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The value of Autoimmune Syndrome Induced by Adjuvant (ASIA) - Shedding light on orphan diseases in autoimmunity

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ABSTRACT

Autoimmune Syndrome Induced by Adjuvant (ASIA) is a definition aimed to describe the common etiological process at the root of five clinical entities sharing similar symptomatology: macrophagic myofasciitis syndrome (MMF), Gulf War Syndrome (GWS), sick building syndrome (SBS), siliconosis, and post vaccination autoimmune phenomena. ASIA illustrates the role of environmental immune stimulating agents, or adjuvants, in the instigation of complex autoimmune reactions among individuals bearing a genetic preponderance for autoimmunity. The value of ASIA lies first in the acknowledgment it provides for patients suffering from these as yet ill-defined medical conditions. Equally important is the spotlight it sheds for further research of these poorly understood conditions sharing a common pathogenesis.
In this article we elaborate on the significance of ASIA, review the current evidence in support of the syndrome, and address recent reservations raised regarding its validity.

Contents

1. Introduction

Autoimmune\Auto-inflammatory Syndrome Induced by Adjuvants or ASIA, was first described by Shoenfeld et al. in 2011 [1]. The syndrome relates to five immune mediated conditions: the macrophagic myofasciitis syndrome (MMF), the Gulf War Syndrome (GWS), the sick building syndrome (SBS), siliconosis, and post vaccination autoimmune phenomena [2–4]. All share similar clinical characteristics including myalgia, myositis, arthralgia, neurological manifestations, skin manifestations, dry mouth, cognitive alterations, fever and chronic fatigue syndrome [5].

ASIA was described with the aim of delineating a potential common pathway of autoimmune pathogenesis - the syndrome attempts to group these poorly defined clinical entities, believed to be of an autoimmune nature, on the basis of their shared feature: all are linked to an environmental immune stimulatory factor, i.e. adjuvant.

While the effects of the environment on autoimmunity are vastly established [6–9], ASIA aims to organize under a single umbrella the existing evidence regarding certain environmental factors which possess immune stimulatory properties, in order to shed light on a common

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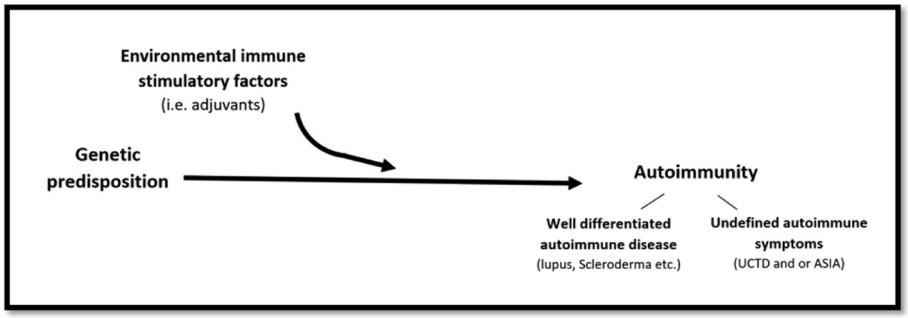

Fig. 1. Schematic illustration of the process of autoimmunity development. ASIA may serve to describe the principle pathogenesis of all autoimmune conditions. This process entails an exposure of a genetically prone individual to an external immune stimulatory trigger, resulting in overt autoimmunity, which may manifest as a well-recognized autoimmune disease such as lupus, or rather present as a collection of autoimmune symptoms which may be referred to as UTCD or as ASIA, depending on clinical presentation. Abbreviations: UCTD - undifferentiated connective tissue disease; ASIA – autoimmune syndrome induced by adjuvants.

pathway of autoimmune pathogenesis. Such environmental immune stimulators, or adjuvants, include among others, injectable silicone [10] and aluminum salts [11], as well as various infectious agents [12,13]. Whereas most of these factors have already been individually linked to the development of autoimmunity [12–17], ASIA relates to the principle underlying shared mechanism of adjuvant induced autoimmunity, in genetically prone individuals (Fig. 1).

1.1. The validity of ASIA

In a recently published article aimed at refuting the existence of ASIA [18], Ameratunga et al. claim that the fact that patients with defined autoimmune diseases may fit the diagnostic criteria of ASIA represents evidence to the irrelevance of the syndrome. However, since the definition of ASIA was designed to describe all autoimmune processes induced by adjuvants, it is inherent to the definition that certain expressions of specific autoimmune diseases fit the ASIA criteria. In fact, in a recently published analysis of 300 patients from the international ASIA registry, 89% of the patients were diagnosed with an additional autoimmune condition(5). These rates may be partly attributed to the genetic profile of ASIA patients, which predisposes them to autoimmunity. However, the most frequent autoimmune disease reported in association with ASIA was Undifferentiated Connective Tissue Disease (UCTD), implying that there is an autoimmune process among these patients that is still poorly defined ("undifferentiated").

Indeed, we would like to see a future where all patients fitting the ASIA criteria will have been diagnosed with a specific autoimmune disease with an elaborately explored mechanism and, accordingly, a perfect cure. Nevertheless, until we reach such utopian times, ASIA facilitates the designation of medical attention and scientific research into these ill-defined conditions of common pathogenesis.

1.2. Scientific evidence in support of ASIA

The scientific theory behind ASIA rests on paradigms already broadly acknowledged in published autoimmunity research:

First, the crucial role of genetic susceptibility in the development of autoimmunity. Numerous studies have demonstrated the significant correlation between certain genetic profiles and various autoimmune diseases [19,20]. Of the many genetic loci implicated in predisposition to autoimmunity, most prominent are those encoding for MHC class II molecules, which are responsible for antigen presentation to immune cells. Though the exact mechanism linking these molecules to autoimmunity remains undefined, an accepted theory relates to aberrant presentation of antigens to autoreactive T lymphocytes, resulting from these allelic variations of the MHC molecules, such as certain HLA DRB1 alleles [21–24]. In fact, it was suggested that the genetic susceptibility to autoimmunity which results from carrying these certain MHC alleles, is nothing but a reasonable evolutionary toll, as these genetic traits may have provided a survival advantage for those with an overactive immune system, which would be more effective in fighting infections [23,24].

Thus, while certain environmental factors, such as gluten, are relatively abundant, only those individuals possessing the predisposing MHC alleles, such as HLA DQ8, may develop autoimmunity upon exposure, as is the case with Celiac patients.

The second foundational paradigm of ASIA relates to the role of adjuvants in immune stimulation. The term adjuvant originates from the Latin word '*adjuvare*', to assist. Indeed, in 1989, in a seminal paper by Charles Janeway, he described adjuvants as "the immunologist's dirty little secret", as they are the necessary additive every immunologist must apply in order to induce a significant, 'researchable' immune response(25). Hence, adjuvants have been serving for decades as an imperative tool in experimental research of the immune system, due to their ability to produce widespread activation of various immune cells, creating a metaphoric magnifying glass, in order to enhance, and accelerate models of immune response. A principle example for this can be found in the pivotal study of Witebsky et al., who in 1957 created the first experimental model of Hashimoto thyroiditis in rabbits [26]. In order to obtain clinical thyroiditis, the thyroglobulin antigens injected to the animals were combined with complete Freund's adjuvant, demonstrating the crucial role of adjuvants in the research of autoimmunity.

Yet adjuvants are now used extensively outside the laboratories of immunologists, and can be found in a wide array of medical as well as non-medical contexts. In light of the substantial immune stimulatory properties of adjuvants, it is not at all surprising that many of these substances, previously considered benign, have been implicated to directly induce autoimmunity. In fact, the notion that adjuvants may contribute to the development of autoimmune diseases is in no way a novelty of ASIA, but rather dates back as far as the early 1980 when reports began accumulating on a condition referred to as the "human adjuvant disease", consisting of autoimmune symptoms suggestive of connective tissue disease following silicone implantation or injection [27–29]. Further evidence on the role of adjuvants in the development of autoimmunity was provided in a series of experiments in various murine models, demonstrating the capacity of several adjuvants to induce a significant increase in inflammatory cytokine production associated with the appearance of lupus related autoantibodies [30–33].

While these findings clearly demonstrate the potential of certain adjuvants to directly induce autoimmunity, the theory of ASIA refers to a broader interplay entailing exposure of genetically susceptible individuals to adjuvants, alongside additional environmental factors which may provoke autoimmunity. Accordingly, the presence of silicone, for example, which is known for its adjuvant properties [10], in the breast implants of a woman with a significant family history of autoimmunity, might substantially increase her own risk for autoimmunity. This

autoimmune reaction may manifest as a complex of unexplained symptoms including chronic fatigue, arthralgia, myalgia, asthenia, skin abnormalities and fever [34–36], referred under ASIA classification as 'siliconosis'.

1.3. The importance of ASIA in clinical practice

This hypothetic *scenario* of a genetically susceptible woman suffering from siliconosis following silicone breast implantation, exemplifies the importance of defining ASIA.

ASIA provides numerous frustrated patients, who develop multiple autoimmune symptoms following exposure to adjuvants, with a simple definition for their genuine medical condition, which was previously referred to as obscure and perhaps even dismissed. Though there is yet much to unravel regarding this autoimmune process, the definition enables physicians to address these patients in the proper context of scientific research, treatment and prevention. Regarding the described *scenario* for example, it stands to reason that women with a known predisposition for autoimmunity should be advised by the physicians to avoid silicone breast implantation [37].

Furthermore, by approaching such cases as an autoimmune syndrome and collectively researching them, we broaden our understanding of their underlying pathogenesis and most importantly - we may reveal potential beneficial medical interventions. Such was the case in a study conducted by De Boer et al. [38], who reported that excision of implants lead to clinical improvement in a large series of 200 women suffering from ASIA associated with silicone implants.

Finally, acknowledging ASIA, an autoimmune process induced by adjuvants, has important ramifications on patients who developed significant disability following adjuvant exposure in terms of financial compensation. Naturally the implications on various branches of the pharma industry result in a somewhat volatile discussion, which seems to become even more fervent when approaching one specific aspect of ASIA – the post vaccination phenomena.

1.4. ASIA and vaccines

Much of the opposition to the research of ASIA seems to stem from the suggested implications of the syndrome on the practice of vaccination. In recent years we have been witnessing significant polarization of the discussion regarding vaccines. Faced with the rising tide of vaccine opposers (most originating from nonscientific background with unconventional arguments), the medical community seems to be cultivating parallel escalating contra extremism: it appears that in the current defensive climate any hint of scientific critique regarding the efficacy or safety profile of a given vaccine is responded to with overwhelming wrath, accompanied by personal slander and reflexive dismissal, often without proper evaluation of the issues raised [39].

One recent example for such publication bias may be found in the case of a paper reporting behavioral changes in mice following administration of the Gardasil vaccine, which was mentioned by Ameratunga and colleagues as well [18]. The paper, which was withdrawn from the journal 'Vaccine' [40] after being successfully approved by the journal appointed peer reviewers, was later published in the journal 'Immunological research' [41] following fulfillment of a repeated peer review. Furthermore, similar findings were published almost simultaneously by a separate group [42]. This chain of events points to the fact that the study was withdrawn for reasons other than 'methodological flaws' as was suggested by Ameratunga et al. [18], but rather due to political considerations aiming to avoid criticism of vaccines.

This antagonism to criticism is rather absurd when considering the generally accepted consensus that every effective medical intervention results in certain side effects. Vaccines, in this aspect, are no exception to the rule, as is evident from examples of previous vaccines which have been withdrawn due to an unsatisfactory risk to benefit ratio, such as the 'Rotashield' vaccine (Table 1) [39].

The link between vaccine administration and the rapidly rising incidence of autoimmune/immune mediated events have been constantly reported. Table 2 lists many of the autoimmune-related adverse events reported following vaccine administration, retrieved by an extensive and comprehensive literature search.

It appears as though many physicians are eager to dismiss reports of vaccine induced adverse events as unsubstantiated evidence of causality. Yet in the present era of omnipotent pharmaceutical companies which often expedite vaccines to the market based on hastily conducted safety studies [43–45], it is not unusual for significant adverse effects to be initially revealed through case reports and case series. Therefore, while these sporadic reports obviously do not suffice to determine causality, they should be viewed as red flags, indicating the need for further investigation. Hence stems the utmost importance of publicizing such case series and properly addressing them. The new international ASIA registry, which joins existing databases of vaccine related adverse events, provides a vital platform for recognizing these red flags [46].

However, as such publications are all too often interpreted as "anti-vaccines", perhaps it is worth reiterating that an educated discussion of the potential adverse effects of vaccines in no way diminishes the importance of vaccines as life-saving interventions. ASIA was not defined in order to "blame" vaccines for autoimmunity, but rather to address the role of environmental adjuvants as a whole in the induction of autoimmunity among populations at risk [47]. These adjuvant factors range from certain molds referred to in sick building syndrome, through silicone which may induce siliconosis, to combinations of antigen particles and aluminum which may induce post vaccination autoimmunity. Therefore, while the diagnostic criterion in ASIA regarding induction of improvement upon removal of the inciting agent does not apply for vaccines, as it is impossible to extract the injected vaccine, this does not, as was suggested by Ameratunga et al., undermine its validity for other subtypes of ASIA, such as siliconosis and sick building syndrome. Implying that since this criterion may not apply to all ASIA cases the syndrome is not valid, is akin to suggesting that since not all rheumatic fever patients suffer from Sydenham's chorea, this clinical entity should be dismissed. Furthermore, there are ample papers describing the aggravating effect caused by cumulative doses of vaccines in certain settings, leading to relapses and exacerbations in autoimmune phenomena, as was summarized in a paper published in the 'Journal of Autoimmunity' several years ago [48].

Table 1
Selected vaccine preparations that were withdrawn as result of adverse events.

Vaccine	Year of withdawal	Events leading to vaccine withdrawal	Ref.
Fluvax® [Influenza vaccine]	2010	Increased febrile adverse events, convulsions, and vomiting. Most events occurred in healthy children within 12 h of vaccination. In the in vitro model, IFN-, IL-1, IL-6, IL-10, IP-10 and MIP-1 levels were significantly higher when measured at and 24 h in cultures stimulated with Fluvax® compared with alternative 2010 trivalent vaccine preparations.	[82]
LYMErix™ [Lyme vaccine]	2002	Vaccine recipients experienced more local reactions, including redness or swelling at the injection sites as well as systemic symptoms such as myalgia, fever or chills. Vaccinated group had more arthralgia as compared to placebo group. VAERS database included 905 reports of mild self-limited reactions and 59 reports of arthritis associated with vaccination.	[83,84]
RotaShield [rotavirus vaccine]	1999	Multiple cases of intussusception	[85]

Table 2
Autoimmune disorders associated with various vaccine preparations.

Vaccine-targeted pathogen	Autoimmune disorder associated with the vaccination	Ref №
Rabies	Guillain-Barré syndrome, polyneuritis, acute disseminated encephalomyelitis, transverse myelitis, neuromyelitis optica, immune thrombocytopenic purpura	[86–98]
Influenza	Transverse myelitis, acute disseminated encephalomyelitis, narcolepsia, vasculitis, immune thrombocytopenia, Evan's syndrome, optic neuropathy, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/drug-induced hypersensitivity syndrome, Churg-Strauss Syndrome, polymyositis and autoimmune myopathies, giant cell arteritis, polymyalgia rheumatica, subacute thyroiditis and dyserythropoesis, Bell's palsy and paraesthesia, inflammatory bowel disease, autoimmune hemolytic anemia, pemphigus	[49,99–150]
Hepatitis A	Neuromyelitis optica, immune thrombocytopenia, autoimmune hepatitis	[94,151,152]
Hepatitis B	Arthritis, chronic fatigue syndrome, inflammatory myopathies, systemic lupus erythematosus, transverse myelitis, vasculitides, lichen planus, bullous pemphigoid, myasthenia gravis, multiple sclerosis, uveitis, reactive arthritis, rheumatoid arthritis, pemphigus, undifferentiated connective tissue disease, GBS	[153–162]
Human papilloma virus	Neuromyelitis optica, mixed connective tissue disease, RA, vasculitis, cerebral vasculitis, primary ovarian failure, postural tachycardia syndrome, coeliac disease	[4,163–175]
Tetanus	Inflammatory myopathies, Guillain-Barré syndrome, dermatomyositis, systemic lupus erythematosus, type 1 diabetes mellitus and anti-phospholipid syndrome	[103,176,177]
Diphtheria/pertussis/tetanus	Transverse myelitis, optic neuritis, GBS, SLE, inflammatory myopathies, antiphospholipid syndrome, autoimmune hemolytic anemia	[178,179]
Lyme disease	Autoimmune arthritis, arthralgia	[180–182]
Yellow fever	Neurotropic disease, characterized by encephalitis, meningoencephalitis, Guillain-Barré syndrome, viscerotropic disease	[122,183–194]
Measles, mumps, rubella	Arthritis, immune thrombocytopenia, thrombocytopenic purpura, transverse myelitis, fibromyalgia, Guillain-Barré syndrome	[195–214]
Meningococcus	Bullous pemphigoid, neurobehavioral disorders (anorexia nervosa and chronic tic disorder), systemic lupus erythematosus, Guillain-Barré syndrome	[178,215–218]
Pneumococcus	Bullous pemphigoid, polyserositis	[218–220]
Hexavalent vaccine	Bullous pemphigoid	[221,222]
Herpes zoster	Arthritis, alopecia areata	[223]
Anthrax	Rheumatoid arthritis, oral pemphigus vulgaris	[224,225]
Smallpox	Eczema vaccinatum, progressive vaccinia, postvaccinal encephalitis, vaccinia necrosum, myocarditis, and dilated cardiomyopathy	[122,226–228]
Poliovirus	Paralytic poliomyelitis	[122]
Tick-Borne encephalitis virus	Narcolepsy	[229]

Substantial support for the validity of ASIA and specifically post vaccination induced autoimmunity may be found in the numerous examples of infections which can induce autoimmunity. Suggested mechanisms of infection induced autoimmunity include epitope spreading, bystander activation, clonal expansion and molecular mimicry [12,13]. This relationship between infections and autoimmunity is one of the reasons to supply the public with effective vaccines which can prevent infections and thus reduce resultant autoimmunity. However, the same mechanisms of infection induced autoimmunity may theoretically apply for the relationship between vaccines and autoimmunity. Molecular mimicry in particular has been widely explored as the mechanism behind several vaccine induced autoimmune manifestations [49–53]. It was suggested [54] the exposure of the immune system to a stimulant such as the adjuvants contained in vaccines, leads to diminished immune tolerance. In the setting, pathogen derived particles from vaccines which are similar to human proteins may induce an immune response against these 'self-proteins', thus leading to autoimmunity.

Thus, while continuing to promote vaccines as crucial medical interventions, we should simultaneously constantly strive to improve the current products which are not devoid of limitations. One interesting direction offered by our group is to develop vaccines which contain unique viral peptides, namely peptides which are not homologous to the human proteome (as are the peptide contained in most current vaccines) [55]. Such non-homologous peptide vaccines have the potential to eliminate vaccine induced molecular mimicry and autoimmunity.

1.5. The role of aluminum in ASIA

In their article, Ameratunga et al. focused much of their efforts to refute ASIA on one specific subject referred to under the ASIA umbrella - the contribution of aluminum to the development of autoimmunity. Ameratunga et al dismissed a possible role of aluminum in immune stimulation by referring to a study from Denmark [56]. In this study, patients with allergic rhinitis who were treated with aluminum-containing allergen preparations as immunotherapy, had a lower incidence of autoimmunity compared with those on conventional treatment. Ameratunga et al. concluded that these results represent a strong argument against the existence of the ASIA syndrome caused by aluminum-containing vaccine adjuvants. However, the authors chose to ignore several pivotal principles which shed a different light on the relationship between aluminum and the ASIA syndrome;

First, the attempt to present aluminum as a safe and tolerant compound on the basis of the Danish research alone ignores existing robust clinical and experimental evidence, well describing the toxic effects of aluminum, especially in terms of neurotoxicity. Poisoning attributed to aluminum was first reported in 1921 [57], in a case study describing a metal worker who had loss of memory, tremor, jerking movements, and incoordination following exposure to aluminum. Later, aluminum has been shown to disrupt metal balance within cells, inducing mitochondrial failure and generation of reactive oxygen species [58]. Today, the toxicity of aluminum in humans is well described, with possible causal relationships between a high aluminum body burden and a number of neurological disorders and disease states. Aluminum has been shown to interfere with intracellular cascades and induce production of inflammatory signals [59]; induce severe degeneration of cholinergic neurons [60]; impair murine fetal brain development [61]; and induce brain inflammation gliosis leading to neurological deficits [62]. These findings are in line with other studies that found an association between aluminum exposure and the development of Alzheimer disease and in human and animals [63].

Another well-described toxicity associated with the use of aluminum is the syndrome of dialysis encephalopathy, a progressive neurological disease which usually causes death within six to eight months. It was observed in chronic renal failure patients on regular hemodialysis, characterized by dementia, speech disturbances, myoclonus and seizures. The association with aluminum toxicity was first indicated as the underlying cause of this syndrome in the 1970s, following the report of higher brain gray-matter aluminum values in all patients with the dialysis encephalopathy syndrome compares to control subjects [64]. Later,

strong biochemical and epidemiological data confirmed the implication of aluminum in the pathogenesis of this disease [65]. In view of the known toxicity, aluminum has been withdrawn from the dialysate, and it has been recommended that the minimum amount of aluminum-containing, phosphate-binding gels should be administered to control serum phosphorus levels [66].

Second, there is a growing body of evidence in the current literature for the risk of toxicity associated with the use of aluminum in sub-cutaneous immunotherapy (SCIT) [67]. Adverse reactions in individuals receiving allergy immunotherapy have been reported, including foreign body granulomas [68], urticarial [69], sub-cutaneous sarcoidosis [70,71], progressive circumscribed sclerosis [72,73], and cutaneous-sub-cutaneous pseudolymphoma [73]. A comprehensive review from Germany discusses the acute and chronic toxicity of aluminum in allergen-specific subcutaneous immunotherapy [74]. Of note, the authors describe the propensity of aluminum to form small focal accumulations in body tissues, including the brain, which can arise over the life-time of an individual. Aluminum salts have been used in allergy therapy for many decades and are assumed to be safe based on pharmacovigilance databases – subjective reports of adverse events from the register of spontaneous reports or from clinical studies [74]. This kind of database is certainly not suitable to detect causal relationship between SCIT and the development of diseases, especially since autoimmune diseases could have a latency period.

Third, the simplistic comparison offered by Ameratunga et al. of aluminum doses in SCIT to those contained in vaccines, disregards the fundamental chemical differences between the two compounds: Vaccines contain, in addition to adjuvants, pathogen derived antigenic particles, often produced through cell cultures which may entail additional contaminants (both infectious and non-infectious) [75,76]. The antigens, and or contaminants, can act alongside the adjuvants to induce autoimmunity through various mechanisms such as molecular mimicry, epitope spreading, and bystander activation [7,77].

It is further worth mentioning that the Danish study was not a randomized controlled trial (RCT), but rather an observational study, and therefore could not accurately assess the safety of the aluminum component of SCIT – for that to be assessed properly, an RCT should have been conducted comparing aluminum-containing and aluminum-free allergen desensitization immunotherapy. Furthermore, since vaccines are administered to millions of people worldwide, and not everyone develops serious adverse manifestations, it is obvious that the genetic susceptibility of an individual has an important role in vaccine–autoimmunity interactions [21]. The Danish study evaluated individuals with allergic diseases, a population with different genetic characteristics from the population known to be at risk of developing autoimmunity following adjuvant exposure.

Lastly, it is difficult to ignore the fact that A. Linneberg, who is the first Author of the Danish paper referring to the safety of SCIT, has declared to receive honoraria for lectures from ALK-Abello, the pharmaceutical company that produces the assessed SCIT discussed in the paper.

We suggest therefore that caution should be applied in drawing such substantial conclusions from this single study.

1.6. Animal models and ASIA

Ameratunga and colleagues raised their further reservations [78] that the definition of ASIA has led to the execution of unethical experiments in animal models. They refer to eleven publications regarding mostly murine models of autoimmunity and one ovine models. The importance of mutual genuine critique among the scientific community cannot be overstated, as it is the tool through which science improved, and therefore this perspective is of potential value in pointing to aspects in these animal experiments which may be improved in order to produce better evidence. Such is the mention of missing detail in certain experimental protocols described (which may be easily rectified by raising a direct query within the publishing journal), and such is the attention drawn to the relatively low number of animals in some of the experiments, which is unfortunately a frequent limitation in animal research.

Other issues raised are at the root of the ethical scientific debate of animal experimentation and have no direct relationship with ASIA. Such is the issue of utilizing Complete Freund's Adjuvant (CFA) in animal models. While CFA has been traditionally the prototype adjuvant used in laboratories [25], progress in science and ethical approaches have led to increasing attempts to avoid this substance in animals, and in fact one of the publications mentioned by Amertunga as an example of unethical application of CFA was a murine study designed to demonstrate aluminum adjuvants may replace CFA in vaccination of mice for research purposes [79]. The administration of CFA in some of the mentioned publications is an outdated practice in the current ethical standard. However, the generalizing character of the criticism by Amertunga omits the fact that out of the four mentioned experiments using CFA, three examined additional adjuvants which are currently used in administered vaccines, while the rest applied actual marketed vaccines in their animal injections, undermining the notion that the adjuvants examined were irrelevant to common medical practice.

It is also worth mentioning that some of the claims raised by Amertunga and colleagues appear inaccurate if not haphazard, such as the claim of inappropriate adjuvant doses used in the publication by Khan et al. [80]. Khan details elaborate explanations under 'materials and methods' of the calculations performed in order to calibrate the vaccine doses administered to mimic human doses.

Yet, it seems the most important reservation that should be raised regarding this perspective brought by Amertunga is more fundamental: The attempt to address all animal experiments referring to ASIA at once, as if the purpose of these eleven studies by various groups was solely to validate ASIA, seems rather artificial. Each study, with is advantages and flaws, was individually designed to assess the potential value or shortcomings of a specific medical intervention. The existence of ASIA as a clinical definition bears no relevance to the important practice of assessing the clinical effects of various differing adjuvants through animal models. Simply put, as long as aluminum is injected to humans there will be scientists experimenting with aluminum injections to animals in a constant search of safer interventions, regardless of whether ASIA is acknowledged or not.

2. Conclusions

In this paper we set out to review the theoretical basis behind the definition of ASIA and its relevance in clinical practice. We further addressed several key points raised recently by Ameratunga et al. [78,81] in an attempt to refute the validity of the syndrome.

ASIA is a condition aimed at defining several 'orphan' clinical entities, based on acknowledged paradigms in autoimmunity - While most distinct autoimmune diseases are well accepted to be associated with certain genetic profiles as well as numerous attenuating environmental "adjuvant" factors (be it smoking, sun exposure or certain infectious agents), ASIA merely implies that the same principles of pathogenesis may apply for the yet undefined, though distinct, complex of symptoms which are reported in certain individuals following exposure to various adjuvants.

The importance of addressing these collections of autoimmune symptoms resulting from adjuvant exposure as one entity, or syndrome, is twofold: First, for the patients, who without a clear medical definition may wander endlessly though healthcare systems with no validation for their maladies and more importantly, without proper treatment.

Second, and perhaps most significantly, for furthering future research aimed at characterizing important environmental adjuvants, the immune reactions they induce, and possible preventive as well as curative measures.

We hope that through increased understanding and further evaluation of the patient population, combined with continued study of

adjuvants and their effects on the immune system, a more rational foundation may be set for the development of improved medical interventions such as vaccines, which could possibly reduce expressions of this immune mediated syndrome.

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