and accelerate new vaccine development.

With respect to GWS, unfortunately the wars will continue, making it necessary to study the individuals deployed in areas of conflict in relation to newer genetic, chemical and biological factors, and to determine the role of psychological stress, immune–neuroendocrine interactions and vaccines on the appearance of functional somatic syndromes as part of ASIA.

In relation to SBI, these will continue to be used; therefore, it is convenient to improve breast implants and recommend surgeons to identify individuals with a risk of developing ASIA. It is important that surgeons have the capability to detect susceptible individuals to AID or the ones that already have these diseases.

Finally, modeling substances, especially illegal mineral oil with aesthetic purposes, may produce AID and could be life threatening. New studies are necessary to understand better genetic, epidemiological and pathogenic factors involved and likewise, to identify more substances such as mercury and others that may trigger ASIA.

### Financial and competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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## Key issues

- Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) includes four entities: postvaccination phenomena, Gulf War syndrome, macrophagic myofasciitis syndrome and siliconosis.
- The principal environmental factors of ASIA are aluminum hydroxide, silicone, squalene and mineral oil.
- The clinical spectrum of ASIA, due to postvaccination phenomena clinical manifestation, includes vasculitis, systemic lupus erythematosus, inflammatory myopathy, rheumatoid arthritis, neurological syndromes, inflammatory bowel disease, autoimmune thrombocytopenia and nonspecific autoimmune manifestation.
- Gulf War syndrome is attributed to the multiple vaccinations in a short period of time, smoke from oil-well fires or depleted uranium from shells, as well as physical and psychological stress. The majority (95%) of overtly ill deployed Gulf War syndrome patients, had antibodies to squalene.
- Silicone, a synthetic polymer, is considered to be a biologically inert substance; however, silicone may mediate autoimmune diseases, mainly scleroderma, although controversy about this issue remains to be settled.
- Mineral oil used for cosmetic purposes is another example of a cause of ASIA.

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