Article title: Review of Toxins Associated with Autoimmune Diseases

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Review of Toxins Associated with Autoimmune Diseases

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ABSTRACT

Aim of this article is to review the literature about the toxins that might be involved in the pathogenesis of autoimmune diseases. Almost 70% of all autoimmune diseases are caused by environmental factors, including toxic chemicals. Genetic factors contribute to approximately 30% of all autoimmune diseases.

INTRODUCTION

Studies have shown that genetic predisposition accounts for approximately 30% of all autoimmune diseases. The rest, 70%, are due to environmental factors, including toxic chemicals, dietary components, gut dysbiosis, and infections¹.

TRICHLOROETHYLENE

Trichloroethylene (TCE) is an industrial solvent known for being neurotoxic, hepatotoxic, nephrotoxic, immunotoxic and carcinogenic. Cooper and coworkers reviewed the literature about the role of TCE in autoimmunity, and concluded that the consistency among the studies and the concordance between the studies in mice and humans support an etiologic role of TCE in autoimmune disease, but multi-site collaborations and studies of preclinical immune markers are needed to further develop this field of research².

Substantial evidence from mechanistic, clinical, and epidemiologic studies indicates that exposure to TCE and/or its metabolites (including chloral hydrate, trichloroacetic acid, trichloroacetaldehyde hydrate, and dichloroacetyl chloride) could influence the incidence of autoimmune disorders. Research on autoimmune mouse models, including the MRL^{+/+} lupus mouse, has provided strong and consistent support for a role of TCE. This has included studies of exposures at environmentally relevant concentrations through multiple routes (inhalational, dermal, and oral). Studies of humans with high occupational or environmental exposures have also shown links between TCE and inflammatory immune responses, systemic sclerosis, and severe generalized hypersensitivity skin disorder³.

DRUG-INDUCED AUTOIMMUNITY

The chemicals most often associated with development of autoimmunity in humans are medications. A large list of drugs have been shown to induce systemic lupus erythematosus (SLE)-like disease, but **procainamide** and **hydralazine** are considered to be of high risk⁴.

SILICA

The association of silica and development of systemic autoimmune diseases such as SLE and scleroderma, stems from exposure during occupations such as mining, construction, glass and pottery production⁵.

ASBESTOS

Asbestos is another naturally occurring silicate mineral, composed of long, thin fibrous crystals. Several epidemiological studies have linked exposure to asbestos to autoimmune diseases⁶.

A case-control study among the current and former residents of Libby who had worked at the vermiculite mine revealed increased self-reporting of autoimmune diseases including systemic lupus erythematosus, scleroderma, and rheumatoid arthritis⁷.

TOXIC OIL SYNDROME

Xenobiotic-induced scleroderma, or pseudoscleroderma, has been associated with occupational exposures, especially occupational exposure to solvents⁸.

In the early 1980s in Spain, ingestion of adulterated cooking oil lead to an outbreak of pseudoscleroderma. The causative agent was identified as rapeseed oil, originally destined for industrial use but refined to remove the anilide denaturant and then sold as cooking oil for human consumption. Thousands of people were ultimately affected with more than 1,000 deaths being ascribed to what is called Toxic Oil Syndrome⁹.

METAL-INDUCED AUTOIMMUNITY

Mercury, silver and gold all produce autoimmunity in mice but the pathological consequences differ, with silver and gold exposure resulting in a less severe response that typically includes the production of anti-nuclear antibodies but lacks glomerular deposits of immunoglobulin and complement¹⁰⁻¹³.

Human exposure to mercury has been implicated as an environmental trigger in the induction of autoimmunity, although a non-autoimmune-mediated nephropathy is the more common outcome^{14, 15}.

IODINE

Autoimmune thyroiditis, also known as chronic lymphocytic or Hashimoto's thyroiditis, is characterized by autoantibodies to thyroid-specific antigens such as thyroglobulin and thyroperoxidase that lead to inflammation and eventual impairment of the thyroid gland¹⁶.

Excess iodine ingestion has been identified as a contributing factor in the induction and exacerbation of autoimmune thyroiditis^{17, 18}.

TIENILIC ACID, DIHYDRALAZINE, HALOTHANE

Various chemicals and drugs have been implicated in autoimmune liver diseases including tienilic acid, dihydralazine, and halothane in autoimmune hepatitis¹⁹.

Primary biliary cirrhosis which is characterized by anti-mitochondrial antibodies is also argued to be associated with environmental factors²⁰.

PRISTANE

Tetramethylpentadecane (TMPD) is a common constituent of mineral oil and is found in a number of processed foods made for human consumption. It is also known as pristane. Exposure can elicit lipogranulomas (follicular lipidosis), a chronic inflammatory response, in a

number of organs (liver, spleen, lymph nodes²¹).

TCDD

The halogenated aromatic hydrocarbon 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most potent of the dioxins and is an unintentional by-product of many industrial processes. TCDD is also a contaminant of the herbicide Agent Orange²². Previous epidemiological studies suggest that while TCDD does influence the human immune system there is little evidence of autoimmunity⁴.

HEXACHLOROBENZENE

Exposure to the fungicide hexachlorobenzene (HCB) is associated with a form of hepatic porphyria called porphyria turcica, which resembles porphyria cutanea tarda, a disease caused by altered porphyrin metabolism. Porphyria turcica is associated with bullous skin lesions, mainly in sun-exposed skin areas, that heal with severe scars, primarily affects children 6–16 years of age²³.

Exposure to HCB can also produce neurological, dermatological, and orthopaedic abnormalities that may persist for decades²⁴.

SMOKING

Numerous case-control and cohort studies have demonstrated higher risk for the development of rheumatoid arthritis (RA) in relation to smoking history, with a higher risk in rheumatoid factor (RF)-positive or ACPA-positive RA²⁵.

There appears to be a higher risk associated with greater exposure, in particular, after 10 pack-years of smoking in women, and the risk of RA remains elevated for up to 20 years after smoking cessation²⁶. A meta-analysis of the studies of smoking and thyroid disease suggests that current smoking results in higher risk for both Graves' disease and Hashimoto thyroiditis. Cigarette smoking has been reported as a risk factor for Graves' ophthalmopathy in particular²⁷.

The relationship between smoking and inflammatory bowel disease is complex in that it is likely that current smoking contributes to the development of Crohn's disease, but is protective for the development of ulcerative colitis^{28, 29}.

HAIR DYES, COSMETIC PRODUCTS

Permanent hair dyes containing aromatic amines could be a risk factor for SLE, but the most carefully conducted epidemiologic studies have failed to identify an association between hair dyes

and SLE^{30, 31}. Investigation conducted by Cooper and coworkers (2010) found an association between employment involving nail polish or nail applications and risk of SLE³⁰. The use of hair dyes was significantly associated with a higher risk of primary biliary cirrhosis (PBC) in a study conducted in the United Kingdom³².

In a U.S. study, nail polish use was significantly more frequent among women with PBC than among control women³³.

The single case-control study of RA found that women who were occupationally exposed to hairdressing chemicals were at greater risk than unexposed women for developing RA³⁴.

IONIZING RADIATION

There is convincing evidence that external radiation treatment for cancer increases the risk of autoimmune thyroiditis and Graves' disease, especially in treatment for cancers of the neck region^{35, 36}.

A pooled analysis of two case-control studies of multiple sclerosis (MS) conducted in Sweden reported that occupational exposure to ionizing radiation (in hospitals or industry) was associated with over four-fold higher risk of MS³⁷.

BIOLOGICAL FACTORS AND INFECTIONS

Ingestion of gluten contributes to the development of gluten-sensitive enteropathy (GSE). Ingestion of certain lots of L-tryptophan contributes to the development of eosinophilia-myalgia syndrome. Epstein-Barr virus infection contributes to the development of MS. Early introduction of complex foods contributes to development of diabetes type 1 and GSE. Low vitamin D dietary intake and blood level contribute to development of MS²⁵.

CONCLUSION

Studies have shown that almost 70% of all autoimmune diseases are caused by environmental factors, including toxic chemicals, whilst genetic factors contribute to approximately 30% of all autoimmune diseases. Therefore, further investigation on toxic chemicals that might be associated with pathogenesis of autoimmune diseases is mandatory. Prevention of autoimmunity in humans relies greatly on the prevention of exposure to incriminated toxins that can cause, trigger and/or worsen autoimmune diseases. **Immune-toxins** must be replaced with at least less toxic, if not non-toxic chemicals. In addition to that, healthy balanced diet and healthy gut microbiome also play a very important role.

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