MÆDICA - a Journal of Clinical Medicine

EDITORIAL

Autoimmune diseases and their environmental triggers

Manole COJOCARU, MD, PhD[a], Inimioara Mihaela COJOCARU, MD, PhD[b], Isabela SILOSI, MD, PhD[c]

[a]Department of Clinical Immunology,"Colentina" Clinical Hospital, Bucharest, Romania
[b]Clinic of Neurology, "Colentina" Clinical Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[c]Discipline of Immunology, University of Medicine and Pharmacy, Craiova, Romania

ABSTRACT

Autoimmune diseases are caused by the body's own immune system getting confused and wrongly attacking the body's good cells. Estimates of the prevalence of autoimmune diseases in the population may be 4% or higher. The cause(s) of autoimmune disorders remain unknown.

Considerable evidence supports a role for environmental agents in inducing autoimmune disorders. Screening studies should help identify environmental factors that can trigger autoimmune diseases. Autoimmune disorders may result from multiple interactions of genes and environmental factors. Even if you inherit a genetic predisposition, the autoimmune disease will not occur unless there is an environmental trigger. There are several suspects in the search for triggers: viruses, bacteria, diet, toxins, radiation, metal, estrogen, chronic infections, and so on. Defining specific pathogenic environmental mediators that may trigger the development or progression of autoimmune disease remains a focus of increasing investigative effort.

Autoimmune diseases, which affect at least 5% of the population, might be prevented by avoiding those environmental factors that trigger the disease (primary prevention). This review focuses on the role of environmental factors in the development and exacerbation of autoimmune diseases.

Key words: immune response, autoimmune diseases, environmental triggers

The basic definition of an autoimmune disease is a disorder caused by an autoimmune response, i.e., an immune response directed to something in the body of the patient. Our understanding of autoimmune diseases has progressed tremendously in the last 20 years. Most autoimmune diseases are relatively rare and most are not fatal. Autoimmune diseases can affect virtually every site in the body including the endocrine system, connective tissue, gastrointestinal tract, heart, skin, and kidneys (1).

Autoimmune diseases result from a combination of genetic, immunologic, hormonal, and environmental factors. Unfortunately, we do not know vary many of the triggers. It must be emphasized, that these environmental triggers act only in individuals with a genetic predisposition and not in the

Address for correspondence:
Manole Cojocaru, MD, PhD, "Colentina" Clinical Hospital, 19-21 Stefan cel Mare Blvd, Zip Code 020125, Bucharest, Romania
email address: mcojocar@cmb.ro

population at large. Although an autoimmune response occurs in most persons, clinically relevant autoimmune disease develops only in susceptible persons. Even with a genetic predisposition, most people do not develop an autoimmune disease unless something external acts on their body. It must be emphasized, however, that these environmental triggers act only in individuals with a genetic predisposition and not in the population at large. The disorders result from the synergistic action of a genetic predisposition (evidence based on familial and twin concordance studies) and some environmental factors. It has long been recognized that environmental influences play an important role in the risk of developing autoimmune diseases. Time-latency considerations implicate stochastic factors or chance in the etiopathogenesis of autoimmunity, whether they are somatic mutations or successive random gene-environment interactions (2,3).

Genetics accounts for about half of the risk of developing an autoimmune disease. The other half is the agent in the environment which triggers the process. In an individual with a susceptible genotype, exposure to environmental factors (such as sunlight, diet, allergens, infectious agents or environmental toxins) can act to initiate an autoimmune process. Autoimmune disease rates have been on the rise in developed country in the last 50 years compared to their developing neighbors, presumably because people in less developed countries are exposed to more pathogens.

Infection as a possible trigger for autoimmune disorders has long been proposed. Infectious agents are suspected triggers or modulators of autoimmune diseases. Infectious agents are the most often cited environmental factors implicated as triggers of autoimmune diseases. In addition, chronic reactive arthritis (Reiter's syndrome) follows a variety of infections that include sexually transmitted Chlamydia trachomatis as well as gastrointestinal Salmonella, Shigella, Yersinia, and Campylobacter. Products of microorganisms, such as lipopolysaccharide (LPS), bacterial DNA and viruses, act as adjuvants and substantially improve immune responses to unrelated antigens. Viral infections have received particular attention in SLE studies, with findings of virus-like inclusions in renal biopsy tissue. Microbial products can improve T-cell responses to self as well as foreign antigens. Bacterial LPS and mycobacteria can induce various autoimmune diseases, sometimes in the absence of any additional antigen besides that provided by the host itself. Whether or not infections, acting as adjuvants, induce autoimmune disease in the human population is not known. Evaluations of infectious exposures in studies of RA are inconstant and difficult to interpret. Urinary tract infections and rubella were found to be associated with an increased risk of RA in women. A paradoxical observation has been the strong association of certain microbial organisms with autoimmune diseases. For example, Klebsiella pneumoniae and Coxsackie virus B have been strongly correlated with ankylosing spondylitis and type 1 diabetes mellitus, respectively. This has been explained by the tendancy of the infecting organism to produce superantigens which are capable of polyclonal activation of B-lymphocytes, and production of large amounts of antibodies of varying specificities, some of which may be self-reactive.

There are very rarely link between autoimmune disease and parasites. Microbial infection can also cause polyclonal activation of autoreactive lymphocytes.

Gene-environment interactions may be the key to proposed associations between type 1 diabetes and Coxsackievirus/enteroviruses or to the notion that infectious agent(s) may be causally related to the development of multiple sclerosis (MS), rheumatoid arthritis (RA), and numerous other autoimmune diseases. Disparate social environmental factors and medical status have been associated with the onset of autoimmune disorders such as type 1 diabetes mellitus. Infectious agents may induce the breakdown of immunological tolerance and the appearance of autoreactivity. There is evidence that the development of certain autoimmune diseases may be associated with a bacterial or viral infection that stimulates production of antibodies and immune cells called T cells, which are targeted against bacterial proteins that closely resemble "self" proteins, leading to cross reactivity with healthy tissues. The autoreactive T cells may play a useful role in promoting the immune response to infection. However, the specific relationship between infection and autoimmunity is still unclear. The exact mechanisms by which infection induces a particular autoimmune disease are unknown. In the case of streptococcus, it is believed than

an antigen of the microorganism resembles an antigen present in the heart and that a cross-reactive immune response to the infecting microorganism causes immune-mediated damage to the heart. The phenomenon is referred to as molecular mimicry between the infectious agent and self. The concept of molecular mimicry is a viable hypothesis in the investigation of the etiology, pathogenesis, treatment, and prevention of autoimmune disorders. In other instances, microorganisms or local inflammation may alter antigens of the host so that the immune system sees them as foreign. Infections may also increase immune cell expression of co-stimulatory molecules and thus promote autoimmune responses. The classic example is streptococcal infection leading to development of an autoimmune cardiomyopathy.

Microbial superantigens are known to cause toxic shock, and are reasonable candidates for a role in induction of autoimmunity. A classic example is the central role of the group A beta-hemolytic Streptococcus in the development of rheumatoid heart disease. Acute Guillain-Barré syndrome, an acute autoimmune demyelinating polyneuropathy, has been associated with a number of bacterial and viral infections, and reactive arthritis has been linked to a variety of intestinal infections (viral or Campylobacter jejuni infections). Indirect evidence has implicated a number of infections in type 1 diabetes and MS, and it has focused renewed attention on the possible role of Epstein-Barr virus (EBV) in SLE and RA. Thus, differences between the stimulation of male and female innate immune responses by pathogens must also be studied. (4,5).

Within the adaptive immune system, processes such as lymphoid and myeloid cell development, antigen processing and presentation, cytokine production, natural killer cell function, tolerance induction and the regulatory influences on these processes need further clarification in males versus females. The environment can also affect the immunoreactivity of the individual by shifting the balance of T cells within the individual between inflammatory, interferon (IFN)-g-producing Th1 cells and IL-4-and IL-5-producing Th2 cells. Directly or indirectly, bacterial and viral infections usually induce T-cell differentiation into Th1 cells. Infectious agents affect the ability of T cells to detect self antigens by cross-reaction (molecular mimicry). Many autoimmune diseases are much more common in women than in men. However, autoimmune diseases that develop in men often are more severe. The age at which the infection occurs may also influence the development of autoimmune disease (6,7).

The reason for this sex-related difference is not known, but it may reflect the involvement of hormones in regulation of the immune response. Interestingly, men with RA have significantly lowered testosterone concentrations. The interactions of estrogen or estrogenic compounds with autoimmune disease become increasingly important as more compounds with estrogen-like structures are observed in the environment (for example, dioxin) and as estrogenic compounds are utilized in medicine (hormone replacement therapy, oral contraceptives). Understanding the role of estrogens and other hormones in autoimmune disease is particularly important in light of the increasing number of people exposed through medical interventions or unintentionally to a wide range of synthetic chemicals that have estrogenic or anti-estrogenic activity. The serious need for further medical research examining the potential range of environmental factors and the role they may play in the development of autoimmune diseases. However, a strong association has been noted in observational studies between the use of hormone replacement therapy and the onset of SLE. The exposure of humans to environmental estrogens is believed to increase over the year through the consummation of meat and milk products of livestock that are fed with synthetic estrogens. In fact, prenatal diethylstilbesterol exposure has been linked to autoimmune disorders, although further confirmation is needed. Other opportunities for studying the effects of hormones on immune and autoimmune responses are during oral contraceptive (OC) use and estrogen replacement therapy. The use of OC pills and hormonal replacement therapy (HRT) was associated with a slightly increased risk of SLE development. We cannot protect ourselves from all potential risk factors, not least because there are still so many which have yet to be identified (8).

Lifestyle factors contribute to the development or progression of autoimmune disease. For example nutritional factors that

affect immune function and the interaction between dietary factors and other exposure are important areas of research. Antioxidants may play a role in immune function, particularly with respect to autoimmunity (9).

The literature is sparse or contradictory concerning the influence of occupational agents such as solvents or dietary factors such as coffee or meat, despite reports published in 2004 that related the consummation of red meat to the risk for RA (10,11).

The use of permanent hair dyes in women was associated with a borderline increase in the risk of developing SLE, with higher risk among those with a longer duration of dye use. Recent research suggest possible genetic risk factors for the development of myositis following silicone implants and vaccines.

Cigarette smoking was associated with an increased risk of developing RA. Cigarette smoking has been identified as a risk factor leading to the development of lupus nephritis with poor outcome. Smoking may be associated with a reduced risk of ulcerative colitis, an inflammatory bowel disease (12,13).

Food can also be a source of chemicals which have been implicated in the acquisition of autoimmune disease. There are some examples where the presence of a particular substance in the diet might possibly be related to an autoimmune disease. Toxins and chemicals have been linked to autoimmune diseases. Processing resulting in the loss of protective agents from the diet as well, may also be a contributing factor. Sometimes components of the diet may influence the development of disease, for example, in autoimmune diseases of the thyroid, dietary iodine may be an important initiating factor. Sometimes components of the diet may influence the development of disease; for example, in autoimmune diseases of the thyroid, dietary iodine, a critical component of thyroid hormone, is an important environmental risk factor in autoimmune thyroid disease. Abnormal immune responses may also be due to a deficiency of a specific substance (14-17). For example, selenium deficiency has been linked with autoimmune thyroiditis and cardiomyopathy; some people with these disorders improve when given selenium supplements. (18).

Psychological mechanisms are directly linked by hormonal and nervous system signals, influencing the need for insulin. Stress is important, whether it is environmental, psychological or physiological. It has previously been observed that stress from major life events may contribute to the onset of RA. It has been hypothesized that various autoimmune diseases such as diabetes mellitus type 1 and MS are exacerbated by psychological stress. Pregnancy is a stress, as is lactation. This fluctuation of disease activity during and after pregnancy has been explained by a hormonal environment during pregnancy that favors a Th2 response. In MS and RA, this environment may suppress the ongoing Th1 responses to central nervous system and joint antigens, whereas in SLE, a Th2 environment would enhance antibody production and possibly exacerbate disease progression. Interestingly, men with RA have significantly lowered testosterone concentrations (19).

Certain chemical agents and drugs can also be associated with the genesis of autoimmune conditions, or conditions which simulate autoimmune diseases. A number of drugs have been associated with the onset of autoimmune disease. We know there are certain drugs that can induce lupus-like syndrome in genetically-susceptible individuals that remits when the drug is discontinued. Other drug-induced autoimmune diseases have been described, including some of the hemolytic anemias, thrombocytopenias, and the leukopenias. Foreign substances may act as haptens and render autoantigens immunogenic. These include but are not limited to trimethoprim, nitrofurantoin, carprofen, phenylbutazone, phenobarbital, primidone, diethycarbamazine. Drugs can also alter the immune repertoire (20).

Another autoimmune disease, SLE, may be precipitated by exposure to sunlight. Ultraviolet (UV) light may damage cells and release new antigens. Some symptoms of some autoimmune diseases have been observed to worsen with exposure to ultraviolet (either UVA or UVB) radiation (UVR), most notably skin rashes in SLE. Neonatal SLE rash is the most common manifestation and usually presents within a few weeks of birth and is often induced by exposure to UV light. Together these results suggest a mechanism by which genetically predisposed individuals may develop autoantibodies as a result of UVR exposures. Ultraviolet radiation from sun exposure can exacerbate disease in patients with SLE. Other epidemiologic studies suggest that UV exposure may be protective in

MS and RA. Ultraviolet light can cause inflammation, induce cellular apoptosis, and cause tissue damage (21).

Relatively few studies have been conducted on the relationship between occupational exposure to chemicals and toxins and development of autoimmune disease. The possible role of exposure to various metals in autoimmune disease has been explored primarily through laboratory and animal studies. Metals are generally not thought to cause autoimmunity; in fact, they are usually inhibitory to immune cell proliferation and activation. However, a few metals can induce lymphocyte proliferation and subsequent autoimmunity. These include mercury, nickel, beryllium, gold and silver. Mercury, gold, and silver, for example, can induce lymphocyte proliferation and subsequent autoimmunity. Genetically-susceptible mice develop a lupus-like condition when dosed with mercury, silver, or gold. It is likely, however, that the autoimmune disorders that result from exposure to various metals occur through distinct mechanisms. Dental amalgam may be a risk factor in autoimmune diseases. Results imply that, in some patients with thyroiditis, mercury from dental amalgam can stimulate the production of antinuclear antibodies (ANA). Mercury induces activation and proliferation of T and B cell subsets with significant transient T cell-dependent polyclonal B cell activation (22).

Other environmental exposure have been studied, but associating such exposures with specific disorders is difficult. Exposure to occupational crystalline silica has been identified as a strong risk factor for developing autoimmune disease. Some epidemiologic information suggests an association between silica and both scleroderma and SLE in certain industrial settings. The experimental and epidemiologic literature relating to crystalline silica (quartz), asbestos exposure and autoimmune disease is quite extensive. Silica has a strong adjuvant effect on immune responses, resulting in increased proinflammatory cytokine production and immune cell activation. Studies of highly exposed individuals (such as miners, granite workers, and silicosis patients) have shown strong associations (a relative risk of 3.0 and higher, with some studies reporting more than a tenfold increased risk) with RA, scleroderma, SLE, and glomerulonephritis (23).

Epidemiologic studies suggest a possible link between solvents and a variety of autoimmune diseases, but such an association remains speculative. Over exposure to pesticides and toxins may also induce autoimmunity. Increased serum DDE (a metabolite of DDT) concentration was associated with increased total numbers of lymphocytes and decreased lymphocyte responsiveness to mitogen. In humans, some epidemiological studies have reported increased levels of autoantibodies following exposure to pesticides. These include hormone supplementation, pesticides, insecticides, fungicides, and foods and herbal products. Similarly investigations of exposure to pesticides and estrogenic compounds are areas of considerable research interest, but they require additional exploration. More recently, the prevalence of ANA in human sera was found to be associated with lifetime exposure to some pesticides, but not DDT and methoxychlor, suggesting that occupational exposures to pesticides may be related to the development of SLE (24,25).

Additional research has exploired possible relationships between autoimmune disease and exposures to organic compounds, principally the halogenated hydrocarbon trichloroethylene (TCE) and polychlorinated biphenyls (PCBs). TCE metabolites have been associated with SLE, systemic sclerosis, and other autoimmune disorders. Similarly, a few epidemiologic studies have examined occupational exposures to dioxins (26).

Finally, certain environmental factors are probably required to trigger the disease. If the environmental agent can be identified and the patient warned to avoid it, the autoimmune disease may never occur, even in the most highly predisposed individual (27).

CONCLUSION

Systemic autoimmunity is a multigenic trait that is significantly influenced by environmental factors. Medications may trigger autoimmunity.

A new area in need of further research is the interaction between genetic and

environmental factors. An interesting inverse relationship exists between infectious diseases and autoimmune diseases.

Better understanding of these risk factors will likely lead to a better understanding of mechanisms for the onset of autoimmune diseases.

Effective strategies for prevention will require identification of environmental triggers before the onset of clinical disease.

REFERENCES

1. **Tsonis IA, Avrameas S, Moutsopoulos HM** – Autoimmunity and pathophysiology. *Journal of Autoimmunity* 2007; 29: 203-205
2. **Rose NR** – Mechanisms of autoimmunity. *Semin Liver Dis* 2002; 22(4);387-394
3. **Eroglu GE, Kohler PF** – Familial systemic lupus erythematosus: The role of genetic and environmental factors. *Ann Rheum Dis* 2002; 61:29-31
4. **Fairweather D, Kaya Z, Shellam GR, et al** – From infection to autoimmunity. *J Autoimmun* 2001; 16: 175-186
5. **Guarneri F, Guarneri C, Benvenga S** – Helicobacter pylori and autoimmune pancreatitis: Role of carbonic anhydrase via molecular mimicry? *J Cell Mol Med* 2005; 9:741-744
6. **Kukreja A, Maclaren NK** – Current cases in which epitope mimicry is considered as a component cause of autoimmune disease: immune-mediated (type 1) diabetes. *Cell Mol Life Sci* 2000; 57(4):534-541
7. **Fairweather D, Afanasyeva M, Rose NR** – Cellular immunity: a role for cytokines: *In Handbook of systemic autoimmune diseases, Vol I. Doria A, Pauletto P, editors. Elsevier:* Amsterdam; 2004; p. 3-17
8. **Cooper GS, Dooley MA, Treadwell EL, et al** – Hormonal and reproductive risk factors for development of systemic lupus erythematosus: results of a population-based, case-control study. *Arthritis Rheum* 2002; 46(7):1830-1839
9. **Olsson AR, Skogh T, Wingren G** – Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann Rheum Dis* 2001; 60: 934-939
10. **Aho K, Heliovaara M** – Risk factors for rheumatoid arthritis *Ann Med* 2004; 36:242-251
11. **Heliovaara M, et al** – Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis *Ann Rheum Dis* 2000; 59:631-635
12. **Cooper GS, Dooley MA, Treadwell EL, et al** – Smoking and use of hair treatments in relation to risk of developing systemic lupus erythematosus. *J Rheumatol* 2001; 28(12):2653-2656
13. **Vestergaard P, Rejnmark L, Weeke J, et al** – Smoking as a risk factor for Graves' disease, toxic nodular goiter, and autoimmune hypothyroidism. *Thyroid* 2002; 12(1):69-75
14. **Weetman AP** – Autoimmune thyroid disease: propagation and progression. *Eur J Endocrinol* 2003; 148(1):1-9
15. **Roti E, Uberti ED** – Iodine excess and hyperthyroidism. *Thyroid* 2001; 11(5):493-500
16. **Papanastasiou L, et al** – The effect of iodine administration on the development of thyroid autoimmunity in patients with nontoxic goiter. *Thyroid* 2000; 10(6): 493-497
17. **Rose NR, Bonita R. Burek CL** – Iodine an environmental trigger of thyroiditis. *Autoimmun Rev* 2002; 1(1-2):97-103
18. **Gartner R et al** – Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab* 2002; 87(4):1687-1691
19. **Oya H, et al** – The differential effect of stress on natural killer T (NKT) and NK cell function. *Clin Exp Immunol* 2000; 121(2):384-390
20. **Aster RH** – Drug-induced immune cytopenias. *Toxicology* 2005; 209:149-153
21. **Ponsonby AL, McMichael A. van der Mei I** – Ultraviolet radiation and autoimmune disease: insights from epidemiological research. *Toxicology* 2002; 181-182:71-78
22. **Cooper GS, Miller FW, Germolec DR** - Occupational exposures and autoimmune diseases. *Int Immunopharm* 2002; 2:303-313
23. **Parks CG, Cooper GS, Nylander-French LA et al** - Occupational exposure to crystalline silica and risk of systemic lupus erythematosus. *Arthritis Rheum* 2002; 46:1840-1850
24. **Holsapple MP** – Autoimmunity by pesticides: a critical review of the state of the science. *Toxicol Lett* 2002; 127(1-3):101-109
25. **Vine MF et al** – Plasma 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) levels and immune response. *Am J Epidemiol* 2001; 153(1):53-63
26. **Gilbert KM, Griffin JM, Pumford NR** – Trichloroethylene activates CD4+ T cells: potential role in an autoimmune response. *Drug Metab Rev* 1999; 31(4) 901-916
27. **Shepshelovich D, Shoenfeld Y** – Prediction and prevention of autoimmune diseases: Additional aspects of the mosaic of autoimmunity. *Lupus* 2006; 15:183-190