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Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: Insights from an analysis of 500 cases

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Abstract

Background: We investigated the pattern of reported immune diseases in the ASIA registry.

Methods: Data from 500 subjects exposed to adjuvants from the ASIA syndrome international registry were analysed.

Results: The patient mean age was 43±17 years and 89% were female. Within the reported immune diseases 69% were well defined autoimmune diseases (autoimmune, autoinflammation, and mixed pattern diseases). Amongst the well-defined immune diseases following the exposure to adjuvants, polygenic autoimmune diseases were significantly higher that autoinflammatory disorders (92.7% vs 5.8%, respectively, $p<0.001$). Polygenic autoimmune diseases such as connective tissue diseases were significantly linked with the exposure to HBV vaccine (OR 3.15 [95%CI 1.08-9.23], $p=0.036$). Polygenic autoinflammatory diseases were significantly associated with the exposure to influenza vaccination (OR 10.98 [95%CI 3.81-31.67], $p<0.0001$).

Conclusions: Immune conditions following vaccination are rare, and among these, polygenic autoimmune diseases represent the majority of the well-defined immune diseases reported under the umbrella ASIA syndrome. However, vaccines benefit outweighs their autoimmune side effects.

Keywords: ASIA syndrome; international syndrome registry; vaccines; foreign material; silicone implants.

Introduction

The term autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first coined in 2011 with the aim of codifying a growing number of disorders characterised by innate and adaptive immune system dysregulation after adjuvant exposure [1]. The term adjuvant denotes several substances that drive innate immune system pattern recognition receptor (PRR) activation and are commonly used in vaccines to boost immune reactivity towards antigens [2,3]. Many substances beyond vaccine adjuvants such as liquid paraffin, silicone gel, acrylamides, hyaluronic acid, and methacrylate compounds have adjuvant properties [4-6]. Aluminium is the adjuvant most commonly incorporated into vaccines and after many years of widespread use, contrasting data on its toxicity and immune adverse events have been reported [7,8]. Nevertheless, over the last decade, a number of case reports and series reported that vaccines containing aluminium adjuvant might occasionally be associated with serious immunological adverse events including autoimmune diseases [9-11].

Autoimmune diseases are conditions that result from a complex interplay between genetic background and environmental triggers such as infection, dysbiosis, drugs or adjuvants [12-14]. Self-directed inflammation with loss of tolerance, with dysfunction of dendritic cell, B and T cell with the induction of immune reactions against self-antigens is relatively rare [15]. Of note, the vast majority of people who are exposed to different adjuvant subtypes do not develop autoimmune phenomena. It is now well recognised that inflammation against self may not be autoimmune in nature but rather an innate immune mediated or what is termed an autoinflammatory response.

It is now widely accepted that at the population level, many diseases viewed as autoimmune actually have a predominantly innate immune mediated or autoinflammatory based pathology such as inflammatory bowel disease or polymyalgia rheumatica [15]. It is further recognised that diseases previously viewed as autoimmune including psoriasis and allied seronegative arthropathies are intermediate innate-adaptive overlap disorders. Therefore, an immune diseases can be classified as

autoimmune or autoinflammation and according to the gene involvement, each be can be stratified into monogenic or polygenic disease.

In order to better understand the link between the different adjuvants and the spectrum of inflammation against self, an international registry of ASIA syndrome was created in 2011 [16]. A preliminary 300 patient analysis in 2016 showed that most of the ASIA syndrome patients were female and had a mean age of 38 years. Furthermore, the most common reported disease was undifferentiated connective tissue disease (UCTD), found in 26% of the cases [16].

Thus, the aim of the previous study was to increase the awareness of existing conditions that may emerge following the exposure to an adjuvant although a cause-effect relationship is debatable due to the paucity of the described clinical cases, a lack of precise temporal-causal link, and the multitude of exposures to suspected adjuvants. In the current study, we performed an updated analysis of the registry by adding all the cases accumulated between April 2016 and January 2019, giving a total of 500 cases of ASIA syndrome. We also explored the relationship between different immune-mediated disease subtypes (autoimmune versus autoinflammation or intermediate diseases) followed the exposure to various adjuvants.

Material and methods

Instrument

An ad hoc structured questionnaire, developed to collect all data relevant to ASIA syndrome, was administered to rheumatologists and internists worldwide, as previously described [16]. The cases were uploaded into the registry between 2011– 2019 February.

Population: patient inclusion and exclusion criteria

Five hundred sixty-one patients were reported and inserted in the ASIA registry; 61 cases were excluded due to one or more of the following reasons: i) they did not fulfil the inclusion criteria (meeting one major criterion or one minor and one major) (1), ii) having missing data or insufficient details, iii) when the adjuvant was considered to have no biological plausibility (No experimental models to support the link between the suspected adjuvants and the induction of the well-defined autoimmune condition) iv) when the period between the disease onset and adjuvant exposure was over 5 years, v) non-specific self-limited reactions within few days after vaccination (e.g. fever, arthralgia and myalgia). Thus, the final cohort consisted of 500 patients with ASIA syndrome.

Measures (autoimmune, autoinflammation and mixed pattern diseases)

We stratified the well-defined immune mediated diseases into polygenic autoimmune diseases, polygenic autoinflammatory and mixed pattern diseases according to McGonagle et al. immune diseases classification proposed in 2006 [15]. The latter, defines an autoimmune self-directed inflammation as a disorder where B and T cell are the main players, the disease initiates in primary and secondary lymphoid organs leading to loss of tolerance, with development of immunity against self-antigens and autoantibodies may predate the clinical disease by several years [15]. On the other hand, autoinflammatory disorder is where local factors at the tissue target resulted in innate immune system mediated tissue damage [15]. Disease with MHC-class I associations including psoriasis and allied disorders that also show a propensity for tissue specific injury and disease expression were designated as mixed pattern diseases (intermediate diseases). Where a clearly well-defined immune diagnosis was not possible according the criteria above, we classified into undefined immune disorder.

Statistical analysis

Data related to symptoms, main clinical manifestations, antibody profile status, and diagnosed autoimmune diseases were downloaded from the website and transferred to an ad hoc Excel spreadsheet. Before proceeding with any data handling and manipulation, figures were visually inspected for capturing potential outliers. Continuous variables were computed as mean±standard deviation, whereas categorical parameters were expressed as percentages, where appropriate. Student's t-test, chi-squared test, analysis of the variance were employed to look at comparisons among the different subgroups of the studied ASIA cohort. All statistical analyses were carried out with the commercial software "Statistical Package for the Social Sciences" (SPSS for Windows, version 24.0, IBM, USA).

Results

Patients demographic information

A total of 500 ASIA syndrome patients (mean age 43±17 years, median 44 years, range 0-83 years) were recorded in the registry with a female predominance (89%) and 46.6% were smokers. 13.8% had already another prior autoimmune disorder before the exposure to vaccines or foreign materials and 25.8% had a family member with an autoimmune/autoinflammatory disorder. Autoimmune susceptibility, given by either a personal or a familiar history of well-defined autoimmune condition, could be documented for 35.4% of cases. Furthermore, 23.8% reported a history of allergy or an atopic profile (46.2% with drug hypersensitivity, 14.3% with allergy to nickel, 9.2% had asthma, conjunctivitis or rhinitis, 8.4% with food hypersensitivity, 5.0% with skin rash, including urticaria, angioedema, dermatitis, and, finally, 1.7% had allergy to latex; the remaining 15.2% of cases to other allergens, including hay fever, grass, pollen, and pneumo-allergens).

Well-defined polygenic autoimmune diseases

Among the well-defined immune diseases well-defined polygenic autoimmune diseases were the most commonly reported and represented 93% of the reported conditions. Among these, UCTD and Sjögren's syndrome were with the highest prevelance with a percentage of 38.8% and 16.8% among autoimmune diseases, respectively. Stratifying according to the type of vaccination received, a statistically significant association was found for HBV vaccine (OR 6.72 [95%CI 3.3513.48], p<0.0001) (Table 2).

Well-defined polygenic autoinflammatory diseases

The polygenic autoinflammatory diseases represented 5.8% of the well-defined immune conditions. The most common polygenic autoinflammatory diseases to be reported in the registry were GCA (40%) Crohn's disease (30%) and PMR (20%). Patients with polygenic autoinflammatory diseases had a statistically significant association was with influenza vaccination exposure (OR 10.98 [95%CI 3.81-31.67], p<0.0001) (Table 2).

Mixed pattern diseases (MHC class I associated disease)

Patients with psoriatic arthritis (PsA), ankylosing spondylitis, psoriasis Behcet’s disease or undifferentiated-spondyloarthritis were studied separately as mixed pattern diseases or intermediates between innate and adaptive immunity (Table 2). No significant association was found, either in terms of exposure to vaccines or exposure to foreign material.

Incubation time between adjuvant exposure and immune disease onset stratified by immune disease subtype

No differences could be found in terms of onset time between polygenic autoimmune and autoinflammatory and mixed pattern diseases (median 1.5 week, 1 week and 1 week, respectively) following vaccination.

Co-occurrence of different well-defined autoimmune/autoinflammatory diagnosis

Among the total cases of ASIA syndrome, 5.2% subjects presented more than 1 well-defined autoimmune/autoinflammatory diagnosis. Stratifying according to the type of vaccine administered, a statistically significant association between having more than one well defined immune disease with HBV vaccine (OR 3.15 [95%CI 1.08-9.23], p=0.0362) has been found. Co-occurrences that were reported in our study included primary biliary cholangitis with Sjogren's syndrome, autoimmune thyroiditis with type I diabetes mellitus, and autoimmune thyroiditis with type I diabetes mellitus.

Undefined diagnosis of autoimmune/autoinflammatory disease

Thirty-one percent (31%) of patients had an undefined diagnosis of autoimmune/autoinflammatory disorder. The common features reported among these subjects were arthralgia 71.0%, chronic fatigue 43.2% and fever 38.7%. Complaining of an undefined diagnosis was associated with smoking (OR 1.81 [95%CI 1.04-3.15], p=0.0361), but not with exposure to overall vaccines or foreign material. Among these subjects, the overall rate of positivity for autoantibodies was 16.7% which is far lower than the overall positivity in those with well-defined immune disease (55.4%).

Clinical Symptoms of ASIA syndrome cases

Complaints of myalgia was associated with female sex (OR 27.40 [95%CI 1.06-710.72], p=0.0463) and with a positive family history for autoimmune disorders (OR 14.87 [95%CI 1.03-214.48],

p=0.0475). With respect to vaccines, myalgia was specifically associated with exposure to human papilloma virus (HPV) vaccine (OR 85.55 [95%CI 1.65-4,426.05], p=0.0271). Pruritus was found to associated with influenza vaccination (OR 3.90 [95%CI 1.77-8.62]. Further details regarding the reported symptoms among ASIA patients are reported in Table 1. These symptoms are not specific for certain immune-mediated disorders and thus not necessarily of autoimmune nature.

Laboratory findings among ASIA syndrome cases

Concerning the autoantibody profile status, 54.4% of patients had a positive autoantibody test. Specifically, 48.2% were ANA positive, 7.0% were rheumatoid factor (RF) positive, 6.0% were positive for anti-SSA, 3.8% positive for anti-TPO, 3.4% positive for anti-dsDNA, 2.2% for centromere, 2.0% for anti-Sm, 1.8% for anti-RNP, 1.0% for anti-Scl70 and, finally, 1.0% for anti-SSB. Stratifying for disease subtype, 55.4% of patients with well-defined immune disease and 16.7% of those with undefined autoimmune/autoinflammation disease and were positive for at least one autoantibody.

Exposure to adjuvant foreign material in ASIA syndrome cases

The median time between exposure to foreign material and the onset of clinical symptoms was one month and ranged from 2 weeks to 5 years. Identified foreign materials were silicone (in 12.5% of cases), hyaluronic acid (HA) (in 29.2% subjects), Mineral oils (Mo) (in 20.8% individuals) and polyacrylamide (PAM) (in 37.5% of cases). The two most commonly reported polygenic autoimmune diseases after the exposure to a foreign material were UCTD, and Sjogren's disease with a percentage of 19.4% and 2.6%, among the well-defined well-defined immune diseases, respectively. Further details are reported in Table 2.

Exposure to vaccines in ASIA syndrome cases

The median duration time between exposure to vaccination and onset of symptoms was one week (2 days – 5 years). 48.2% of the population developed clinical symptoms after exposure to at least 1 vaccine (more in detail, 86.7% to 1 vaccine, 10.0% to 2 vaccines, 2.9% to 3 vaccines, and 0.4% to more than 3 vaccines). Stratifying according to the type of vaccine administered, 26.4% of the sample developed ASIA syndrome after exposure to hepatitis B virus (HBV) (in detail, 21.9% after the first dose, 24.8% after the second dose, and 53.3% after the third dose). 11.2% of the population developed ASIA syndrome after exposure to influenza vaccine, 10.0% after exposure to HPV vaccination (12.5 after the first dose, 25.0% after the second dose, and 62.5% after the third dose), and 8.4% after exposure to diphtheria-tetanus-pertussis (DTP) immunisation. With lower rates, 2.6% of cases developed after exposure to measles, mumps, and rubella (MMR) immunisation, 2.0% after exposure to hepatitis A virus (HAV) vaccine (in detail, 80.0% after the first dose, and 20.0% after the second dose), 0.8% after exposure to H1N1 influenza vaccine and, finally, 0.4% after exposure to pneumococcal vaccine.

Pharmacological treatment

2.4% and 10.2% were treated with biologics and disease-modifying antirheumatic drugs (DMARDs), respectively, whereas 13.6% hydroxychloroquine and 34.0% prednisone or other glucocorticoids.

Comparison between the two registry studies (2011-2016 January vs 2016 February- 2019 February).

Comparing the ASIA syndrome cases inserted between 2011-2016 January (previously published paper [16]) to those form 2016 February- 2019 February, the rate of the classic symptoms (arthralgia chronic fatigue, myalgia, sleep disturbances, general weakness, neurological manifestations, cognitive impairment) of ASIA has increased, with few exceptions (arthritis, chronic rash, mouth ulcers and postural orthostatic tachycardia syndrome (POTS), which tended to decrease, and photosensitivity, which remained stable) (Table 3).

Tables 4 shows the changes in terms of rate in well-defined immune clinical diagnosis between our previously published paper and the current update. More in detail, well-defined immune diagnoses tended to decrease, with few exceptions (PsA, psoriasis and undifferentiated-spondyloarthritis, connective tissue diseases (CTDs) such as Sjogren's syndrome, antiphospholipid syndrome (APS) and mixed connective tissue disease (MCTD), organ-specific disorders including dysautonomic neuropathy and autoimmune thyroiditis, primary biliary cholangitis (PBC) and celiac disease, panniculitis, alopecia, inflammatory polyarthritis and autoimmune recurrent abortions).

Discussion

The mechanistic explanation behind the development of an autoimmune/autoinflammation disease is extremely complex and thought to be a result of a complex interplay of several factors, especially environmental and genetic ones [17,18]. To prove a cause-effect link between a compound and a clinical disorder is one of the hardest and complicated issues in medicine and normally requires at least two elements: reproducible statistically significant association and plausible underlying mechanisms.

Some scholars claim that the link between vaccine administration or exposure to foreign material and the insurgence of autoimmune/inflammatory and immune mediated events is only alleged, and constitutes a prejudice and a "false myth" that reduces/deters vaccination coverage [4]. However,

despite being rare, this link is real [7]. Vaccine adverse events, indeed, rarely occur and to be properly captured require large epidemiological surveys (such as cohort studies) or meta-analytical network investigations, which are sufficiently statistically powered to detect such relations. Nevertheless, a significant link between influenza immunisation and Guillain-Barrè syndrome has been reported [19]. Also the exposure to MMR vaccine has been associated with immune thrombocytopenic purpura onset [20]. A link between yellow fever immunisation and the insurgence of viscerotropic and neurotropic diseases, oral vaccination against poliovirus or exposure to smallpox vaccine and the occurrence of neurological complications was also reported [21-23]. Given that other side-effects occurred after vaccination, there is the need of evidence-based studies. Due to the dearth of information and robust data, ASIA is an adequate umbrella term to gather together events and reactions apparently unrelated, which share exposure to vaccines, silicone or other foreign material as common root [9]. However, we would like to stress that these clinical phenomena have an extremely low occurrence rate. Immunisation practices offer many clinical benefits, having contributed to the eradication and control of several communicable diseases and thus improving and enhancing the human quality of life [7].

Wang et al. [24] have recently performed a meta-analysis pooling 16 observational studies, finding a significantly increased risk of SLE (RR=1.50 [95%CI 1.05-2.12], p=0.02) and an increased risk of RA (RR=1.32 [95%CI 1.09-1.60], p=0.004) following immunisation. The relative risk (RR) remained elevated and significant, also after reducing the time between vaccine administration and the insurgence of autoimmune disorder.

Adjuvants can interact with different components of the immune system including both innate and adaptive immunity [25,26]. To facilitate the comprehension of such complex link between vaccine-adjuvants and immune-mediated events, a classification has been proposed by Koenig and co-authors [27]. Classical adaptive immune diseases induced by (dysregulation mainly of B and T cells) are at one end of the spectrum and pure innate diseases (dysregulation of the innate immune cells or due to

permeability barrier defects, excessive tissue repair process, and remodelling responses) are on the other side [14]. Thus, adjuvants that activate innate immune components such as myeloid cells, neutrophils, Toll-like receptors (TLRs), and the inflammasome are expected to induce predominantly innate immune disorders and therefore lead to the development of autoinflammaotry phenotype of adjuvant mediated disorders. By contrast, compounds that activate predominately adaptive immune mechanisms such as antigen presentation, antibody production, B cells, and T cells are more often linked with autoimmune conditions. In our study, well-defined polygenic autoimmune diseases were reported to be induced more frequently following exposure to HBV vaccine, whereas polygenic autoinflammatory disorders were more often reported after exposure to influenza vaccination. Of note, several vaccines include different adjuvants, yet the exact the exact mechanism of action of the different adjuvants is yet to be defined.

According to our study, different vaccine-adjuvants were able to induce either autoimmune or autoinflammation disorders, although with predilection for certain self-inflammation subtype. Nevertheless, our data strongly suggest that autoimmune diseases are far more common than autoinflammatory diseases after the exposure to vaccine adjuvants. In the past, macrophagic myofasciitis (MMF) and gulf war syndrome were more frequently reported than these days. Whether this is related to change of adjuvant types or other factors is yet to be clarified.

Concerning exposure to foreign material, silicone are polymers that are commonly used in various medical applications [6]. These compounds significantly elicit immune system activation and responses, leading to tissue alterations and injuries. Different studies have shown that silicone breast implants (SBIs) may be associated to fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth [28-30]. A robust proof of this is given by the fact that removing SBIs leads to amelioration of the symptoms [31]. In addition, we have recently performed a nation-wide cross-sectional study including more than 24 thousand women with SBIs and more than 98 thousand matched with SBIs to assess the link between SBIs and autoimmunity [6]. The adjusted risk of being

diagnosed with an autoimmune/rheumatic disorder was computed to be 1.22 [95%CI 1.18-1.26]. The most prominent associations with SBIs (OR>1.5, p<0.001) were found with Sjögren's syndrome (OR 1.58), systemic sclerosis (SSc; OR 1.63) and sarcoidosis (OR 1.98).

The international ASIA registry contributes to the advancement of vaccine- and foreign material-related knowledge in terms of their safety profile and potential adverse events, updating and expanding our previously published report. Furthermore, it shows that the vast majority of the well-defined immune diseases to be reported are of autoimmune nature rather than autoinflammation or intermediate immune diseases. Further studies, including well-conducted, high quality large epidemiological surveys and randomized trials, are needed to confirm and replicate our findings.

In conclusion, it is extremely important to highlight that the main objective of the current study is not to discourage vaccinations, which are crucial against certain infections. Our findings show that potential adjuvant associated immune mediated disorders are predominantly autoimmune in nature rather than innate or autoimflammatory in nature. Immune conditions following vaccination are relatively rare, but should not be underestimated and thus the production of better compounds acting as adjuvants with a better efficacy and safety profile should be promoted. Nowadays and according to the literature, the benefits of vaccinations far outweigh the risk of immune side effects.

Tables.

Table 1. The prevalence of the various clinical manifestations reported in the ASIA registry cohort.

Clinical findings	Frequency	Prevalence (%)
Arthralgia	369	73.8%
Chronic fatigue	328	65.6%
Myalgia	254	50.8%
Sleep disturbances	219	43.8%
Fever	194	38.8%
General weakness	247	49.4%
Arthritis	136	27.2%
Neurological manifestations	175	35.0%
Cognitive impairment	172	34.4%
Sicca symptoms	95	19.0%
Raynaud's phenomenon	98	19.6%
Chronic rash	64	12.8%
Lymphadenopathy	141	28.2%
Photosensitivity	55	11.0%
Mouth ulcers	29	5.8%
Postural orthostatic tachycardia syndrome	13	2.6%
Myositis	13	2.6%

Table 2. Description pf the well-defined autoimmune/inflammatory diagnoses

Well-defined clinical diagnosis	Number of patients	Age	Gender	Exposure to vaccines	Exposure to foreign material
Polygenic autoinflammatory diseases					
GCA/PMR					
Giant cell arteritis	8	67-80 years, 74.5±5.4 years	8 females	Influenza vaccine (8)	-
Polymyalgia rheumatica	4	64-71 years, 66.0±3.4 years	3 females, 1 male	Influenza vaccine (3)	-
Adult Still's disease	1	27 years	Female	-	Silicone
IBD					
Crohn's disease	6	11-48 years, 22.7±14.6 years	4 females, 2 males	HBV (4), influenza vaccine (1), DTP vaccine (1)	-
Ulcerative colitis	1	11	Female	HBV vaccine	-
Mixed pattern diseases					
MHC-I-opathies					
Ankylosing spondylitis	1	35 years	Female	HAV vaccine	-
Spondyloarthritis	3	34-38 years, 36.0±2.0 years	3 males	Influenza vaccine (2), H1N1 vaccine (1)	-
Behçet's disease	1	18 years	Female	HPV vaccine	-
Psoriatic arthritis	1	61 years	Female	-	-
Psoriasis	1	30 years	Female	DTP vaccine	-
Polygenic autoimmune diseases					
Vasculitides					
ANCA-associated vasculitis	2	53–54 years, 53.5±0.7 years	2 females	HAV vaccine (1), influenza vaccine (1)	-
Polyarteritis nodosa	1	32 years	Female	HBV vaccine	-
HS purpura	1	12 years	Female	HPV vaccine	-
RA, SLE and CTD					
UCTD	113	15-83 years, 48.5±15.6 years,	101 females, 12 males	HBV vaccine (32), influenza vaccine (30), DTP vaccine (13), Td vaccine (12), smallpox vaccine (7), polio vaccine (5), HAV vaccine (6), HPV vaccine	Metal implant (34), tooth amalgam (13), IUD (10), silicone (10), PAL and HA/skin fillers (1)

				(3), H1N1 vaccine (2), pneumococcal vaccine (1), MMR vaccine (1), yellow fever vaccine (1), measles vaccine (1)	
Systemic lupus erythematosus	18	14-70 years, 39.7±15.7 years	16 females, 2 males	HBV vaccine (12), MMR vaccine (3), influenza vaccine (3), HPV vaccine (3), TD vaccine (2), DTD vaccine (1), DTP (1), oral typhoid vaccine (1), HAV vaccine (1), JE vaccine (1)	Mo (2), silicone (1)
Sjogren's syndrome	49	25-72 years, 46.6±12.0 years	48 females, 1 male	DTP vaccine (7), HBV vaccine (6), HPV vaccine (3), oral typhoid vaccine (1), HAV vaccine (1), MMR vaccine (1), JE vaccine (1), influenza vaccine (1)	HA (3), silicone (2), PAC (2), PAL (1), Mo (1)
RA	10	16–47 years, 29.7±9.9 years	10 females	HBV vaccine (9), HPV vaccine (1)	-
Systemic sclerosis/morphea	5	31–55 years, 44.8±11.4 years	5 females	HBV vaccine (2)	Silicone (2), PAC (1), metal implant (1), skin filler (1), IUD (1)
Dermatomyositis	2	6 years	1 female, 1 male	HBV vaccine (2)	-
Recurrent polychondrytis	1	39 years	Female	DTP vaccine	Silicone

APS	2	40-57 years, 48.5±12.0 years	2 females	HBV vaccine	-
MCTD	4	33-45 years, 40.8±5.3 years	3 females, 1 male	HBV vaccine (3), influenza vaccine (1), HAV vaccine (1)	-
Organ specific					
Multiple sclerosis / optic neuritis / neuromyelitis optica	20	15–55 years, 31.2±8.9 years	18 females, 2 males	HBV vaccine (18), HPV vaccine (2)	-
Diabetes mellitus type 1	13	4-69 years, 17.8±17.7 years	7 males, 6 females	HBV vaccine (11), HPV vaccine (2)	-
GBS	8	11–66 years, 36.4±24.2 years	6 females, 2 males	HBV vaccine (4), influenza vaccine (2), HAV vaccine (1), DTP vaccine (1), HPV vaccine (1)	-
Dysautonomic neuropathy	15	12-64 years, 45.1±16.9 years	14 females, 1 male	HPV vaccine (13)	-
POTS	6	12–22 years, 16.8±3.8 6 years	6 females	HPV vaccine (6)	-
Autoimmune liver diseases	6	11-39 years, 25.2±10.8 years	5 females, 1 male	HBV (6), influenza vaccine (1), MMR vaccine (1)	-
Transverse myelitis	4	14–67 years, 33.0±23.7 3 years	3 females, 1 male	HAV vaccine (1), HBV vaccine (3), DPT vaccine (1), HPV vaccine (1), MCV4 vaccine (1)	-
Autoimmune encephalitis	2	17–37 years, 27.0±14.1 years	2 males	HBV vaccine (2)	-
Hemolytic anemia	1	14 years	Male	HBV vaccine	-
Autoimmune thyroiditis	2	14-40 years, 27.0±18.4 years	2 females	HPV vaccine (1)	-
Adrenal insufficiency	1	9 years	Female	HBV vaccine	-

Inflammatory polyradiculopathy	1	53 years	Male	Influenza vaccine	-
PBC	2	52-56 years, 54.0±2.8 years	2 females	-	PAC and HA (1), PAL (1)
CIDP	1	52 years	Female	HBV vaccine	-
Celiac disease	1	7 years	Male	DTP vaccine, HBV vaccine	-
Others autoimmune/rheumatic diseases					
Sarcoidosis	4	35-53 years, 45.8±7.9 years	3 females, 1 male	DTP vaccine (1), HBV vaccine (1)	PLA (1), HAM (1), HA (1)
Panniculitis	2	32-39 years	2 females	HPV vaccine (1)	-
Alopecia	1	11 years	Female	HBV vaccine	-
Macrophagic myofasciitis	1	13 years	Female	HPV vaccine	-
Inflammatory polyarthritis	1	62 years	Female	HBV vaccine	-
Autoimmune recurrent abortions	2	32-39 years, 35.5±4.9 years	2 females	-	-
Juvenile RA	2	4–15 years, 9.5±7.8 years	1 female, 1 male	HBV vaccine (2)	-
Fibromyalgia	36	11–66 years, 28.0±14.2 years	34 females, 2 males	HPV vaccine (16), HBV vaccine (14), influenza vaccine (1), HAV vaccine (1)	Silicone (6)
CFS	11	12–54 years, 29.7±17.9 years	7 females, 4 males	HBV vaccine (8), HPV vaccine (2), DTd vaccine (1), intranasal influenza vaccine (1), HAV vaccine (1), oral typhoid vaccine (1), JE vaccine (1)	Silicone (1)

CIDP: chronic inflammatory demyelinating polyneuropathy, CTD: connective tissue disease, DTP: diphtheria/tetanus/pertussis, HA: hyaluronic acid, HAV: hepatitis A virus, HBV: hepatitis B virus, HPV: human papilloma virus, IUD: intrauterine devise, JE: Japanese encephalitis, MCTD: mixed connective tissue disease, MCV4: meningococcal conjugate vaccine 4, MMR: mumps/mumps/rubella, Mo: mineral oil, PAC: polyacrylamide gel, PAL: polyalkylimide gel, POTS: postural orthostatic tachycardia syndrome, SLE: systemic lupus erythematosus, UCTD: undifferentiated connective tissue disease.

Table 3. Changes in clinical symptoms of ASIA syndrome frequency and percentage between our previously published paper and the current update.

Clinical findings	Overall frequency and percentage (01/2016-02/2019 – present paper)	Frequency and percentage (2011-01/2016 – previous paper)	Frequency and percentage (02/2016-2019 – present update)	Change
Arthralgia	369 (73.8%)	184 (61.3%)	185 (92.5%)	↑
Chronic fatigue	328 (65.6%)	178 (59.3%)	150 (75.0%)	↑
Myalgia	254 (50.8%)	147 (49.0%)	107 (53.5%)	↑
Sleep disturbances	219 (43.8%)	112 (37.3%)	107 (53.5%)	↑
Fever	194 (38.8%)	101 (33.7%)	93 (46.5%)	↑
General weakness	247 (49.4%)	100 (33.3%)	147 (73.5%)	↑
Arthritis	136 (27.2%)	88 (29.3%)	48 (24.0%)	↓
Neurological manifestations	175 (35.0%)	78 (26.0%)	97 (48.5%)	↑
Cognitive impairment	172 (34.4%)	63 (21.0%)	109 (54.5%)	↑
Sicca symptoms	95 (19.0%)	55 (18.3%)	40 (20.0%)	↑
Raynaud's phenomenon	98 (19.6%)	48 (16.0%)	50 (25.0%)	↑
Chronic rash	64 (12.8%)	47 (15.7%)	17 (8.5%)	↓
Lymphadenopathy	141 (28.2%)	43 (14.3%)	98 (49.0%)	↑
Photosensitivity	55 (11.0%)	33 (11.0%)	22 (11.0%)	↔
Mouth ulcers	29 (5.8%)	18 (6.0%)	11 (5.5%)	↓
POTS	13 (2.6%)	13 (4.3%)	0 (0.0%)	↓
Myositis	13 (2.6%)	7 (2.3%)	6 (3.0%)	↑

Table 4. Changes in well-defined clinical diagnosis between our previously published paper and the current update.

Well-defined clinical diagnosis	Total number of patients	Number of patients (2011-01/2016 – previous paper)	Number of patients (02/2016-2019 – update)	Change
Polygenic autoinflammatory diseases				
GCA/PMR	12 (2.4%)	11 (3.7%)	1 (0.5%)	↓
Adult Still's disease	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
IBD	7 (1.4%)	6 (2.0%)	1 (0.5%)	↓
Mixed pattern diseases				
MHC-I-opathies	7 (1.4%)	2 (0.7%)	5 (2.5%)	↑
Ankylosing spondylitis	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Psoriasis	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Behçet's disease	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Psoriatic arthritis	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Undifferentiated-SpA	3 (0.6%)	0 (0.0%)	3 (1.5%)	↑
Polygenic autoimmune diseases				
Vasculitides	4 (0.8%)	4 (1.3%)	0 (0.0%)	↓
ANCA-associated vasculitis	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓
Polyarteritis nodosa	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
HS purpura	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
RA, SLE and CTD	204 (40.8%)	127 (42.3%)	77 (25.7%)	↓
UCTD	113 (22.6%)	78 (26.0%)	35 (17.5%)	↓
SLE	18 (3.6%)	18 (6.0%)	0 (0.0%)	↓
Sjogren's syndrome	49 (9.8%)	11 (3.7%)	38 (19.0%)	↑
RA	10 (2.0%)	10 (3.3%)	0 (0.0%)	↓
Systemic sclerosis/morphea	5 (1.0%)	5 (1.7%)	0 (0.0%)	↓
Dermatomyositis	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓
Recurrent polychondrytis	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
APS	2 (0.4%)	1 (0.3%)	1 (0.5%)	↑
MCTD	4 (0.8%)	1 (0.3%)	3 (1.5%)	↑
Organ specific	83 (16.6%)	70 (23.3%)	13 (6.5%)	↓
Multiple sclerosis / optic neuritis / neuromyelitis optica	20 (4.0%)	20 (6.7%)	0 (0.0%)	↓
Diabetes mellitus type 1	13 (2.6%)	12 (4.0%)	1 (0.5%)	↓
GBS	8 (1.6%)	8 (2.7%)	0 (0.0%)	↓
Dysautonomic neuropathy	15 (3.0%)	7 (2.3%)	8 (4.0%)	↑
POTS	6 (1.2%)	6 (2.0%)	0 (0.0%)	↓
Autoimmune liver diseases	6 (1.2%)	5 (1.7%)	1 (0.5%)	↓
Transverse myelitis	4 (0.8%)	4 (1.3%)	0 (0.0%)	↓
Autoimmune encephalitis	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓
Haemolytic anaemia	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Autoimmune thyroiditis	2 (0.4%)	1 (0.3%)	1 (0.5%)	↑
Adrenal insufficiency	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Inflammatory polyradiculopathy	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
PBC	2 (0.4%)	1 (0.3%)	1 (0.5%)	↑

CIDP	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Celiac disease	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Other autoimmune/rheumatic diseases	60 (12.0%)	53 (17.7%)	7 (3.5%)	↓
Fibromyalgia	36 (7.2%)	36 (12.0%)	0 (0.0%)	↓
CFS	11 (2.2%)	11 (3.7%)	0 (0.0%)	↓
Sarcoidosis	4 (0.8%)	3 (1.0%)	1 (0.5%)	↓
Panniculitis	2 (0.4%)	0 (0.0%)	2 (1.0%)	↑
Alopecia	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Macrophagic myofasciitis	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Inflammatory polyarthritis	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Autoimmune recurrent abortions	2 (0.4%)	0 (0.0%)	2 (1.0%)	↑
Juvenile RA	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓

GCA: giant cells arteritis, PMR: polymyalgia rhematica, IBD: inflammatory bowel disease, SpA: spondyloarthritis, HS purpura: henoch schonlein purpura, RA: rheumatoid arthrtitis, SLE: systemic lupus erythematosus, CTD: connective tissue disease, UCTD: undifferentiated connective tissue disease, APS: antiphospholipid syndrome, MCTD: mixed connective disease, GBS: guillain-barré syndrome, POTS: postural orthostatic tachycardia syndrome, PBC: primary biliary cholangitis, CIDP: chronic inflammatory demyelinating polyneuropathy, CFS: chronic fatigue syndrome.

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Author Contributions

A.W., N.L.B. and Y.S. designed the study and wrote the manuscript. A.W., N.L.B., M.A., J.A.R., E.E.V, C.B. and M.Q collected and analysed the data. A.W., M.A., D.M., G.D. and H.A., and Y.S. mainly interpreted the results. A.W., N.L.B., D.M., C.B., G.D., H.A. and Y.S. added critical discussions on analyses and results. All authors reviewed the manuscript.

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