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Autoimmune/inflammatory syndrome induced by adjuvants (ASIA): clues and pitfalls in the pediatric background

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Abstract The development and increasing diffusion of new vaccinations and global immunization protocols have aroused burning debates about safety of adjuvants and their immunogenicity-enhancing effect in vaccines. Shoenfeld and Agmon-Levin have grouped under the term "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) a complex of variable signs and symptoms that may occur after a previous exposure to different adjuvants and also external environmental triggers, even eliciting specific overt immune-mediated disorders. This entity subsumes five medical conditions: post-vaccination phenomena, gulf war syndrome, macrophagic myofasciitis syndrome, siliconosis, and sick building syndrome, but the relevance and magnitude of the syndrome in the pediatric age is fundamentally limited to post-vaccination autoimmune or inflammatory disorders. The occurrence of vaccine-triggered phenomena represents a diagnostic challenge for clinicians and a research conundrum for many investigators. In this paper, we will analyze the general features of ASIA and focus on specific post-vaccination events in relation with the pediatric background. In the presence of a favorable genetic background, many autoimmune/inflammatory responses can be triggered by adjuvants and external factors, showing how the man himself might breach immune tolerance and drive many pathogenetic aspects of human diseases. Nonetheless, the elective application of ASIA diagnostic criteria to the pediatric population requires further assessment and evaluations. Additional studies are needed to help clarify connections between innate or adaptive immunity and pathological and/or protective autoantibodies mostly in the pediatric age, as children and adolescents are mainly involved in the immunization agendas related to vaccine-preventable diseases.

Keywords Post-vaccination phenomena · Adjuvants · Gulf war syndrome · Macrophagic myofasciitis syndrome · Siliconosis · Sick building syndrome

Introduction

Vaccinations began more than 200 years ago as a life-saving medical experiment against smallpox due to Edward Jenner, who had used a poxvirus similar to the "variola virus." Nowadays, following different development techniques, vaccines may contain live attenuated viruses, inactivated or killed whole-cell organisms and viruses, inactivated bacterial exotoxins (also named toxoids), and fragments of the pathogen, all acting to mimic disease agents and actively stimulate the immune system. Adjuvants, defined as any substance that acts to accelerate, lengthen, or strengthen antigen-specific immune reaction when used in combination with vaccine antigens, have been essential for directing the adaptative immune response especially in the first year of life: Inorganic or organic chemicals, mineral oils, detergents, macromolecules, and even bacterial products have been used to this

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goal [1]. Beyond desired outcomes, an adjuvant might also trigger undesired specific or nonspecific manifestations of autoimmune and inflammatory diseases in certain predisposed individuals, and widespread vaccination protocols even in areas previously difficult or impossible to reach have arousen an ancient burning debate about vaccine safety in children and adolescents [2].

Yehuda Shoenfeld and Nancy Agmon-Levin have grouped under a distinct syndrome, entitled "autoimmune/inflammatory syndrome induced by adjuvants" or ASIA, the collection of signs and symptoms that may occur after a previous exposure to different adjuvants contained in different vaccines [3]. In addition, various environmental factors entailing an immune adjuvant activity, such as silicone and pollutants, involved in the pathogenesis of defined and non-defined immune-mediated diseases, have been included in the description of ASIA. This new syndrome subsumes five medical conditions: (a) post-vaccination phenomena, which are the most relevant ASIA-related disorders in the pediatric age, (b) gulf war syndrome (GWS), (c) macrophagic myofasciitis syndrome (MMS), (d) siliconosis, and (e) sick building syndrome (SBS). All these entities share similar manifestations, including muscle, joint, nervous system symptoms, and fever [4]. Adjuvants involved in ASIA can also provoke a definite autoimmune process, though mechanisms linking the non-antigenic activation of the innate immunity as well as the adjuvant-dependent expression of various regulatory cytokines with the evolution of an autoimmune response into a full blown disease are unraveled [5]. Major and minor criteria were proposed for the diagnosis of ASIA: the presence of at least two major or one major and two minor criteria must be ascertained for diagnostic purposes (Table 1). These criteria were validated by Zafrir et al. in 93 patients who received hepatitis B vaccination within 6 weeks before ASIA onset, of whom 28.7 % were children: In this cohort 80/93 patients (86 %), comprising 23/34 (68 %) children, fulfilled the required criteria for ASIA and experienced the appearance of typical manifestations, therefore fulfilling the first two major criteria. Minor criteria were experienced by only 4 patients. Among 13 patients who did not fulfill the ASIA criteria, 11 were children, 9 of whom were diagnosed with type 1 diabetes mellitus [6]. By this reason, the extension of the proposed ASIA diagnostic criteria to the scenery of pediatric patients requires further clinical and epidemiologic studies.

In this paper, we will analyze the role of environmental factors and the genetic susceptibility to the pathogenesis of ASIA, showing the spectrum of its clinical manifestations and focusing on the post-vaccination phenomena, which are the most frequent pediatric disorders framed in the context of ASIA.

Table 1 Proposed criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants (ASIA): The presence of at least two major or one major and two minor criteria must be ascertained for diagnostic purposes

Major criteria
Previous exposure to an external stimulus (i.e., vaccine, adjuvant, silicone, nucleic acids, fragments of bacterial cell walls)
Appearance of one of the following "typical" manifestations:
Myalgia, myositis, or muscle weakness
Arthralgia and/or arthritis
Chronic fatigue, non-refreshing sleep, or sleep disturbances
Neurologic manifestations (especially if associated with demyelination)
Memory loss and cognitive impairment
Fever
Dry mouth
The removal of the inciting agent induces improvement
Typical biopsy of the involved organs
Minor criteria
Appearance of autoantibodies (i.e., rheumatoid factor, anti-smooth muscle, anti-nuclear, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, anti-myelin basic protein, anti-adrenal cortex, anti-cardiolipin, anti-thyroglobulin, anti-thyroid peroxidase, and anti-mitochondrial autoantibodies) or autoantibodies directed against the suspected adjuvant
Other clinical manifestations (i.e., irritable bowel syndrome)
Association with specific HLA[a] haplotypes (i.e., HLA DRB1, HLA DQB1)
Development of autoimmune diseases (i.e., systemic lupus, erythematosus, systemic sclerosis, Sjögren's syndrome, multiple sclerosis, autoimmune thyroiditis, autoimmune hepatitis, etc.)

Modified from Ref.# 15

[a] *HLA* human leukocyte antigen

The link of Asia with environmental and genetic factors

The prevalence of autoimmune diseases is determined by a mosaic of genetic susceptibilities, loss of immune regulations, changes in the hormonal milieu, and exposure to different environmental factors, also including vaccines and immune adjuvants. The response to a vaccine differs substantially due to the genetic background of the recipient, but the actual vaccination schedule excludes any try to customize its implementation strategies [7]. Although exposure to vaccine adjuvants is common, adjuvant-related diseases are relatively rare. The role of individual susceptibility can explain the rarity of autoimmune and/or inflammatory events following the exposition to a wide range of environmental factors (from infectious triggers to natural adjuvants). External triggers, such as bacterial products and house molds, have also been associated with different immune-mediated conditions through a variety of mechanisms in the context of a peculiar genetic background: subverted autoantigen expression, induction of

novel antigens, modification of surface antigens, antigen translocation, T cell dysregulation, polyclonal activation of B cells, antigenic cross-reactivity, molecular mimicry due to sequence homology or structural similarity with multiple antigens, epigenetic regulation of inflammatory pathways, etc. [8]. Genetic, hormonal, and environmental factors are globally considered to be critical in the etiology of autoimmune and also inflammatory phenomena, but their distinct specific contribution is not yet established [9]. Also for the prototypical autoimmune disease, i.e., systemic lupus erythematosus, the underlying triggers have remained elusive, and multiple interacting environmental and genetic factors might contribute to the onset and perpetuation of the disease [10]. With regards to genetic susceptibility to ASIA-related disorders, there are few studies specifically dedicated to post-vaccination phenomena. On the other hand, GWS has been associated with two genetic polymorphic sites of the enzyme paraxonase, involved in the hydrolysis of organophosphate pesticides and nerve gases, influencing their toxicity to mammals and man [11], while MMS has been associated with the HLA class II allele DRB1*01 [12].

Adjuvants and Asia

The concept that the immune response to pathogen antigens can be improved by the addition of certain compounds into the vaccine formulation was demonstrated about 100 years ago, when aluminum salts were introduced. Immune responses induced by vaccines containing highly purified antigens with improved tolerability and safety profiles remain suboptimal without the help of adjuvants, which enhance the magnitude and affect the type of the antigen-specific response [13]. The most common adjuvant used in human vaccines is aluminum (alum), a nanocrystalline compound spontaneously forming submicron-sized agglomerates, including aluminum hydroxide, and its main mechanism of action is the activation of innate immune pathway via NLRP3-inflammasome, a cytoplasmic multiprotein complex that mediates the cleavage of the inactive precursor of interleukin-1β (IL-1β) to bioactive IL-1β, combined with release of uric acid and host DNA from necrotic cells [14, 15]. The consolidation of the desired antigen at the injection site with subsequent slower release to antigen-presenting cells was another mechanism explaining aluminum adjuvanticity that has now been discredited [16]. The same proinflammatory network that drives the immunostimulatory effects of alum has the capacity to provoke a variety of signs and symptoms, which are included in the ASIA syndrome and have been comprehensively considered as post-vaccination phenomena [17]. Because alum neurotoxicity is well-demonstrated, it is plausible that traffic of aluminum to the brain might have a role in the pathogenesis of ASIA neurologic clinical features in susceptible individuals [18, 19].

Another adjuvant approved for human vaccines is MF59, a sub-micrometer oil-in-water emulsion of squalene, polyoxyethylene sorbitan monooleate and sorbitan trioleate, which induce the production of proinflammatory cytokines, the expression of adhesion molecules, and the activation of antigen-presenting cell genes; moreover, it has been shown that mineral oils promote anti-chromatin/DNA autoantibody production, suggesting that they can prime an autoimmune process [20].

AS03 is an adjuvant system composed of α-tocopherol, squalene, and polysorbate 80 in an oil-in-water emulsion. In various nonclinical and clinical studies, high levels of antigen-specific antibodies were obtained after administration of an AS03-adjuvanted vaccine, permitting antigen-sparing strategies [21]. AS03 has been shown to enhance the vaccine antigen-specific adaptive response by activating the innate immune system locally and by increasing antigen uptake and presentation in draining lymph nodes, a process that is modulated by the presence of α-tocopherol in AS03 [21].

Silicone is the synthetic polymer used in different medical products, showing also the capability of stimulating a local macrophage activation, and resulting in overproduction of cytokines and reactive oxygen species [22]: A fibroproliferative response with potential development of connective tissue diseases and scleroderma-like features can be observed following the application of silicone [23]. Moreover, silicone implants increase levels of C-reactive protein and correlate with different proinflammatory and procoagulatory markers, such as IgM anti-cardiolipin antibodies, confirming the immunogenic properties of silicone itself [24].

Other adjuvants, essentially ligands for pattern recognition receptors, act by inducing the innate immunity, targeting the antigen-presenting cells, and subsequently influencing the adaptative immune response. Moreover, new adjuvants are being developed that are natural ligands or synthetic agonists for pattern recognition receptors, double-stranded RNA, oligodeoxynucleotides, fragments of bacterial cell walls, such as muramyl dipeptide, and Toll-like receptors ligands, which are potent inducers of innate and adaptative immunity [13].

Clinical manifestations of Asia

Post-vaccination phenomena

A number of autoimmune and immune-mediated disorders have been reported mainly as case reports following

Table 2 List of the vaccines which are reported to be associated with the development of autoimmune or immune-mediated disorders

Vaccine	Autoimmune or immune-mediated disorder
Hepatitis B virus	Polyneuropathy, Guillain–Barré syndrome, acute disseminated encephalomyelitis, multiple sclerosis, transverse myelitis, myasthenia gravis, uveitis, Henoch–Schönlein purpura, polyarteritis nodosa, erythema nodosum, lichen ruber planus, pemphigus, idiopathic thrombocytopenic purpura, reactive arthritis, rheumatoid arthritis, systemic lupus erythematosus, undifferentiated connective tissue disease, chronic fatigue syndrome
Hepatitis A virus	Henoch–Schönlein purpura, idiopathic thrombocytopenic purpura
Anthrax	Systemic lupus erythematosus
Diphtheria, pertussis, and tetanus	Optic neuritis, Guillain–Barré syndrome, systemic lupus erythematosus
Influenza	Guillain–Barré syndrome, acute disseminated encephalomyelitis, narcolepsy, systemic lupus erythematosus, rheumatoid arthritis, Henoch–Schönlein purpura, vasculitis, reactive arthritis
Measles, mumps, and rubella	Henoch–Schönlein purpura, idiopathic thrombocytopenic purpura, acute disseminated encephalomyelitis
Mumps	Type 1 diabetes mellitus, Guillain–Barré syndrome
Rabies	Polyneuritis, Guillain–Barré syndrome, acute disseminated encephalomyelitis
Poliomyelitis (oral vaccine)	Guillain–Barré syndrome
Swine flu	Multiple sclerosis
Yellow fever	Kawasaki syndrome
Bacillus Calmette–Guérin immunotherapy (for urinary bladder carcinoma)	Reactive arthritis, Reiter's syndrome, polymyositis/dermatomyositis
Haemophilus influenzae type b	Type 1 diabetes mellitus
Streptococcus pneumoniae	Henoch–Schönlein purpura
Neisseria meningitidis	Henoch–Schönlein purpura
Human papilloma virus	Systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Siögren's syndrome, systemic sclerosis, dermatomyositis, vasculitis, acute disseminated encephalomyelitis, primary ovarian failure, secondary amenorrhea, postural tachycardia orthostatic syndrome

Modified from Ref.# 15

different vaccinations (Table 2), and even severe or life-threatening clinical conditions may occur in a subset of patients. An increasing number of animal models provide a valid proof of concept for different ASIA-related rheumatologic conditions following vaccinations combined with the production of different autoantibodies [25]. Mostly live attenuated vaccines are prone to stimulate the development of autoimmune diseases [26]. The clinical spectrum of ASIA due to post-vaccination phenomena includes neurologic diseases, vasculitides, systemic lupus erythematosus, inflammatory myopathies and arthropathies, autoimmune thrombocytopenia, inflammatory bowel diseases, and organ-specific autoimmune manifestations.

Several neurologic diseases have been reported following vaccinations, such as multiple sclerosis, demyelinating neuropathy, and mostly Guillain–Barré syndrome, an acute polyradiculoneuropathy starting with acute symmetric motor paralysis and areflexia, characterized by the presence of autoantibodies directed against gangliosides [27]. Lots of vaccinations have been related to the appearance of Guillain–Barré syndrome, including tetanus toxoid, rabies, mumps, rubella, oral poliovirus, and hepatitis B vaccine. Actual data appear conflicting as regards the relationship existing between Guillain–Barré syndrome and influenza vaccination, as a wide population study performed over 3 million individuals has proved, showing also that there were no cases of recurrent Guillain–Barré within 6 weeks after any vaccine [28]. Another post-vaccine disease which has been reported also in a pediatric scenery is the acute disseminated encephalomyelitis, potentially occurring within different times (3 weeks to 3 months) from rabies, measles, mumps, rubella, hepatitis B, influenza, and human papilloma virus vaccinations [29].

In 2010, concerns were raised in Finland and Sweden about an apparent rise in the incidence of narcolepsy in children and adolescents immunized with the H1N1-

ASO3-adjuvanted pandemic influenza vaccine [30]. Narcolepsy is a chronic disabling neurologic disorder characterized by severe irresistible daytime sleepiness and abnormal sleep-wake patterns [31]. The disorder is uncommon in children younger than 5 years; therefore, the apparently increased incidence of childhood-onset cases was of great concerns. After extensive review, the European Medicines Agency confirmed the existence of this association, which has since been detected in England, Ireland, France, and Norway [32]. In different studies, the time ranges from vaccine to symptom onset varied; nevertheless, data strongly suggested a temporal relation [32]. Although narcolepsy appeared associated with HLA DQB1*0602, which is more common in Northern countries than elsewhere [33], the molecular mechanisms underlying this association remain unknown. However, the lessons learnt emphasize the central role of alert clinicians in reporting of suspected adverse reactions, and the importance of internationally robust post-marketing surveillance strategies as crucial components in future mass immunization programmes.

Moreover, several types of systemic vasculitides have been evaluated as post-vaccination reactions, mostly occurring after influenza vaccines, and histologic findings have revealed necrotizing vasculitis involving small blood vessels in some cases [34]. Henoch–Schönlein purpura, the most common systemic leukocytoclastic vasculitis in childhood, characterized by IgA-containing immune complex deposition in different tissues, has been associated with influenza vaccine, while a pre-existing Henoch–Schönlein purpura may be exacerbated by hepatitis B, influenza, and measles vaccinations [35]. The first 17-year-old girl who developed Henoch–Schönlein purpura after receiving a tetravalent polysaccharide serogroups A, C, W-135, and Y meningococcal vaccine was reported 10 years ago [36]. However, a recent study investigating the Vaccine Safety Datalink found no relationship between a previous meningococcal polysaccharide vaccination and the post-vaccine incidence rate of Henoch–Schönlein purpura in adolescents, highlighting the importance of the evaluation of large case series before drawing conclusions on the safety profile of specific vaccines [37]. The lack of data on the validity of algorithms to identify rare conditions may hamper our ability to determine incidence patterns with respect to infection and vaccination exposures [38]. Further epidemiologic research to define validated methods of identifying cases could improve surveillance using large-linked healthcare databases.

Influenza immunization is recommended worldwide for individuals with chronic underlying disease, and systemic post-vaccine complications such as vasculitis or rheumatic disorders have been rarely reported [39]. However, the link of influenza vaccine with autoimmune diseases is still a huge matter of debate. Giant cell arteritis and polymyalgia rheumatica have been associated with the administration of this vaccine only in people over 50 years, though the exact relationship with the vaccination remains doubtful [40–42].

Vaccines against hepatitis B virus have also been reported in association with autoimmune disorders, though a causal relationship has not been unequivocally established [43]. Protean autoimmune disorders following hepatitis B vaccination have been sporadically reported in adults: optic neuritis, multiple sclerosis, vasculitis, pemphigus, and thrombocytopenic purpura [44]. Post-vaccine arthritides have been observed after hepatitis B vaccination, which may be explained by the presence of immune complexes containing the viral antigen and specific antibodies, as observed during the natural course of hepatitis B virus infection, or by hypersensivity to the vaccine adjuvants (either the organomercury compound known as thimerosal, which was removed in 1999, or aluminum and yeast proteins) [45]. There are conflicting opinions about the potential role of hepatitis B vaccination in the exacerbations of systemic erythematosus lupus, requiring that epidemiological studies be performed to examine this potential association in more detail, quantitate the risk, and identify possible genetic risk factors [45].

Human papillomavirus vaccination has been considered a possible triggering factor for vasculitides in individuals with a genetic predisposition: The quadrivalent human papillomavirus (virus types 6, 11, 16, 19) recombinant vaccine has been associated with systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, dermatomyositis, and systemic sclerosis in adolescents and young adults although a causal relationship has not been unequivocally established [46]. Recently, to investigate the association between HPV vaccination and autoimmune manifestations compatible with SLE or SLE-like disease, the medical history of six women who presented with SLE or SLE-like disease following HPV immunization was collected [47]. In the reported cases, several common features were observed, such as personal or familial susceptibility to autoimmunity or adverse response to a prior dose of the vaccine, both of which may be associated with a higher risk of post-vaccination autoimmunity. Favorable response to immunosuppressant was observed in all patients. In the study, a temporal association between immunization with HPV vaccine and the appearance of a spectrum of SLE-like conditions was reported [48]. Moreover, also severely disabling conditions have been related to HPV vaccination, such as premature ovarian failure in young girls, which might have significant consequences for future prospects of motherhood [49].

Inflammatory myopathies and skin reactions triggered by vaccines against diphtheria, tetanus, and poliomyelitis have been reported also in children and adolescents [50].

All these data highlight that health authorities should continue collecting data on vaccine safety with the goal of improving our knowledge about the specific interactions between the host and adjuvants enclosed in the various vaccines, keeping in mind that latency periods between the vaccine administration and the appearance of clinical symptoms can be longer than the time interval commonly observed in most vaccine risk assessment studies.

Gulf war syndrome

Ill-health has been reported by deployed people during the Persian Gulf and Yugoslav wars of 1991, with symptoms varying between post-traumatic stress syndrome and others suggestive of a direct effect on the immune system, depending on multiple prophylactic medications, exposure to chemical or biologic warfare agents, smoke from oil-well fires, depleted uranium weapons, desert sand, mycotoxins, and other bacterial neurotoxins [51, 52]. The most prevalent symptom in GWS was chronic fatigue, probably depending on non-restorative sleep, caused by episodic hypopnea and frequent arousals; other signs and symptoms included malaise, myalgia, headache, ataxia, diarrhea, bladder dysfunction, arthralgia, gastrointestinal complaint, and fever [53–55]. Iraqi children have also been reported as suffering from undiagnosed wasting diseases, but little information about pediatric manifestations of GWS has come to light [56].

Considering overall the available data, further studies are needed in order to clarify whether multiple vaccinations performed in war times or exposure to environmental factors, combined with other "stressful" events related to deployment, might contribute to the risk of adverse health outcomes in these specific populations [57].

Macrophagic myofasciitis syndrome

In 1998, Gherardi et al. described a new inflammatory myopathy of unknown cause, named MMF, which was characterized by pathognomonic histologic lesions: This unusual post-vaccine inflammatory myopathy, almost exclusively reported in French adults with diffuse arthralgia, myalgia and asthenia, was characterized by densely packed macrophage infiltration with granular periodic-acid-Schiff positive content, on muscle biopsies at the site of vaccination [58]. HLA-DRB1*01 allele was highly represented in people with MMS who had received in the previous decade immunization against hepatitis B or A viruses or tetanus toxoid, all containing aluminum hydroxide as adjuvant. The presence of aluminum inclusions in macrophages suggested an inappropriate reaction to aluminum in predisposed subjects, leading to nonspecific manifestations, such as long-term diffuse myalgia beginning in the lower limbs, muscle weakness, asthenia, arthralgia, fever with elevated serum creatine phosphokinase levels. Central nervous system could also be involved with memory loss, attention decrease, and mood disturbances, while demyelination areas could also be found by neuroimaging studies. In addition, 15–20 % of these patients developed different autoimmune disorders, most frequently multiple sclerosis, Hashimoto's thyroiditis, myasthenia gravis, and dermatomyositis [59].

Less than 15 cases of MMS have been reported in children, and 7, younger than 3 years of age, had typical lesions of MMS on quadriceps muscle biopsy. All these children developed hypotonia and motor or psychomotor delay, while spectrometry revealed high levels of aluminum in the muscle tissue of 3 cases [60]. This means that despite the wide use of vaccines in childhood MMS has been rarely observed in children and its characteristic histologic pattern could not be correlated with a distinctive clinical entity.

Siliconosis

The link between immune-mediated diseases and silicones, a family of synthetic polymers sharing a silicon-oxygen chain with hydrocarbons, was recognized in the original description of ASIA, as they may have an immune adjuvant effect. Initially, silicone was considered an inert material, unable to induce immune reactions, which was incorporated into a myriad of medical devices, i.e., artificial heart valves, joint implants, and ventriculoperitoneal shunts [61–63]. The most common actual medical use of silicone is as component of breast implants, which were first introduced in 1960s for reconstructive and cosmetic purposes [62]. Autoimmune disorders related to silicone are systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, and Sjögren's syndrome, all showing that silicone implants might cause nonspecific foreign body reactions, which might also be associated with autoantibody formation. The development of an overt autoimmune disorder happens only in the presence of a peculiar genetic predisposition, advocating a role of silicone as environmental trigger of autoimmunity [64]. In 1999, a large investigative study using a longitudinal databank showed no relationship between prior silicone breast implants and the subsequent development of fibromyalgia rheumatica and rheumatoid arthritis in adults [65]. Recently, Jara et al. reported a case of an 11-year-old female who was diagnosed with systemic onset-juvenile idiopathic arthritis: The patient underwent silicone breast implants at the age of 22 years, presenting with a transient lupus-like syndrome, but also had a severe reactivation of her systemic onset-juvenile idiopathic arthritis at the age 25 years, when silicone breast implants broke. Removing prostheses led to a

remarkable improvement of the clinical picture [66]. However, no report of siliconosis occurred in the pediatric age has been published.

Sick building syndrome

The term SBS, coined in the mid-1970s, assembled a set of clinical symptoms reported by occupants of a building [67]. The occurrence of nonspecific manifestations among populations living in modern buildings is common in the Western world: dampness and mold in public buildings, private houses, workplaces, and schools have been associated with adverse respiratory symptoms, asthma, and respiratory infections of inhabitants. The major accused trigger of SBS is poor indoor air quality, mostly dependent on air conditioning implants, considered a source of microbial contamination and dispersion of chemicals [68]. According to the quantitative definition of the American Society for Heating, Refrigeration and Air conditioning Engineering, a "sick building" is one where at least 20 % of occupants report health symptoms and discomfort by staying there and relief upon leaving it [69]. In 1984, the World Health Organization estimated that up to 30 % of buildings worldwide had these features [70]. It has been suggested that the nature of the pollutants, the intensity and duration of exposure, and the reactivity of the occupant's immune system influence the clinical manifestations of building-related diseases [71]. A host of symptoms typically observed in SBS includes headache, arthralgia, fatigue, lethargy, eye and throat irritation, nasal congestion, dyspnea or asthma, dysosmia, nausea, skin rashes, dizziness, and sleep disturbances [72]. Many external factors have been shown to be associated with the prevalence of such symptoms, and moreover, as considered in the proposed diagnostic criteria of ASIA, the presence of autoantibodies directed to the suspected adjuvant may be detected in SBS. Gray et al. [73] demonstrated that a subject exposed to mixed mold mycotoxins in a water-damaged building had a higher risk to produce autoantibodies with subsequent increased risk of autoimmunity.

Children are also implicated in autoimmune or inflammatory disorders, which can be framed in the context of SBS. Emenius et al. examined the impact of building characteristics and indoor air quality on recurrent wheezing in 4,089 infants, born in predefined areas of Stockholm, during their first 2 years of life; their houses were investigated and ventilation rate, humidity, temperature, and nitrogen dioxide measured. The authors found that relatively new apartment buildings, single-family houses with crawl space/concrete slab foundation, and elevated indoor humidity were associated with recurrent wheezing in infants [74]. However, preventive or corrective actions in cases of SBS often fail, though Sauni et al. [75] demonstrated that remediating buildings damaged by dampness and mold reduce asthma-related symptoms and the number of respiratory infections in children.

Allergy or hypersensitivity after different vaccines has been reported, although they are rare adverse events [76]. To further minimize their occurrence and to provide adequate care to those affected, careful monitoring of immunization programs and case management is required. To address these issues, vaccine pharmacovigilance systems have been developed [77–79].

Conclusive remarks

Vaccines remain crucial for the eradication of infectious diseases [80, 81]: Increasing sustained immunization efforts have allowed to eradicate smallpox and to lower the global incidence of poliomyelitis so far by 99 % [72]. However, in spite of undisputed success of immunization campaigns more than 3 million deaths still occur each year from vaccine-preventable diseases [73].

The accumulation of many reports and the temporal association between vaccinations or exposition to a large amount of external triggers and autoimmune or inflammatory diseases have led different authors to hypothesize the presence of a causal link. Such a link does not necessarily means that the vaccine, with its adjuvants and preservatives, or the external trigger is the single initiator of the autoimmune or inflammatory process, but rather it may act as an accelerator of an overt disease presentation or as a contributor to the exacerbation of non-symptomatic diseases in certain individuals genetically prone to manifest such a disease.

Hence, ASIA results as a newly defined condition, which has been related to the presence of a common denominator identified in the substances used to accelerate, prolong, or enhance antigen-specific immune responses, namely adjuvants, but also to different external environmental triggers. In the presence of a favorable genetic background, many autoimmune/inflammatory responses can be triggered by adjuvants and external factors, showing how the man himself might breach immune tolerance and drive many pathogenetic aspects of human diseases. Nonetheless, the elective application of ASIA diagnostic criteria to the pediatric population requires further assessment and evaluations.

Additional studies are needed to help clarify connections between innate or adaptive immunity and pathological and/or protective autoantibodies mostly in the pediatric age, as children and adolescents are mainly involved in the immunization agendas related to vaccine-preventable diseases. Even case reports can provide the first insight into new biologic principles helping a better understanding of

mechanisms of action of different adjuvants in the pathogenesis of post-vaccination autoimmune and/or inflammatory phenomena observed in the pediatric background. These events show the paramount importance of surveillance strategies and highlight the strengths and challenges of international cooperation in signal verification and epidemiological investigations.

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