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ENVIRONMENT AND AUTOIMMUNITY

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Are the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and the undifferentiated connective tissue disease (UCTD) related to each other? A case-control study of environmental exposures

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Abstract The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is an entity that includes different autoimmune conditions observed after exposure to an adjuvant. Patients with undifferentiated connective tissue disease (UCTD) present many signs and symptoms of ASIA, alluding to the idea that an exposure to adjuvants can be a trigger also for UCTD. The aim of this case-control study was to investigate exposure to adjuvants prior to disease onset in patients affected by UCTD. Ninety-two UCTD patients and 92 age- and sex-matched controls with no malignancy, chronic infections, autoimmune disease nor family history of autoimmune diseases were investigated for exposure to adjuvants. An ad hoc-created questionnaire exploring the exposure to vaccinations, foreign materials and environmental and occupational exposures was administered to both cases and controls. Autoantibodies were also analyzed (anti-nuclear, anti-extractable nuclear antigens, anti-double-stranded DNA, anti-cardiolipin, anti-β2 glycoprotein I). UCTD patients displayed a greater exposure to HBV ($p = 0.018$) and tetanus toxoid ($p < 0.001$) vaccinations, metal implants ($p < 0.001$), cigarette smoking ($p = 0.006$) and pollution due to metallurgic factories and foundries ($p = 0.048$) as compared to controls. UCTD patients exposed to major ASIA triggers (vaccinations, silicone implants) ($n = 49$) presented more frequently with chronic fatigue ($p < 0.001$), general weakness ($p = 0.011$), irritable bowel syndrome ($p = 0.033$) and a family history for autoimmunity ($p = 0.018$) in comparison to non-exposed UCTDs. ASIA and UCTD can be considered as related entities in the "mosaic of autoimmunity": the genetic predisposition and the environmental exposure to adjuvants elicit a common clinical phenotype characterized by signs and symptoms of systemic autoimmunity.

Keywords Adjuvants · ASIA syndrome · Undifferentiated connective tissue disease · Vaccinations · Metal implants

Introduction

Several conditions in the field of autoimmunity are characterized by non-specific signs and symptoms that cannot be included in any well-defined diagnostic category, such as chronic fatigue, myalgia, muscle weakness, arthralgia or arthritis. The term "undifferentiated" used to describe all these conditions not only reflects an undefined clinical picture but also a poor knowledge of the underlying etiopathogenic mechanisms.

The definition of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [1] has shifted the attention toward adjuvants as triggers of various pathological entities

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of autoimmune etiology. Adjuvants are indeed substances that can enhance the immune response and that sometimes, in particular conditions, can induce themselves an immune response. Similarly to ASIA, the undifferentiated connective tissue disease (UCTD) is an autoimmune condition characterized by non-specific signs and symptoms, alluding to the idea that the exposure to adjuvants can also be a trigger of UCTD.

The aim of this case-control study was to investigate the exposure to different adjuvants in patients affected with UCTD and in age and sex-matched controls, as well as to evaluate whether UCTD patients can fall within the spectrum of ASIA.

Materials and methods

Patients and controls

Ninety-two patients with UCTD were enrolled at the Unit of Rheumatology and Clinical Immunology at Spedali Civili of Brescia (Italy). The diagnosis of UCTD had been performed according to the current international criteria [2]. Ninety-two age- and sex-matched healthy controls were selected according to the following exclusion criteria: presence of any systemic or organ-specific autoimmune disease in both the subject and its first-line relatives, history of malignancy, or chronic infectious diseases (with particular focus on viral hepatitis). Fifty-three controls (57.6%) were blood donors attending the blood bank of the same hospital. Both patients and controls were enrolled after signing a written informed consent. The study was approved by the local Ethic Committee in Brescia and performed in accordance to the good clinical practice and to the Declaration of Helsinki.

Questionnaire

The exposure to various potential triggers of autoimmunity was investigated through a questionnaire that was created ad hoc for the study. The list of investigated items is reported in Table 1. Vaccinations were investigated in the 10 years before disease onset for UCTD patients or before the survey for controls. This time span was chosen based on the literature reporting the occurrence of autoimmune manifestations many years after a vaccination [3, 4]. We considered significant as environmental exposure the proximity to landfills, highways, airports and metal or chemical factories in a range of 5 km for more than 20 years. Allergies were investigated according to the patient's history as we did not check for allergies with tests. UCTD patients were administered an additional questionnaire exploring disease features: fever, general weakness, weight loss, myalgia, myositis, arthralgia, arthritis, pruritus, chronic rash, lymphadenopathy, chronic pain, sleep disturbances, chronic fatigue (Visual Analogic Scale score from 0 to 10), cognitive impairment, irritable bowel syndrome, postural hypotension, postural tachycardia and neurological manifestation. Additional information were also retrieved from clinical charts.

Table 1 Items evaluated in the study questionnaire

Vaccinations
- Anti-HAV
- Anti-HBV
- Anti-tetanus toxoid
- Anti-diphteria and tetanus toxoid
- Anti-MMR
- Anti-smallpox
- Anti-HPV
- Anti-influenza
- Anti-pneumococcus
- Anti-meningococcus
- Anti-haemophilus influenzae
- Anti-yellow fever
- Anti-typhus

Foreign materials
- Piercings
- Earrings
- Tattoos
- Intra uterine devices (IUD)
- Tooth amalgams
- Heart valves
- Cardiac pacemakers
- Joint replacements or bone fracture fixation with metal implants
- Contact lenses
- Silicone breast implants
- Cutaneous fillers
- Metal dental implants

Invasive operations

Abortion history

Cigarette smoking

Allergies
- Food allergies
- Seasonal allergies
- Drug allergies
- Cosmetic allergies
- Metal allergies

Immunotherapy

Environmental factors
- Industrial pollution (aluminum, dioxin, polychlorinated biphenyls, etc.)
- Proximity to landfills, highways, airports, metal or chemical factories

Abbreviations: *HAV* hepatitis A virus, *HBV* hepatitis B virus, *MMR* measles, mumps and rubella

Blood samples and laboratory tests

Serum samples were drawn from UCTD patients and controls for the detection of autoantibodies. Anti-nuclear

autoantibodies (ANA) were tested by indirect immunofluorescence on HEp2 cells (BioRad, Hercules, CA, USA) with the starting dilution 1:160. Antibodies directed at extracted nuclear and other cellular antigens were detected by ELISA screening (ANA Screen 9 ELISA, Euroimmun, Germany) followed by Immunodot for the characterization of antibody specificity (FullANA DOT KIT, Alphadia, Belgium). Anti-dsDNA antibodies were detected by radioimmunometric assay (Farr assay; IBL, Hamburg, Germany). Anti-cardiolipin (aCL) [5] and anti-β2 glycoprotein I (anti-β2GPI) [6] were tested by validated home-made ELISA methods.

Statistics

Continuous variables were reported as mean and standard deviation, while percentages were reported for categorical variables. Comparisons among groups were performed by the Student *t* test for continuous variables and by chi-square or Fisher's exact tests for categorical variables. All statistical tests were two-tailed, and a p value <0.05 was considered statistically significant.

Results

Table 2 reports demographic information of the enrolled subjects and those items that were significantly different between cases and controls. In Table 3, the differences between exposed and not exposed UCTD patients are reported. We found in particular a higher prevalence of anti-β2GPI in UCTDs who had received a tetanus vaccine in the 10 years before the diagnosis (14/46, 30%) in comparison with UCTD patients who did not receive it (6/46, 13%) ($p = 0.043$). We also found an increased frequency of possible ASIA triggers in UCTD patients as compared to controls (89.1 vs 57.6%, $p < 0.001$). The difference was also significant when restricted to "major" ASIA triggers (vaccinations and silicone implants) (64.1 vs 30.4%, $p < 0.001$) (Table 4). UCTD patients exposed to "major" ASIA triggers displayed either more familiarity for autoimmunity or a higher frequency of typical ASIA manifestations such as chronic fatigue, general weakness and irritable bowel syndrome, as compared to non-exposed UCTD patients (Table 4).

Discussion

The exposure to adjuvants as a trigger for autoimmunity has been formalized into a novel entity called ASIA, which includes several clinical conditions presenting with signs and symptoms of autoimmunity [1, 7]. In UCTD, many of these features are detectable, suggesting that these two entities may share a common etiopathogenic background. Our case-control study was aimed at exploring the exposure to several different adjuvants and environmental factors in order to assess to what extent UCTD patients could be part of the ASIA spectrum.

Compared to sex- and age-matched healthy controls, UCTD patients were more frequently exposed to the following adjuvants: metal implants (mostly dental implants), hepatitis B virus (HBV) and tetanus toxoid vaccinations and cigarette smoking.

The possibility that metal implants stimulate an autoimmune/inflammatory response is well documented in the literature, especially for implants used in dentistry [8]. At the mitochondrial level, metals bind enzymes and proteins and are recognized by the immune system of susceptible individuals, triggering an abnormal response, which can lead to the development of allergies and autoimmune diseases. The exposure to metal implants was indeed claimed to be responsible for fibromyalgia and chronic fatigue syndrome [9]. Regarding environmental exposure to metals, we found that cases were more frequently living close to metallurgical factories and foundries (less than 1 km of distance; for a wider distance of 5 km, the difference between cases and controls was not significant). We know from the literature that a prolonged exposure to metal dust can induce autoimmunity and air pollution is an established trigger factor for autoimmune diseases [10]. An emblematic example of autoimmune diseases being induced by pollution dust comes from people experiencing the terroristic attack at the World Trade Center in New York on 11 September 2001. Debris and dust created by the collapse of the World Trade Center remained in the air for a long time, exposing the workers to an amalgam of glass fibers, silica, asbestos, polycyclic aromatic hydrocarbons, dioxin, furans and polychlorinated biphenyls. The firefighters and the policemen who worked at the site of the attack were found to have an increased incidence of autoimmune diseases. Rescuers developed rheumatoid arthritis (RA), spondyloarthritis, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), primary Sjögren's syndrome (pSS) and anti-phospholipid syndrome (APS) more frequently than the general population [11].

The association between vaccinations and autoimmune phenomena is rooted in the literature. Autoimmunity can emerge as either simple appearance of autoantibodies or as a full-blown autoimmune disease. We found that UCTD cases were more frequently exposed to HBV and tetanus toxoid vaccination in the 10 years prior to disease onset as compared to controls. Both vaccines contain indeed adjuvants, so we can speculate that they may have played a role in stimulating the immune system. This might be consistent with some reports in the literature showing that vaccines can cause autoimmune reactions even after a long time span [3, 4]. However, this finding cannot currently produce any indication to change the approach towards vaccinations. Autoimmunity is a complex and multifactorial phenomenon and emerges from a predisposing genetic background; therefore, it is likely that, for

Table 2 Characteristics of UCTD patients and controls (only significantly different items between UCTD and controls are reported)

	UCTDs (n = 92)	Controls (n = 92)	Fisher's exact test and chi-square test
Demographics			
Female, n (%)	81 (88%)	81 (88%)	–
Age at survey (years), mean (standard deviation)	50 (±16)	50 (±16)	–
Age at disease onset (years) , mean (standard deviation)	44 (±15)	–	–
Environmental exposures			
1) HBV vaccination[a], n (%)	11 (11.9%)	2 (2.1%)	$p = 0.018$
2) Tetanus toxoid vaccination[a], n (%)	46 (50.0%)	18 (19.5%)	$P < 0.0001$
3) Metal implants, n (%)	33 (35.9%)	12 (13.0%)	$P < 0.0001$
4) Ever smoker, n (%)	37 (40.2%)	23 (25.0%)	$p = 0.028$
Current smoker or past smoker in the 10 years before disease onset for cases and before survey for controls, n (%)	31 (33.6%)	15 (16.3%)	$p = 0.006$
5) Proximity to great metal factories and foundries, n (%)	11 (11.9%)	3 (3.2%)	$p = 0.048$
Allergies			
Total allergies, n (%)	49 (53.3%)	25 (27.2%)	$p < 0.001$
Drug allergies, n (%)	26 (28.3%)	7 (7.6%)	$p < 0.001$
Seasonal allergies, n (%)	19 (20.6%)	9 (9.7%)	$p = 0.048$
Food allergies, n (%)	11 (11.9%)	3 (3.2%)	$p = 0.040$
Autoantibodies			
Anti-nuclear antibodies, n (%)	91 (98.9%)	10 (10%)[b]	$p < 0.0001$
Anti-ENA, n (%)	38 (41.3%)	1 (1%)	$p < 0.0001$
Anti-dsDNA, n (%)	11 (11.9%)	0	0.001
aCL IgG and/or IgM, n (%)	15 (16.3%)	1 (1%)	$p = <0.0001$
Anti-β2GPI IgG and/or IgM, n (%)	20 (21.7%)	7 (7.6%)	$p = 0.007$

Abbreviations: *HBV* hepatitis B virus, *ENA* extractable nuclear antigens, *dsDNA* double-stranded DNA, *aCL* anti-cardiolipin antibodies, *β2GPI* β2 glycoprotein I

[a] Vaccination in the 10 years before onset for patients and before survey for controls

[b] Seven individuals with low-titer positivity, 1:160, three individuals with high-titer positivity 1:640

most individuals, the benefit of vaccinations overweighs the risk of inducing autoimmune conditions. At least, such a benefit-risk balance could be assessed individually, ideally on a genetic basis and thoroughly discussed with the subject.

UCTD patients were also more frequently cigarette smokers as compared to controls. Cigarette smoking affects both acquired and innate immunity, increasing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1, interleukin-6, interleukin-8 and granulocyte macrophage-colony stimulating factor and decreases the levels of anti-inflammatory cytokines, such as interleukin-10 (12). The role of smoking in the development of SLE and RA is well documented [12–14]. In addition, smoking can lead through different mechanisms to an increased production of immunoglobulins E (IgE) and the subsequent development of asthma and atopic disease [15]. UCTD cases were found to be more allergic to drugs, metals or foods than controls. Such an increased frequency of allergies in UCTD patients may be partly explained by their smoking habit. This finding supports the assumption that UCTD patients carry a genetic predisposition to dysfunction of the immune system. Both autoimmune diseases and allergies are exaggerated responses to an antigen: in the first case to a self-antigen and in the second to an external antigen [16].

Table 3 Comparison between exposed and non-exposed UCTD patients in relationship to those items that were more frequently found in UCTD patients as compared to controls

1) UCTD and HBV vaccination			
	HBV (n = 11)	No HBV (n = 81)	Fisher's exact test or chi-square test
Metal implants[a], n (%)	0	33 (40.7%)	p = 0.007
Contact lenses, n (%)	5 (45.5%)	6 (7.4%)	p = 0.003
2) UCTD and tetanus toxoid vaccination			
	Tetanus (n = 46)	No tetanus (n = 46)	Fisher's exact test or chi-square test
Anti β2GPI, n (%)	14 (30%)	6 (13%)	p = 0.043
3) UCTD and metal implants			
	Metal implant (n = 33)	No metal implant (n = 59)	Fisher's exact test or chi-square test
HBV vaccination, n (%)	3 (9.1%)	24 (40.7%)	p = 0.002
HBV vaccination in the 10 years before onset, n (%)	0 (0%)	11 (16.9%)	p = 0.007
Purpura[b], n (%)	6 (18.2%)	0	p = 0.002
4) UCTD and cigarette smoking			
	Smoker (n = 37)	No smoker (n = 55)	Fisher's exact test or chi-square test
Tattoo, n (%)	9 (27%)	4 (7.3%)	p = 0.008
Purpura, n (%)	5 (13.5%)	1 (1.8%)	p = 0.037
5) Proximity to metal factories and foundries			
	<1 km (n = 11)	>1 km (n = 81)	Fisher's exact test or chi-square test
aCL, n (%)	4 (36.6%)	9 (11.1%)	p = 0.046

Abbreviations: *HBV* hepatitis B virus, *β2GPI* β2 glycoprotein I, *aCL* anti-cardiolipin antibodies

[a] All the UCTD patients with metal implant did not have HBV vaccine in the 10 years before onset

[b] All the UCTD patients with purpura have a metal implant

The analysis was restricted to UCTD patients by comparing those who were exposed to significant adjuvants and those who were not. We found that purpura, the hallmark of cutaneous vasculitis, was associated with smoking and metal implants (particularly, all the patients with purpura had been exposed to metal implants). This finding is supported by previous reports showing the effects of smoke on the microcirculation [17]. Another intriguing association was found between anti-β2GPI and vaccination against tetanus toxoid. It is well recognized that the tetanus toxin and β2GPI share a sequence of six peptides (TLRVYK) [18–20] and through the mechanism of molecular mimicry, the production of

Table 4 Exposure to "major" and "minor" ASIA triggers in controls and UCTD patients

Exposure to ASIA triggers: UCTDs vs controls			
	UCTDs (n = 92)	Controls (n = 92)	Fisher's exact test and chi-square test
"Major" ASIA triggers, n (%)	59 (64.1%)	28 (30.4%)	p < 0.001
"Major" + "minor" ASIA triggers, n (%)	82 (89.1%)	53 (57.6%)	p < 0.001
Exposure to ASIA triggers: exposed UCTDs vs not exposed			
	UCTDs Exposed (n = 59)	UCTDs Not exposed (n = 33)	Fisher's exact test and chi-square test
Chronic fatigue, n (%)	44 (74.5%)	11 (33.3%)	p < 0.001
General weakness, n (%)	24 (40.6%)	5 (15.1%)	p = 0.011
Irritable bowel syndrome, n (%)	11 (18.6%)	1 (3.0%)	p = 0.033
Familiarity for autoimmunity, n (%)	33 (55.9%)	10 (30.3%)	p = 0.018

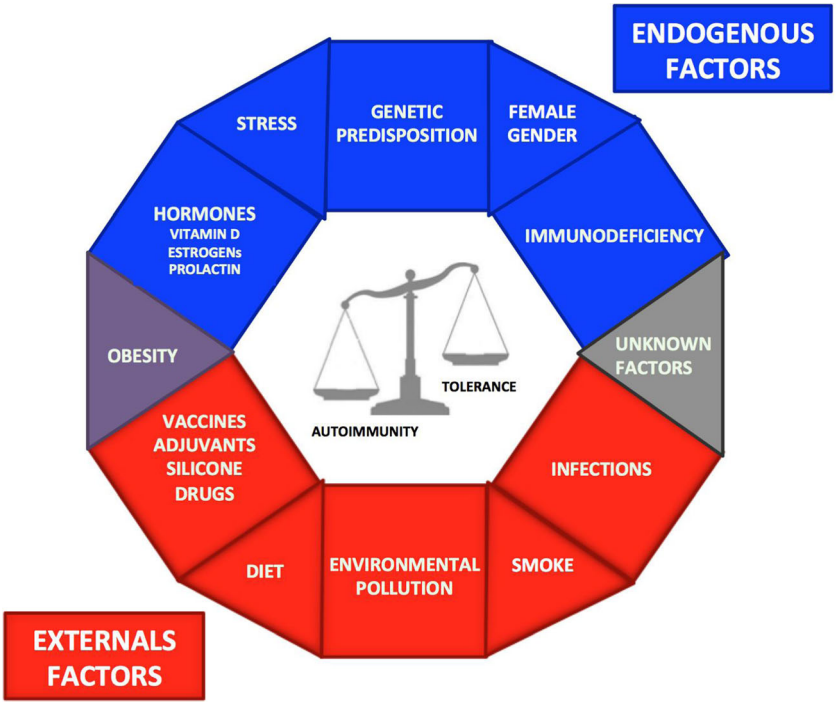

Fig. 1 Mosaic of autoimmunity adapted from [29]

anti-β2GPI was observed in mice after tetanus immunization [18–20]. Such antibodies can be pathogenic and lead to the clinical manifestations of APS [21].

As the main scope of our study was to assess how many UCTD patients could be part of the ASIA spectrum, we subdivided the potential ASIA triggers in "major" and "minor" according to the level of evidence coming from the literature. Major triggers were silicon and adjuvanted vaccines [22–26]. Among 92 UCTD patients, 64.1% had been exposed to at least one of the major ASIA triggers, while the percentage rose to 89% when considering also the minor triggers. Both the exposure to major and minor ASIA triggers were significantly higher in UCTDs as compared to healthy controls ($p < 0.001$), confirming that UCTD patients may had been more prone to respond to environmental stimuli.

By comparing UCTD patients exposed to major triggers and those who were not, we found a higher frequency of chronic fatigue ($p < 0.001$), general weakness ($p = 0.011$) and irritable bowel syndrome ($p = 0.033$). Chronic fatigue and general weakness are key symptoms of ASIA, as well as the irritable bowel syndrome, which is one of the minor criteria for the diagnosis of ASIA. Exposed UCTD patients displayed more frequently a family history of autoimmunity ($p = 0.003$). These findings suggest that UCTD and ASIA are linked to each other and the clinical phenotype is probably the outcome of a trigger/adjuvant acting on a genetic background prone to autoimmunity.

In conclusion, we can suggest that ASIA and UCTD are two related entities in the "mosaic of autoimmunity" [27, 28] (Fig. 1). The genetic predisposition and the environmental exposure to adjuvants elicit a common clinical phenotype characterized by signs and symptoms of systemic autoimmunity. Further research should focus on unravelling the mechanisms for different time span between exposure to adjuvants and disease onset and to verify whether UCTD patients could get any benefit from the removal of the adjuvant (whenever possible) as it holds true for ASIA cases.

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Compliance with ethical standards The study was approved by the local Ethic Committee in Brescia and performed in accordance to the good clinical practice and to the Declaration of Helsinki.

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