



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.

F. Scanzi (1), L. Andreoli (1), M. Martinelli (1), M. Taraborelli (1), I. Cavazzana (1), N. Carabellese (1), R. Ottaviani (1), F. Allegri (1), F. Franceschini (1), N. Agmon-Levin (2), Y. Shoenfeld (2,3), A. Tincani (1).

¹ Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Italy;

² Zabudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ³ Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

ABSTRACT

Background/Purpose: The Autoimmune/Inflammatory Syndrome induced by adjuvants (ASIA) [1] 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 control-case study is to investigate prior exposures to adjuvant in 92 patients affected with UCTD and 92 age and sex-matched controls with no family history of autoimmunity.

Methods: An *ad hoc* created questionnaire that lists exposure to the possible triggers of "ASIA", such as vaccinations (HBV vaccine, HAV vaccine, tetanus toxoid vaccine, Haemophilus Influenzae vaccine, MMR vaccine, Pneumococcal vaccine, HPV vaccine) foreign materials (earrings, piercings, tattoos, silicon breast implants, skin fillers, tooth amalgam, contact lenses IUD, cardiac valves, artificial joints, metal implants), environmental and occupational exposures (living and working near metal or chemical factories, landfills, airports or highways) was administered to both cases and controls. For both groups autoantibodies were analyzed (i.e. antinuclear, anti-ENA, anti-dsDNA, anti-cardiolipin, anti-β2glycoprotein I). Continuous variables were reported as mean and standard deviation, while percentages were reported for categorical variables. T-test was calculated for continuous variables while Chi-square or Fisher's exact tests were used for categorical variables. All statistical tests were two-tailed and only a p value < 0.05 was considered statistically significant.

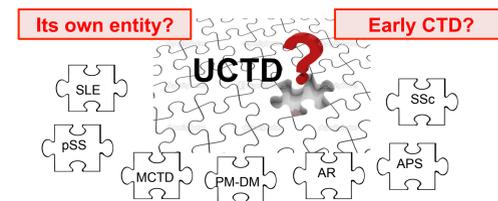
Results: We investigated demographic information of the enrolled subjects and those items that were significantly different between cases and controls. We found differences between the exposed UCTD and the not exposed, some more interpretable than others. In particular, the "molecular mimicry" between β2glycoprotein I and tetanus toxoid was described [2], we indeed found that there is a higher prevalence of anti-β2glycoprotein I in UCTD 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 analyzed the exposition to the ASIA triggers, both in UCTD and controls.

Conclusions: As compared with healthy subjects, UCTD patients appeared to have had a greater exposure to adjuvants: HBV and tetanus toxoid vaccinations, metal implants and cigarette smoking. The increased prevalence of allergies proved that UCTD patients have a more reactive immune system, likely on a genetic basis. Patients resulted to be more exposed than controls to the major ASIA triggers, and the UCTDs exposed presented more symptoms typical of the ASIA than the not exposed ones. Thus we can suggest that ASIA and UCTD are two 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.

[1] Shoenfeld Y, Agmon-Levin N. J Autoimm 2011;36:4-8.
[2] Stojanović M et al. Immunol Res. 2013;56:20-31.

BACKGROUND

Undifferentiated Connective Tissue Disease (UCTD)



Its own entity? **Early CTD?** The term undifferentiated connective tissue disease is used to define conditions characterized by the presence of signs and symptoms suggestive of a systemic autoimmune disease that do not satisfy the classificative criteria for defined connective tissue diseases (CTD).

M. Mosca et al. Undifferentiated connective tissue diseases (UCTD). Autoimmun Rev. 2006 Nov;6(1):1-4. Epub 2006 Apr 19.

Autoimmune/Inflammatory Syndrome Induced By Adjuvants (ASIA)

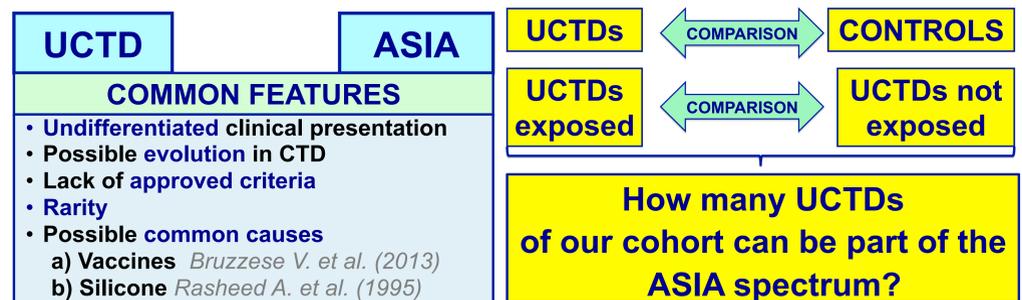
In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves, both in animal models and in humans.

MAJOR CRITERIA	MINOR CRITERIA	ASIA SPECTRUM	COMMON FEATURES
Exposure to external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations	Appearance of autoantibodies or antibodies directed at the suspected adjuvant	Post Vaccination Phenomena	Symptoms typical of: - Chronic Fatigue Syndrome (CFS) - Fibromyalgia (FM)
Appearance of "typical" clinical manifestations: Myalgia, myositis or muscle weakness; Arthralgia and/or Arthritis; Chronic fatigue, un-refreshing sleep or sleep disturbances; Neurological Manifestations especially associated with demyelination; cognitive impairment, memory loss; pyrexia, dry mouth	Other clinical manifestations (i.e. irritable bowel syndrome) Specific HLA (i.e. HLA DRB1, HLA DQB1) Evolution of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)	Macrophagic Myofasciitis Syndrome	
Removal of inciting agent induces clinical improvement		Gulf War Syndrome	Suggestive signs of aberrant immunitary response: - Autoantibodies - Fever - Arthritis - Myositis - Demyelination
Typical biopsy of involved organs		Siliconosis or "Adjuvant disease"	
		Sick Building Syndrome	

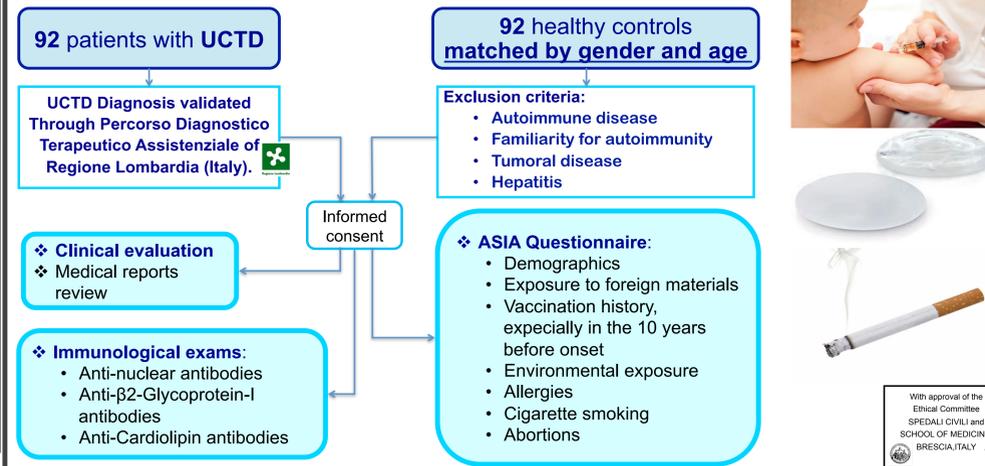
C. Perricone Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects. Journal of Autoimmunity 47 (2013) 1e16

Shoenfeld Y, Agmon - Levin N. J Autoimmun 2011; 36(1): 4-8 "ASIA" - autoimmune/inflammatory syndrome induced by adjuvants

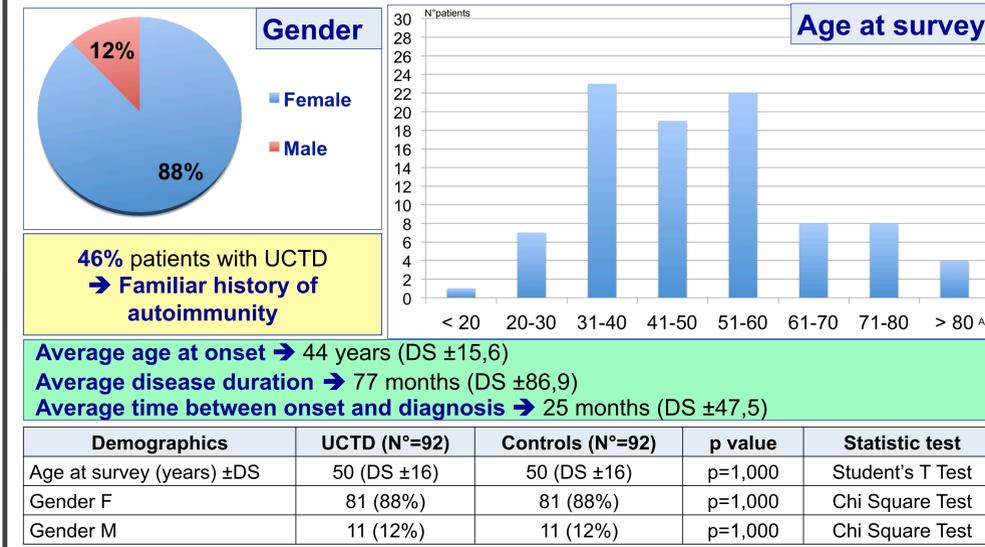
RATIONAL AND AIM OF THE STUDY



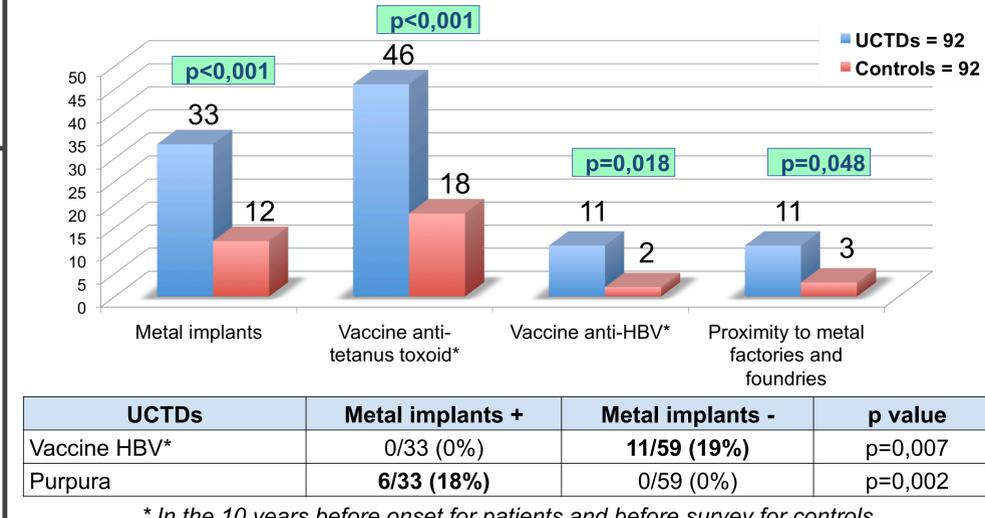
PATIENTS AND METHODS



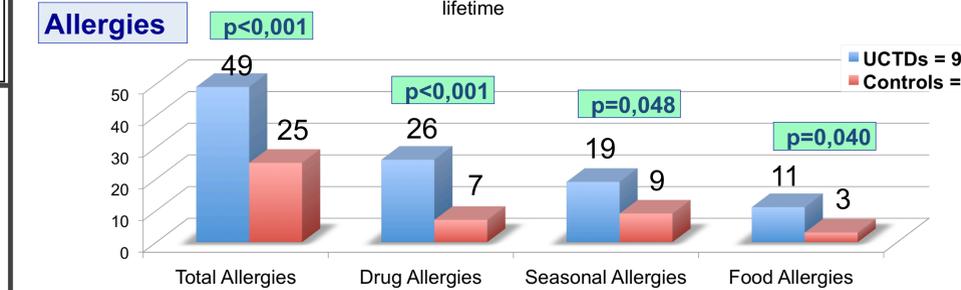
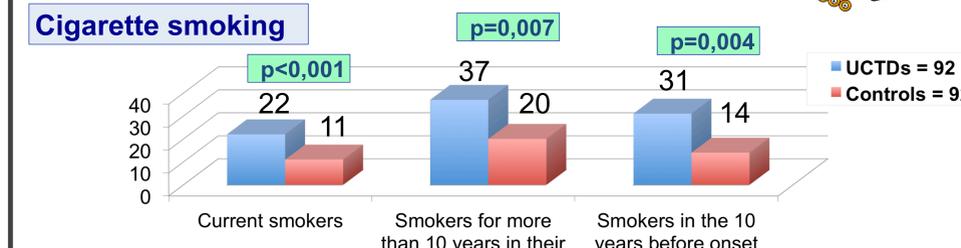
RESULTS 1: Demographics



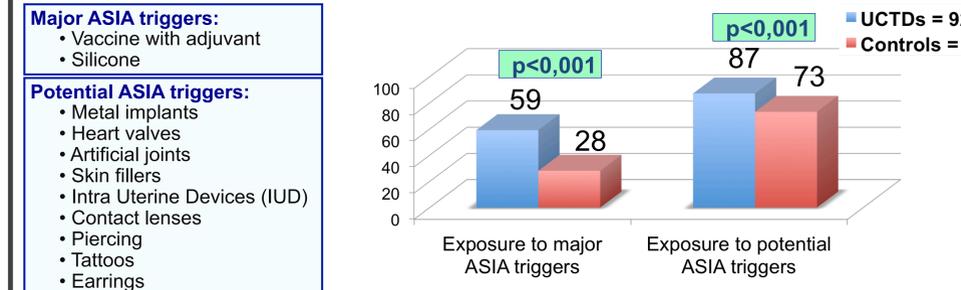
RESULTS 2: Significant Exposure



UCTDs	Vacc. Anti T.T.* +	Vacc. Anti T.T.* -	p value
Anti-β2Glicoprotein I	14/46 (30%)	6/46 (13%)	p=0,043



RESULTS 3: Exposure to ASIA triggers



UCTDs	Major triggers +	Major triggers -	p value
Chronic fatigue	44/59 (75%)	11/33 (33%)	p<0,001
General weakness	24/59 (41%)	5/33 (15%)	p=0,011
Irritable bowel syndrome	11/59 (19%)	1/33 (3%)	p=0,033
Familiarity for autoimmunity	33/59 (56%)	10/33 (33%)	p=0,018

CONCLUSIONS

Our patients with UCTD resulted more exposed than controls to:
1) Metal Implants 2) Vaccination anti-tetanus toxoid* and anti-HBV*
3) Metal factories and foundries (<1km) 4) Smoking.

Nearly half of the patients (57%) have been exposed to the major ASIA triggers and they can be considered as part of the ASIA spectrum. The fact that the exposed UCTDs presented more symptoms typically associated with ASIA supports our conclusion.

As the patients exposed to major ASIA triggers presented more frequently with familiarity for autoimmunity, we suggest that adjuvants are one of the tiles of the "Mosaic of autoimmunity", playing as an environmental trigger on a predisposing genetic background.

Contact: francescoscanzi@hotmail.it