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Review

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Review

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA): past, present, and future implications

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Summary

Adjuvants, as the name indicates, are adjoined material aimed to assist in functioning as when added to vaccines they are meant to boost the effect and strongly stimulate the immune system. The response of the immune system can be unpredictable, and the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was developed to address possible adverse reactions of an autoimmune and inflammatory type that may be caused by adjuvants. While ASIA, as a syndrome, was coined and defined in 2011; reports describing patients with vague and nonspecific clinical symptoms following vaccinations appeared much earlier. In other words, ASIA came to define, arrange, and unite the variety of symptoms, related to autoimmunity, caused not by the vaccine itself, rather by the adjuvant part of the vaccine such as aluminum, among others. Accordingly, the introduction of ASIA enabled better understanding, proper diagnosis, and early treatment of the disorder. Furthermore, ASIA was shown to be associated with almost all body systems and various rheumatic and autoimmune diseases such as systemic lupus erythematosus, antiphospholipid syndrome, and systemic sclerosis. In addition, the correlation between COVID-19 and ASIA was noticed during the pandemic. In this review, we summarized the reported effects of adjuvants and medical literature before and after ASIA was defined, the several ways ASIA can manifest and impact different systems of the body, and the incidences of ASIA during the COVID-19 pandemic. It is important to clarify, that vaccines are among, if not the, most effective means of fighting infectious diseases however, we believe that vaccines manufacturing is not above criticism, particularly when it comes to added substances possessing a risk of side effects.

Keywords: ASIA, vaccine, adjuvant, silicone, COVID-19

Abbreviations: ASIA: autoimmune/inflammatory syndrome induced by adjuvants, APS: antiphospholipid syndrome, COVID-19: coronavirus disease of 2019, CMV: cytomegalovirus, CNS: central nervous system, EBV: Epstein–Barr virus, HAV: hepatitis A virus, HBV: hepatitis B virus, Hib: Hemophilus influenza type b, HPV: human papilloma virus, MMR: measles, mumps, rubella, ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome, POI: primary ovarian insufficiency, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, SLE: systemic lupus erythematosus, SS: Sjören's syndrome, SSc: systemic sclerosis, UCTD: undifferentiated connective tissue disease.

Introduction

Certainly, vaccines have changed the entire face of humanity and took the world population to a turning point by preventing huge amounts of death due to highly contagious and devastating infectious diseases [1–3]. On the other hand, while vaccines are in fact chemical compounds similar to drugs, adverse events have been inevitable throughout their long use. Part of the meant side effects are due to compounds added during the process of manufacturing the vaccines. However, while the main goal of a vaccine is to trigger an immune response manifested by the production of antibodies supposed to be protective against the infectious agent desired to be prevented; immune and autoimmune related side effects are unsurprising, indeed. ASIA, autoimmune/inflammatory syndrome induced by adjuvants, was first coined by Shoenfeld *et al*. [4]. ASIA is characterized by an innate and adaptive immune response following the exposure to an adjuvant and it includes five conditions namely siliconosis, macrophagic myofasciitis syndrome, sick building syndrome, Gulf War syndrome, and vaccination-induced autoimmunity [5]. Adjuvant, the central component of ASIA, is a substance usually added to vaccines in order to increase and amplify the immune reaction to a targeted antigen, which subsequently results in the production of high titers of antibodies to a specific pathogen [6]. Adjuvants that may also trigger ASIA include silicon and heavy metals like mineral oil, guaiacol, iodine gadital, mercury, and titanium which are not used in vaccines [7].

The diagnosis of ASIA syndrome requires at least two major criteria or one major criteria with two minor criteria (Table 1). According to an update published in 2017 [8], since the introduction of ASIA in 2011 until 2016, more than 4000 patients were diagnosed with ASIA. The most severe occurrences of ASIA were associated with human papilloma virus and seasonal influenza vaccines, silicone implants and mineral oil fillers. Similarly, following the emergence of COVID-19

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Table 1: The diagnostic criteria for ASIA syndrome

Major criteria	Minor criteria
1-Exposure to external stimuli (infection, vaccine, silicone, adjuvant) before the onset of clinical symptoms.	1-Appearance of antibodies directed against the adjuvant suspected to be involved.
2-The appearance of typical clinical manifestations:	2-Secondary clinical manifestations (irritable bowel syndrome, interstitial cystitis, etc.).
a.Myalgia, Myositis, or muscle weakness.	3-Evolvement of an autoimmune disease (i.e., MS, SSc).
b.Arthralgia and/or arthritis	4-Antigens specific for human leukocytes (HLA DRB1, HLA DQB1).
c.Chronic fatigue, un-refreshing sleep, or sleep disturbances.	
d.Neurological manifestations (especially associated with demyelination).	
e.Cognitive impairment, memory loss.	
f.Fever.	
3-Typical histological findings after biopsy of offending organs.	
4-Removal of offending agent results in improvement of symptomatology.	

The different criteria are separated into Major and Minor ones. For a condition to be diagnosed as ASIA two major criteria or one major criterion alongside two minor criteria, are needed. SSC = systemic sclerosis; MS = multiple sclerosis.

pandemic, and after the introduction of COVID-19 vaccines, various reports started to appear describing ASIA-like symptoms in individuals vaccinated against COVID-19 [9, 10].

In our current paper, we addressed ASIA from many points of view, including historic, clinical, and diagnostic aspects. In addition, ASIA during the pandemic of COVID-19 was also summarized. By our study, we aimed to summarize current medical literature regarding ASIA and to elaborate on the associations between different adjuvants and potential clinical manifestations under the umbrella of ASIA.

The pre-ASIA era

Before ASIA was coined by Shoenfeld, the prevalence of autoimmune diseases in the setting of vaccinations has already been heavily studied. Not only in the setting of vaccinations, but also in regard to silicone breast implants and tattoos, all which fall under the term "autoimmune/inflammatory syndrome induced by adjuvants" now, this in addition to Gulf War syndrome and other neurological manifestations [11].

For a long time, a variety of autoimmune disorders have been reported following different vaccinations, such as in the 90s. For instance, following a tetanus toxoid vaccine, cases of optic neuritis and myelitis were documented [12]. As for Influenza vaccine, cases of vasculitis [13], reactive arthritis [14], and Guillain–Barre syndrome [15] were reported. In addition to the mentioned ones, cases of immune thrombocytopenic purpura [16] and diabetes mellitus [17] were seen following measles, mumps, rubella (MMR) vaccine.

At the time, and to this day, hepatitis B vaccine is said to be the most associated with autoimmune disorders such as erythema nodosum and polyarthritis [18], immune thrombocytopenia [19], myasthenia gravis [20], uveitis [21], Reiter's syndrome [22], arthritis [23], systemic lupus erythematosus (SLE) [24], CNS demyelination [25], and Evan's syndrome [26]. Furthermore, a case of chronic fatigue syndrome in a lady with silicone breast implants was also reported following hepatitis B vaccination, suggesting that the immunological response to vaccination may have been enhanced by silicone exposure as an adjuvant [27]. Finally, hepatitis A, oral polio, and swine flu vaccines have also been associated with immune thrombocytopenia [28], Guillain–Barre syndrome [29], and multiple sclerosis [30], respectively.

Interestingly, individuals with HLA-B27 antigen, among other HLA antigens (DR2, DR3, DR4), were found to be more prone and susceptible to develop autoimmune disorders following vaccinations [31], especially ankylosing spondylitis, Reiter's syndrome, and uveitis [32].

These findings led to the belief that adjuvants may be the predisposing factor to autoimmune disorders following vaccination, which was further studied by Shoenfeld *et al.*, stating that the immune system recognizes these molecules through toll-like receptors on leukocytes, causing an adjuvant-induced immune response [33]. Multiple adjuvants were described in this context, including virosomes for HBV, HPV, and HAV, MF59 in certain viral vaccines, MPL, AS04, AS01B, and AS02A against viral and parasite illnesses, and cholera toxin for cholera. In humans, certain adjuvants were mentioned as predisposing factors to autoimmune disorders. For instance, mineral oils adjuvants were thought to be a cause of sclerosing lipogranulomas [34]. However, the two biggest adjuvants causing adjuvant-induced autoimmune disorders were, and still are, aluminum and silicone [35]. Aluminum, which is found in hepatitis A and B vaccines, as well as tetanus vaccine, influenza vaccine, and pneumococcus vaccine, was found to be involved in the development of multiple sclerosis, chronic fatigue syndrome and polymyalgia rheumatica [36]. Furthermore, Gulf War syndrome has been reported following the injection of aluminum hydroxide containing vaccine [37]. As for silicone, it was associated with connective tissue diseases [38], scleroderma, SLE, and rheumatoid arthritis [39].

Finally, tattoos have also been reported in the setting of autoimmune disorders. However, at least before ASIA was introduced, tattoo-related autoimmunity was seen to be induced by other treatments. For example, a granulomatous tattoo reaction was seen following an intense light pulse treatment for facial skin rejuvenation [40]. In this case, the authors were unable to determine, what was the exact cause of the granulomatous reaction suggesting that the causative agent could be anything among the collection of various pigments and excipients introduced to the skin. In addition, a sarcoidosis granuloma was also described following interferon-alpha treatment for a head melanoma [41].

The works listed, among others, led to additional studies by Shoenfeld and friends, which resulted in the introduction of ASIA in 2011.

Adjuvants

An adjuvant is a substance aimed to enhance the effect of an agent given concomitantly [42]. Adjuvants were shown to carry their modulating effect by boosting the immune response [43] and can be commonly found in therapeutic/medical devices such as vaccines, silicone breast implants, mineral oils, and cosmetics. Even though adjuvants are safe most of the time, the administration of adjuvants may trigger an autoimmune response in genetically susceptible and predisposed individuals [42].

Vaccine adjuvants play an important in evoking an adequate immune response following the administration of the vaccine shot [44]. Today, a variety of compounds possessing a plethora of different structures are added to vaccines as adjuvants. However, several studies have discussed their possible role in inducing autoimmunity [42]. Aluminum (alum) is the oldest and most common adjuvant used in human vaccines since the 1920s. Aluminum, as an adjuvant, was first used by Alexander T. Glenny in the diphtheria vaccine [45]. The main mechanism behind the alum-enhanced immune response is the activation of NLRP3-inflammasome which leads to the processing of several proinflammatory cytokines including IL-1β [46]. Aluminum also contributes to slower release of antigens similar to depot vaccines [47].

For decades, aluminum was "the one and the only" in the field of developing adjuvant vaccines until late 1990s when MF59 was started to be used as an adjuvant [48]. MF59, namely polyoxyethylene sorbitan monooleate and sorbitan trioleate, is an oil-in-water emulsion of squalene which stimulates the innate immune system [49]. Moreover, MF59 was shown to increase cytokine formation and myeloid cell migration [50]. However, studies suggested that mineral oils can also lead to autoimmunity by triggering anti-chromatin/DNA autoantibody production [51].

Beyond the above-mentioned adjuvants, more recently developed ones are represented by the adjuvant systems (AS), namely AS01, AS03, and AS04 [52]. Candidate vaccines against malaria (RTS,S) and herpes zoster (HZ/su) contain AS01 which is produced by a combination of aluminum hydroxide with monophosphoryl lipid A (MPL) and the purified saponin QS-21 [53]. AS03, used in several influenza vaccines, is based on squalene like MF59 [54, 55], whereas AS04 is produced by a combination of aluminum hydroxide with MPL, and is used as an adjuvant in (HPV)-16/18 vaccine and hepatitis B virus (HBV) [56].

In fact, adjuvants are not limited only to vaccines, many substances such as silicone, liquid paraffin, and mineral oils can have adjuvant properties [57]. The interaction between silicone and the human body has risen with the use of silicone implants for reconstructive and cosmetic purposes [58]. Breast implants, intraocular lenses, artificial heart valves, ventriculoperitoneal shunts, and joints are among medically used structures made of silicone. Many studies, in human and animals, described the local and/or systemic responses and autoimmunity triggered by silicone implants. Watad and colleagues reported that women with silicone breast implants (SBI) are more likely to be diagnosed with autoimmune disorders compared to SBI-free women [59].

Recently, ASIA was reported in association with mineral oil and cosmetic exposure [60, 61]. For cosmetic purposes, injectable oily substances such as paraffin have been used for a long time [62]. In 1899, the first injection of an oily substance was reported to be applied to the scrotum of a young male who underwent bilateral orchiectomy [63]. Later, the method was adapted to breast augmentation and changing body contour. On the other hand, paraffin has been injected into the penile shaft to improve its size and shape. However, paraffin injection was shown to lead to paraffinomas. In Thailand and Myanmar, 680 cases of self-injected mineral oil to penile shaft were reported to experience serious complications including penile pain (84%), swelling (82.5%), induration (42.9%), purulent secretion (21.8%), and ulceration (12.8%) [64].

The pathophysiology of ASIA

Actually, ASIA is a multifactorial syndrome possessing a blend of environmental and genetic factors that contribute to its pathogenesis. Environmental factors are thought to be responsible for many of the classical features of ASIA syndrome. A study linking Undifferentiated connective tissue disease (UCTD) to ASIA syndrome found that UCTD patients exposed to ASIA-related environmental triggers displayed ASIA-associated symptoms such as chronic fatigue and general weakness more frequently [65]. Therefore, environmental factors are considered as a major criterion for the diagnosing of ASIA [66]. External factors, such as silicone or aluminum, may be capable of triggering the immune system and inducing the production of autoantibodies [46]. Silicone, for example, which was initially believed to be inert and not immunogenic, was reported in association with autoimmune phenomena and diseases. Subsequently, silicone breast illness is considered a classical example of ASIA [67]. Numerous studies have shown that silicone could trigger autoimmunity in two possible ways: boosting immune response and molecular mimicry [68]. After silicone is injected, it induces acute inflammation and leads to an increase in cytokine production [69]. Following silicone implantation, a fibrotic capsular tissue with CD4+ lymphocytes, macrophages, and multinucleated giant cells surrounds the implant and forms the so-called siliconoma [70]. A cross-reaction between silicone and naturally silicone-containing structures in human connective tissue such as glycosaminoglycans has been also reported [71].

Meanwhile, genetic factors, which are considered to be among the minor criteria for diagnosis, allow for predisposition of the syndrome [61]. Epigenetics involvement was suspected because exposure to environmental factors is high, while prevalence of ASIA is quite low [72]. The genetic association is mediated by specific HLA antigens implicated in autoimmune diseases. Human leukocyte antigen (HLA) system is a genomic locus of major histocompatibility complex (MHC), the most polymorphic gene cluster of the mammal genome [73]. The presence of HLA-DRB1, HLA-B27, and PTPN22 has been the most common genetic background of the syndrome [31, 66]. Watad *et al.* in an analysis of 500 ASIA cases found that the 89% of the cases were females, and the mean patient age was 43 ± 17 years. This could suggest that females alongside individuals in their 40s are at a higher risk of contracting ASIA syndrome following exposure to adjuvants, compared to males [60].

The pathophysiological mechanisms of ASIA are illustrated in Fig. 1.

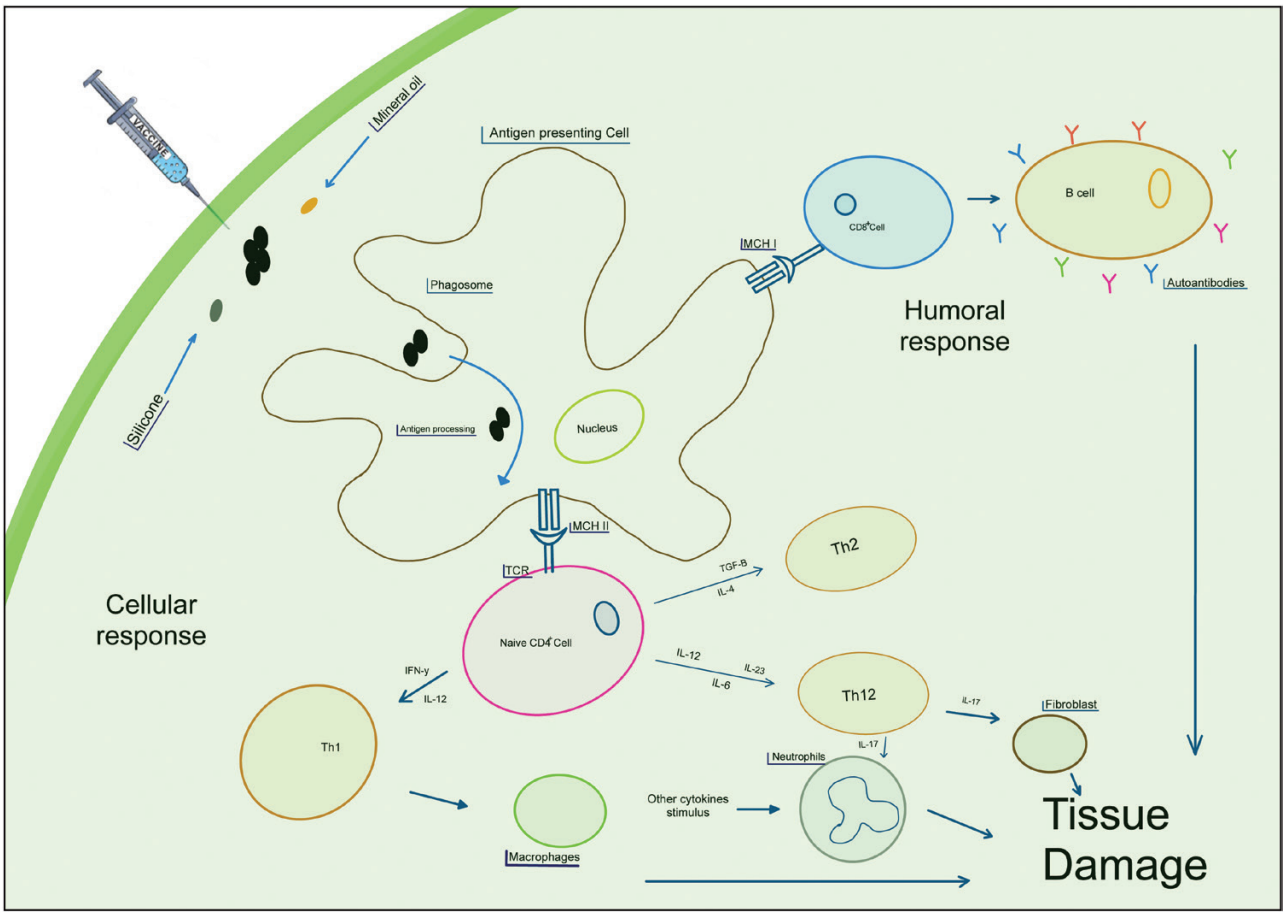

Figure 1: The pathophysiological mechanisms involved in developing ASIA. The process begins with an adjuvant being introduced into the body either by vaccination or other means, and it ultimately results in a multifaceted immune response that ends in tissue damage and autoantibody production.

ASIA and connective tissue disease association

Undifferentiated connective tissue disease

ASIA is a broad umbrella term that encompasses a lot of conditions. Among others, sarcoidosis, Sjören's syndrome (SS), UCTD, silicone implant incompatibility syndrome (SIIS), and immune-related adverse events are considered as classical examples of ASIA due to the fact that they share similar pathogenetic aspects [66].

UCTD is an autoimmune condition resembling ASIA in several facets. The disease is characterized by nonspecific signs and symptoms by which an exposure to adjuvants has contributed to its appearance [74]. In a study summarizing results obtained from the ASIA registry, UCTD was found to be the most commonly reported disease in patients exposed to the HBV vaccine [61]. Moreover, in a case–control study aimed to investigate exposure to different adjuvants in patients with UCTD in comparison to nonexposed patients, it was found that patients exposed to adjuvants described in the major criteria of ASIA, such as vaccines or silicone, either suffered from more autoimmune complications or had a higher frequency of typical ASIA features such as general weakness, irritable bowel syndrome, and fatigue [65].

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is another condition that has been associated with ASIA from different aspects. Characterized by the development of venous and arterial thromboses, gestational manifestations such as fetal death, along with thrombocytopenia [75]; A study of VigiBase, the WHO pharmacovigilance database, recognized 14 drugs that induce APS [76]. Not only drugs but also viral infections can trigger APS either secondary to other autoimmune diseases such SLE or even primary APS [77]. Another group of APS inducers are vaccines including tetanus toxoid vaccine (TTd), influenza virus vaccine, and hepatitis B virus vaccine [78]. Several mechanisms have been theorized such as the presence of adjuvants including aluminum, or the molecular mimicry between phospholipid-binding protein β2 glycoprotein I (β2GPI) peptides and the tetanus vaccine [79]. In APS, autoantibodies are directed towards β2GPI which is a negatively charged non-protein antigen [80].

5.3.Systemic lupus erythematosus

SLE is characterized by the presence of a wide range of autoantibodies alongside multiorgan inflammation [81]. A possible mechanism for the pathogenesis of SLE is through the mitochondrial DNA which serves as an autoantigen that could be targeted by autoantibodies [82, 83]. A systemic review of cohort and case–control studies proposed that vaccinations, specifically HBV and HPV vaccines were associated with an increased risk of SLE [84]. Another study described several different cases diagnosed with SLE, APS, and dermatomyositis after booster shots of diphtheria, tetanus, and pertussis vaccine (DTaP) or TTd [85]. The study suggested

that aluminum adjuvant could be responsible for the induction of SLE via the promotion of cell death which allows nuclear antigens to roam free and potentially activate toll-like receptors (TLRs). Moreover, the study also proposed that aluminum induced production of IL-6 can lead to a cascade of reactions that ultimately could result in autoantibody production furthering the development of SLE [86, 87].

5.4.Systemic Sclerosis

Systemic Sclerosis (SSc) is a rare connective tissue disorder characterized by vasomotor disturbances, fibrosis, and atrophy with the involvement of multiple organs [88]. The main cause is still unknown, but it is believed to be an interplay between environmental, autoimmune, and genetic factors [89]. Specific HLA types have been identified in SSc [90], including HLA-DRB1, which has been linked to ASIA [8]. Moreover, various agents were identified to induce SSc. These agents can be viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19, or nonorganic agents such silica dust, or organic solvents, toluene, xylene, trichloroethylene, and polyvinyl chloride [91].

Endocrine manifestations

ASIA and primary adrenal gland insufficiency

Primary autoimmune adrenal insufficiency, or Addison's disease, is a disorder in which adrenal cortex is unable to produce glucocorticoids and mineralocorticoids efficiently [92]. Clinical manifestations of Addison's disease include fatigue, nausea, dizziness, salt-craving, and hyperpigmentation of the skin and mucosal surfaces [93]. Patients with Addison's disease are known to have autoantibodies against the 21-hydroxylase enzyme, used in the synthesis of adrenal gland hormones [94, 95].

Cases pointing to an association between adrenal insufficiency and exposure to adjuvants have been reported before. To exemplify, a 9-year-old female child presented with adrenal insufficiency after exposure to HBV vaccine [60]. Another case of a 21-year-old Caucasian male patient who developed adrenal crisis 1 week following the administration of influenza vaccine together with diphtheria, tetanus, and acellular pertussis (DTaP) vaccines was documented [96]. Since the patient did not have prior history of adrenal insufficiency and had elevated levels of autoantibodies against 21-hydroxylase, he was diagnosed with autoimmune Addison's disease.

ASIA and primary ovarian insufficiency

Primary ovarian insufficiency (POI) is cessation of menstruation before anticipated age, generally stated of 40 years of age, the menopause [97]. POI is a condition characterized by secondary amenorrhea for four or more months alongside an elevated FSH levels that are normally seen in postmenopausal women. POI affects around 1% of women under 40 year of age and 0.1% of women under 30 years of age [98, 99]. Potential etiologic pathogenetic factors include genetic, iatrogenic, and autoimmune [100]. Autoimmunity is attributable for 4–30% of POI cases in which anti-ovarian antibodies against ovarium antigens of the theca, granulose, corpus luteum, and zona pellucida are present [56, 101]. Little and Ward [102] reported menstrual cycle abnormalities in three unrelated female patients from Austria following HPV vaccine administration. The patients who were treated with oral contraceptive pills to treat the abnormalities were diagnosed eventually with POI. Furthermore, Colafrancesco *et al.* [103] described three patients with secondary amenorrhea, after HPV vaccination in which hormone replacement therapy did not ameliorate the symptoms. The patients had normal sexual development and no genetic abnormalities presented with low levels of estradiol and abnormally high levels of FSH which was suggestive of POI. Moreover, anti-ovarian antibodies were present in one of the patients, and antithyroid antibodies were present in another one. An autoimmune response induced by HPV vaccine explaining the development of POI, was suggested.

However, in a study conducted by Naleway et al,, Kaiser Permanente Northwest electronic health records of POI patients with unknown cause were analyzed to show any association between HPV, DTaP, inactivated influenza and meningococcal conjugate (MenACWY) vaccination and POI development. Even though they could not find any statistically significant association, one case of POI after HPV vaccination was identified [104]. Nevertheless, the short follow-up period and the fact that the patients underwent hormone replacement therapy which could mask the diagnosis of POI which is already difficult to diagnose, were argued [56].

ASIA and type 1 diabetes mellitus

Type 1 diabetes mellitus is a disorder characterized by hyperglycemia due to immune mediated destruction of insulin-secreting cells, β cells, of the pancreas [105]. The destruction of β cells is mediated via autoantibodies against islet cells, insulin, glutamic acid decarboxylase, and protein tyrosine phosphatase [106].

Ruhrman-Shahar *et al.* reported a 14-year-old-female who presented with severe polydipsia, polyuria, and weakness 3 weeks after receiving a booster dose of DTaP vaccine [85]. The patient was positive for autoantibodies against glutamic acid decarboxylase and islet cells eventually diagnosed with type 1 diabetes. Importantly, the case was one among 4 others who received booster DTaP and developed autoimmune diseases. Additionally, a paper from the 90s described a higher incidence of type 1 diabetes mellitus in children who received four doses of Hemophilus influenzae type b (Hib) vaccine at 3, 4, 6, and 14 months of age when compared to children who were vaccinated once at 14 months of age [107].

ASIA and thyroid complications

Subacute thyroiditis is a painful inflammatory thyroid disorder, generally due to viral infections, in which the patients present with systemic symptoms, including fever, swelling, general fatigue, malaise, and sleep disturbances [108]. Grave's disease is an example of autoimmune thyroid disease which primarily affects women and is the main cause of hyperthyroidism due to autoantibodies against thyroid-stimulating hormone receptors [109]. Hsiao *et al.* reported a case of a 25-year-old female who presented with neck pain and swelling on the left side 2 days after influenza vaccine administration [110]. Fine needle aspiration revealed multinuclear giant cell granulomas in the thyroid gland. Another case report of a 36-year-old female patient with tachycardia, anxiety, and tenderness in her neck received H1N1 vaccine one month before the appearance of the symptoms [111]. With the help of thyroid function tests and thyroid scintigraphy, the patient was diagnosed with subacute thyroiditis.

In regard to COVID-19 vaccines and thyroid complications, Pujol *et al.* reported three different cases of thyroid complications after the administration of COVID vaccines [112]. The first dose of Pfizer/BioNTech vaccine was administered to the patients 12 days before the onset of symptoms. Slight increase of the thyroid size, abnormal thyroid function, and the presence of anti-thyroperoxidase and anti-thyroglobulin, as well as scintigraphy showing increased activity of the gland, were suggestive of Grave's disease. Furthermore, Khan and Brassill reported a 42-year-old female with fever, palpitations, and painful left-sided neck swelling 4 days after the second dose of Pfizer/BioNTech COVID-19 vaccine administration [113]. The patient described right-sided neck pain and neck swelling after her first dose of the vaccine as well. Thyroid function test showed hyperthyroidism state and elevated inflammatory markers. After scintigraphy, subacute thyroiditis was confirmed. Additionally, Siolos *et al.* reported 2 cases of thyroiditis following COVID-19 vaccination [114]. The first case occurred 4 days following the first dose of Pfizer/BioNTech vaccine when a 51-year-old female patient presented with nausea, mild anterior neck pain, fever, and tender thyroid gland. Thyroid function test showed hypothyroxinemia and high inflammatory markers. Thyroid scintigraphy confirmed the diagnosis of thyroiditis. In the second case, a 39-year-old female patient who had no prior thyroid disease presented with abnormal thyroid function test during routine laboratory test 3 weeks after the administration of the AstraZeneca COVID-19 vaccine. Thyroid scintigraphy showed decreased uptake. Two weeks later, thyroid function tests returned to normal with no treatment.

Neurological associations of ASIA

ASIA and myalgic encephalomyelitis/chronic fatigue syndrome

Fatigue of unknown cause lasting more than 6 months is the core feature of ME/CFS with at least four accompanying symptoms such as myalgia, arthralgia, memory or concentration deterioration, headache, unrefreshing sleep, tender lymph nodes, and post-exercise malaise [115]. Idiopathic ME/CFS possesses similar features to post-infectious fatigue syndromes; however, the presence of pathogens could not be detected in all affected patients, leading to the idea that similarities could be induced by variety of pathogens and toxic compounds [116, 117]. For instance, vaccines, given their variety of components, are thought to be possible inducing factors of ME/CFS [118]. Actually, aluminum adjuvants in vaccines are thought to cause ME/CFS [119, 120]. In this regard, Gherardi and colleagues demonstrated long-term detection of aluminum hydroxide-associated inflammatory lesions at injection sites of patients who developed diffused myalgias following the administration of aluminum-containing vaccines [121].

Moreover, Horning *et al.* demonstrated that patients with longstanding ME/CFS have an exhausted immune system by substantial drops in IL1b, IL1ra, IL4, IL10, IL12, IL17 and FGFb, whereas selective increases in CCL2, and major monocyte chemoattractant are observed [116, 122]. In case of vaccination with aluminum adjuvant, MCP1/CCL2 expression is upregulated which attracts immune cells engulfing aluminum to the brain [123]. Aluminum adjuvant induced inflammation by stimulating NLRP3 inflammasome leading to fatigue-like behavior in mice due to neuroinflammation [124, 125].

ASIA and transverse myelitis

Transverse myelitis is an immune mediated disorder characterized by neural injury to spinal cord causing weakness, sensory alterations, and autonomic dysfunctions [126]. Transverse myelitis, is thought to possess an autoimmune nature and was found to be associated with several autoimmune diseases including SLE, APS, and Sjogren's syndrome [127]. In an extensive review, post-vaccination transverse myelitis cases were examined with the help of data from PubMed, EMBASE and DynaMed from 1970 to 2009 [128]. In initial research, 37 patients were diagnosed with transverse myelitis after vaccination. Of the patients found, 73% reported clinical symptoms during the first month following vaccination. The involved vaccines were: HBV vaccine (13 cases), MMR or rubella vaccine (6 cases), DTP or DT vaccine (4 cases), rabies vaccine (4 cases), oral polio virus vaccine (3 cases), typhoid vaccine (1 case), pertussis vaccine (1 case), Japanese B encephalitis vaccine (1 cases), and multiple vaccine regimens (2 cases). The study concluded that the common ingredient of found in the vaccines listed, such as an adjuvant, may trigger the same autoimmune disease, transverse myelitis. Moreover, Austin and colleagues reported a case of a 41-year-old male patient with previous history of psoriasis who suffered of headache, leg paresthesia, and sensory loss for 2 months [129]. Medical history revealed yellow fever vaccination 16 months before the onset of symptoms, in addition to influenza A (H1N1) vaccine 2 months prior to the appearance of the neurological symptoms. The combination of clinical findings and spinal cord MRI showing medullar hyperintense lesions led to the diagnosis of transverse myelitis. In the same paper, the authors described three more patients diagnosed with transverse myelitis after receiving influenza A (H1N1) vaccine.

ASIA and Guillain–Barre syndrome

Guillain–Barre syndrome (GBS) is an acute autoimmune neuromuscular condition causing muscle weakness and paralysis which may lead to respiratory failure and death [130]. The causality between vaccination and GBS was established as early as the 70s during swine influenza vaccination among military personnel in the USA [131]. According to that report, 1 case of GBS was reported per 100,000 vaccinated persons resulting eventually in the cessation of the vaccination program. Furthermore, Martin Arias *et al.* conducted a meta-analysis of 39 studies published between 1981 and 2014, indicating an increased risk of GBS following influenza vaccination, with an even higher risk observed in correlation with the administration of 2009 H1N1 influenza vaccine [132].

ASIA and narcolepsy

Narcolepsy is a chronic sleep disorder observed in 25 to 50 people per 100,000 people [133]. Patients with narcolepsy present with symptoms including cataplexy, disrupted nocturnal sleep, sleep paralysis, hallucinations, and obesity [134]. Narcolepsy is considered as an autoimmune disease due to the lack of production of specific neurons producing orexin neuropeptide [135]. Interestingly, after the 2009 H1N1 vaccination program, the diagnosis of narcolepsy in Finland increased in children aged 4–19 following the administration of AS03-adjuvanted vaccine, Pandemrix [136]. The AS03, an approved adjuvant for use in vaccinations, has been associated with ASIA [137]. Similarly, increased risk

of narcolepsy after Pandemrix was also demonstrated in various studies based on data from other European countries [138].

ASIA and acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a monophasic central nervous system disorder in which inflammation and demyelination are seen [139]. More than 70% of ADEM cases are post-infectious or post-immunization [140]. Among the vaccines that were associated with ADEM are rabies, diphtheria-tetanus-polio, MMR, Japanese B encephalitis, pertussis, influenza, and hepatitis B vaccines [141]. Furthermore, in vaccinated populations with the Japanese encephalitis vaccine between 1996 and 1998, 0.2 per 100,000 vaccinees was reported, which is lesser than the 1 per 50,000 to 75,000 vaccinated individuals reported in Denmark [142, 143]. In addition, in a review of neurological adverse events in relation of the smallpox vaccination in the USA between 2002 to 2004, Sejvar *et al.* reported 214 events with 3 ADEM suspected cases [144]. Actually, association with smallpox vaccination is reported to be between 1 in 4000 to 1 in 80,000 following primary vaccination and between 1 in 50,000 to 1 in 450,000 following booster shots [145].

Shoamanesh and friends reported a case of ADEM 2 days after the administration of seasonal influenza vaccine [146]. A 75-year-old female patient with previous history of type 2 diabetes mellitus, dyslipidemia, hypertension, hypothyroidism, and seronegative arthropathy presented with symptoms including headache, malaise, fatigue, nausea, and vomiting. Twenty-nine days post-vaccination, the patient developed left sided hemiplegia and hemianesthesia. Later on, the patient became encephalopathic and developed brainstem involvement eventually diagnosed with ADEM.

ASIA and multiple sclerosis

Multiple sclerosis (MS) is an autoimmune central nervous system disorder characterized by demyelination and progressive paralysis [147].

In 1994, a mass HBV vaccine campaign was conducted in France after the recommendation by World Health Organization in early 1990s. Following the campaign, cases of MS onsets or relapses were reported which led to the hypothesis that HBV vaccine was the causative agent of MS cases in vaccinated people [148]. Actually, such a link between HBV vaccine and MS was suggested earlier upon examining 163 cases of MS versus 1604 controls. According to the study the OR for MS within 3 years of vaccination compared to control was 3.1 (95% CI 1.5, 6.3) [149]. Similar findings were reported by Mikaeloff *et al.* who measured an increased risk of developing MS in a subgroup of children after vaccination with Engerix B vaccine [150].

Vasculitis and ASIA

Reports linking vasculitis to vaccine administration date back to even before the initial description of ASIA [151]. This aspect of ASIA includes giant cell arteritis (GCA), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Henoch-Schonlein purpura, and Raynaud's disease. Watanabe showed that in 45 published reports from 1966 to 2016, 65 patients developed vasculitis following the influenza vaccination, for instance [152]. The study reported 13 large vessel vasculitis, 42 small vessel vasculitis, and 5 single organ vasculitis. GCA, defined as idiopathic and chronic vasculitis of medium and large arteries [153], Soriano *et al.* reported 8 cases of GCA in a range of 20 days to 3 months following the administration of influenza vaccine [154]. Biopsies confirmed the diagnosis of all cases who were previously healthy women with an average age of 73.5 years old. The same study reported the available HLA typing by which HLADRB1*04 variants were associated with the genetic disposition of the patients [155]. Another case of GCA in a previously healthy 74-year-old patient a week following influenza vaccination was also documented [156]. Biopsy findings followed the histologic remarks of GCA and fulfilled 4 out of the 5 American College of Rheumatology (ACR) criteria.

In fact, the vasculitis cases were not limited to influenza vaccination as human papillomavirus vaccine (HPV4) was also reported to induce similar adverse effects. In one of the epidemiological study from the vaccine adverse event reporting system (VAERS), Geier *et al.* stated that among 22,011 adverse events reported in females, vasculitis had the odds ratio of 4 together with the highest life-threatening outcome ratio of 33% [157]. According to the study, vasculitis had the closest onset of the clinical symptoms (around 6 days) after vaccination.

Henoch–Schonlein purpura was another vasculitis following HPV vaccine reported by Watad *et al.* [60]. In an analysis of 500 ASIA cases, one case of a 12-year-old female patient following the HPV vaccination was described. In the same paper, Raynaud's disease, a type of vasculitis mainly effecting digits such as fingers and toes [158], was also reported in the context of ASIA. Raynaud's phenomenon was reported in total of 98 cases out of the 500 ASIA cases (19.6%). This side effect ranked 11 out of the 17 adverse effects reported in the study in terms of frequency.

In addition, ANCA-associated vasculitis was described following several vaccines. Shoenfeld *et al.* reported two cases of ANCA associated vasculitis following both HAV and influenza vaccines in 2011 [4]. Both cases were females aged 53 and 54. Four additional cases were illustrated in another paper addressing the possible correlation between influenza vaccine and new onset as well as relapse of ANCA-associated vasculitis [159].

Silicone breast implants (SBI) and their relation to ASIA is an extensively studied area [69]. One aspect of this relationship is the association of SBI with ANCA-associated vasculitis [160]. Carrera Munoz and colleagues reported a case of 45-year-old Colombian woman who underwent silicon breast implantation at the age of 40 and developed not just one but two severe autoimmune diseases, SSc followed by vasculitis [161]. Histopathological analysis of axillary nodules showed silicone inclusions. Together with the association between SBIs and autoimmune diseases, the paper discussed the chronological relationship between the implants and the subsequent development of ASIA.

Other associations of ASIA

Other than connective tissue, neurological, endocrine, and vascular disorders, many other rare adverse effects were reported under the umbrella ASIA. These conditions include but not limited to non-Hodgkin lymphomas, sarcoidosis, orthostatic tachycardia, myositis, pulmonary fibrosis, and Crohn's disease. Chronic stimulation of the immune system, effects of

silicone breast implants, HBV, influenza, and DTP vaccines were related to the conditions mentioned [60, 162].

Watad *et al.* found Crohn's disease to be the second most common polygenic autoinflammatory disease reported (30%) in an analysis of 500 ASIA patients [60]. Among 6 cases, ranging from 11 to 48 years of age, the disease was associated with one of the HBV, influenza, and DTP vaccines. In the case of sarcoidosis, odds ratio was 1.98 among 4 cases, with a median age of 45.8 years.

Moreover, there have been extensive reports on the effects of silicone on non-Hodgkin lymphoma. Prolonged activation of the immune system is thought to be the underlying mechanism promoting the inflammatory response, as chronic stimulation induced by the adjuvant was found to be associated with higher risk for developing lymphoma [162]. After the silicone implantation, chronic stimulation of B cells could lead to pseudo-lymphoma which might progress into well-defined non-Hodgkin lymphoma [163]. Higher rates of non-Hodgkin lymphoma was also mentioned in other autoimmune diseases, especially in Sjogren's Syndrome [164].

Even though rare, orthostatic tachycardia and myositis were also reported under the umbrella ASIA following the HPV and HBV vaccinations, respectively. A 2.6% prevalence rate was registered for both conditions [60]. Many other conditions, such as Adult-onset Still's disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, recurrent polychondritis, and celiac disease were reported in low rates.

In summary, many autoimmune phenomena have been linked to ASIA following silicone breast implants and different vaccinations. While the benefits from vaccinations outweigh the low risk of adverse effects that have been reported, previously mentioned severe autoimmune diseases should not be underestimated and adjuvants in the vaccines should be improved to have a better safety profile.

COVID-19 and ASIA

Since the initial warnings about a potential SARS-CoV-2 outbreak [165], the globe has been severely affected by the pandemic of COVID-19 [166]. A significant number of patients are suffering from long-term medical and psychological morbidity as a result of the virus, and the current death toll has considerably surpassed 6 million [167]. It is now clearer how severe COVID-19 immunopathology works. The virus, SARS-CoV-2, causes a chaotic, harmful immune response in individuals that are badly afflicted, where autoimmunity is a key component [168]. The Vaccine Adverse Event Reporting System of US Centers for Disease Control and Prevention stated that as of March 28, 2022, more than 550 million doses of the SARS-CoV-2 vaccine have been administered [169]. More than 0.0042% of recipients encountered major adverse events, which included death, severe allergy, thrombotic events and thrombocytopenia, Guillain–Barre syndrome, myocarditis. However, autoimmune responses and symptoms after vaccination have been described and appear to be on the rise as a result of increased vaccination rates [10, 170]. Jara *et al.* concluded 276 published cases of autoimmune side effects of COVID-19 vaccines and found that Guillain–Barré syndrome (151 patients), and vaccine-induced thrombotic thrombocytopenia (93 cases) were the two most common instances [9]. Less common cases have also been documented, including autoimmune liver disorders (8 cases), immune thrombocytopenic purpura (7 cases), IgA nephropathy (5 cases), autoimmune polyarthritis (2 cases), rheumatoid arthritis (2 cases), Graves' disease (4 cases), and SLE (3 cases). However, not all the cases met the ASIA criteria.

Permezel *et al.* reported a case of a 63-year-old man with previous history of type 2 diabetes mellitus, ischemic heart disease, and atrial fibrillation who presented with complaints of vertigo, abdominal pain, and fatigue 12 days after the administration of first dose of AstraZeneca vaccine [171]. One day later, the patient suffered of decrease cognition and disorientation. The diagnosis of ADEM was confirmed after clinical tests, MRI results, and histological findings. In addition, Jara *et al.* demonstrated three cases of autoimmune encephalitis after receiving COVID vaccines (two AstraZeneca, one Moderna) [9]. Two patients were positive for anti-NMD autoantibody and one of was positive for anti-GABA. They concluded that observation of autoimmune reactions post-vaccination widens the ASIA spectrum.

Abdelmaksound and friends [172] summarized 38 cases of vasculitis following COVID-19 vaccination. Among the cases, 24 developed vasculitis after the first dose of the vaccines, 20 cases were leukocytoclastic vasculitis (LCV), 9 cases were IgA vasculitis, 3 cases were lymphocytic vasculitis, and 2 cases were ANCA-associated vasculitis. The median age of the cases was 53, and 65.8% were females. In the same study, both induction and reactivation of vasculitis was observed and the average occurrence of the symptoms was 6.2 days after vaccination. Similarly, Baier *et al.* reported a case of ANCA-associated vasculitis in a 57-year-old previously healthy female with a smoking history [173]. After the wo doses of Pfizer-BioNTech SARS-CoV-2 vaccine and the booster vaccination, the patient developed pulmonary hemorrhage 5 days after the booster dose. Serology testing was positive for both MPO-ANCA and PR3-ANCA. In the same paper, the authors summarized 27 de novo cases of ANCA-associated vasculitis following the SARS-CoV-2 vaccination. Twenty-one of the cases received mRNA vaccination and all cases except one were treated with steroid therapy. An association with HLA-DR was noticed. The authors concluded a rare but potentially severe adverse effects like ANCA-associated vasculitis should be monitored closely considering the large and growing number of vaccinated people in the world.

In fact, the wide range of autoimmune phenomena seen in an association and link with the COVID-19 vaccines were addressed previously in details [10]. Doubtlessly, these autoimmune adverse reactions can be viewed, to a large extent, as part of the spectrum of ASIA [9].

Thyroid complications were reported during the pandemic of COVID-19 as well, as new environmental factors for autoimmune endocrine diseases (AIED) may be represented by the SARS-CoV-2 and the vaccinations against it [174]. Despite widespread COVID-19 vaccination around the globe, the literature has so far described a small number of cases of clinically obvious thyroid impairment. Thyroid dysfunction may be triggered by the SARS-CoV-2 virus as well as its vaccine [175]. In fact, many of the autoimmune thyroiditis cases in the literature meet the ASIA criteria [176]. Subacute thyroiditis is emerging as a recognized complication of the COVID-19 [177]. There were 59 cases of subacute thyroiditis, 29 cases of Graves' disease, two cases of subacute thyroiditis and Graves' disease occurring simultaneously, six cases of painless thyroiditis, and a single case each of thyroid eye disease and hypothyroidism associated with myxedema [178]. With an average of almost 11 days, the interval between vaccination

Table 2: Major studies mentioned correlating COVID-19 vaccinations to ASIA syndrome

Authors	Case description	Conclusion
Iremli *et al.* [181]	Three cases of subacute thyroiditis after inactivated SARS-CoV-2 vaccine (CoronaVac®).	Subacute thyroiditis can result from SARS-CoV-2 vaccine as a phenomenon of ASIA. A few days after receiving the SARS-CoV-2 vaccine, subacute thyroiditis may manifest.
Taskaldiran *et al.* [182]	A 31-year-old woman was admitted to the endocrinology outpatient clinic with the complaint of neck pain following the second dose of the BNT162B2 SARS-CoV-2 (Pfizer/BioNTech) vaccine.	The present study may be the first report to evaluate SAT and Graves' disease as ASIA following mRNA COVID-19 vaccination. Clinicians should be aware of possible vaccine-related complications.
Ratnayake *et al.* [183]	A 75-year-old male presented with pain and tenderness around the front of his neck some 14 days following immunization against COVID-19 with the AstraZeneca vaccine.	Painful thyroiditis 14 days following the AstraZeneca vaccine (ChAdOx1, Vaxzevria).
Das *et al.* [184]	A case of a 47-year-old female who presented with fever and neck pain for 2 weeks following the first dose of the ChAdOx1 nCoV-19 (Astra Zeneca) vaccine. Thyroid function tests (TFT) revealed thyrotoxicosis. Neck ultrasound showed a bulky thyroid with hypoechoic nodules	The case reported a subacute thyroiditis as a part of ASIA.
Vera-Lastra *et al.* [185]	After receiving the SARS-CoV-2 vaccine, two female healthcare workers presented clinical signs of hyperactive thyroid three days later, including raised thyroid hormone levels on thyroid function tests, suppressed thyroid-stimulating hormone, and elevated antithyroid antibodies.	Vaccines have been shown to trigger an immune response that leads to autoimmune thyroiditis. The patients met the diagnostic criteria for ASIA; they were exposed to an adjuvant (vaccine), and they developed clinical manifestations of thyroid hyperfunction within a few days, with the appearance of antithyroid antibodies, despite being healthy before vaccination.
Pujol *et al.* [112]	A 38-year-old female took the first dose of Moderna vaccine 8 days before the onset of the symptoms.	The patient was diagnosed with subacute thyroiditis. The first case of subacute thyroiditis in the context of SARS-CoV-2 vaccination with the Moderna vaccine.
	A 32-year-old male had been vaccinated with the first dose of Pfizer/BioNTech vaccine 10 days prior to the onset of these symptoms.	First case of silent thyroiditis described in the context of SARS-CoV-2 vaccination with Pfizer/BioNtech vaccine.
	A 38-year-old woman received a first dose of the Pfizer/BioNTech vaccine 12 days before the onset of the symptoms. She had a history of schizophrenia.	Thyroid scintigraphy concluded a hyperfunctioning diffuse goiter compatible with Graves' disease.

and thyroid disease ranged from 0.5 to 60 days. Given the brief period of follow-up, the majority of subacute thyroiditis and painless thyroiditis cases reported complete remissions while Graves' disease cases showed persistence. The amount and quality of the available data about thyroid issues following COVID-19 vaccination are limited; thyroid disorders may manifest within 2 months of receiving the vaccine; and among all thyroid conditions following COVID-19 vaccination, Graves' disease, and subacute thyroiditis appear to be more common.

The exact mechanism with which COVID-19 vaccination leads to ASIA syndrome and other immune syndromes is not fully understood yet [9]. Certain studies proposed lipid nanoparticles among other vaccine particles as playing a role in triggering these autoimmune syndromes [179], while others claimed that the inherit ability of the vaccine to boost immunity, could also inadvertently help it act as an adjuvant in causing ASIA syndrome [180].

Leading studies relating COVID-19 vaccination to ASIA are summarized in Table 2.

Conclusion

The wide range of the spectrum of ASIA involvement in almost all body systems alongside the correlation with many rheumatic and autoimmune diseases was illustrated in our paper hereby. In fact, this link was reported long before ASIA was introduced however, the approach that time was unclear, and the symptoms were described as vague and non-specific. There is no doubt, that ASIA appeared to unite, clarify, and

pave the way for better understanding of adjuvants and their contribution to autoimmunity and autoimmune diseases. Such acknowledgment could lead to safer vaccines with improved side effect profile. We believe this was noticed in the introduction and utilization of newer technologies in the development of vaccines during the pandemic of COVID-19.

Conflict of Interests

The authors declare no competing interests.

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Author contributions

Isa Seida: methodology, resources, writing—original draft. Mahmoud Alrais: writing—original draft. Ravend Seida: writing—original draft. Abdulkarim Alwani: writing—original draft. Zeynep Kiyak: writing—original draft. Abdulrahman Elsalti: writing—original draft. Sevval Nil Esirgun: writing—original draft. Tunahan Abali: writing—original draft. Naim Mahroum: supervision, writing—review and editing. The animal research adheres to the ARRIVE guidelines—not applicable.

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Confirmed.

Clinical trial registration

Not applicable.

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