

Etiologic Possibilities for the Development of Rheumatic Diseases Through Environmental Mechanisms

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Living beings and the environment that supports them have a mutual interdependence and therefore any event that occurs within an ecosystem affects all parts. The influence that the environment has on subjects that may develop an illness has been amply recognized. For some autoimmune diseases such as systemic lupus erythematosus (SLE), the possibility of its development under ultraviolet light and prolonged exposure to sunlight has been recognized. Microorganisms may activate other illnesses such as reactive arthritis. Substances such as alfalfa are also able to unleash disease activity. Laboratory workers who manipulate sera of patients with autoimmune rheumatic disorders develop antibodies to the sera that they are working with. It is thus that environmental sciences and focused research allow the development of a new approach to the study of possible pathogenic mechanisms in the appearance of certain rheumatic disorders. This article reviews the main existing evidence and proposes certain hypotheses derived from it.

Key words: Mechanisms. Environment. Rheumatic diseases.

Posibilidades etiológicas para el desarrollo de enfermedades reumáticas por mecanismos ambientales

Los seres vivos y el medio que los sostiene tienen una interdependencia obligada; cualquier evento ocurrido dentro de un ecosistema afecta a todas sus fracciones. El enfoque del proceso salud-enfermedad reconoce las

influencias del medio ambiente. Para enfermedades autoinmunitarias como el lupus eritematoso sistémico (LES) o generalizado se ha reconocido la posibilidad de que se produzca por luz ultravioleta y exposición al sol de manera prolongada. Los agentes microbianos pueden generar otras enfermedades como las artritis reactivas. Sustancias como la alfalfa son capaces de causar alguna enfermedad y los trabajadores de laboratorio que manipulan sueros de pacientes con enfermedades reumáticas autoinmunitarias se tornan positivos a los anticuerpos que están trabajando. Es así que las ciencias ambientales y el enfoque laboral permiten un nuevo abordaje para el estudio de los posibles mecanismos patogénicos en la aparición de algunas enfermedades reumáticas. Este artículo revisa las principales evidencias existentes y plantea algunas hipótesis generadas a partir de esa misma revisión.

Palabras clave: Mecanismos. Medio ambiente. Enfermedades reumáticas.

Introduction

An ecosystem is a group formed by a community of microorganisms that interact among themselves and with the environment they live in; any event that occurs within an ecosystem affects all of its components. Humans develop and are part of an ecosystem which is located within the biosphere, where they receive and modify different characteristics of physical space, which in turn leads to modifications in the short and medium term.¹ In this way, the health-disease process is the result of an existing dynamic interaction where there are reciprocal influences between microorganisms, the environment, and the hosts (humans, for the ends of this discussion). Equilibrium between the abovementioned factors allows for the existence of the most accepted definition among the various conceptions in practical medicine: a state of health, and a lack of equilibrium in this interaction will result in a disease state.² The health-

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disease process has been approached by several currents of thinking such as the positivist, which considered unique causal agents and was fortified by the Koch postulates,³ the psychosomatic theories,⁴ to which S. Freud contributed, and the most current approach which considers etiology as multifactorial.⁵ In this last one, the risk of environmental and work exposure is included as a factor for the development of certain illnesses.⁶⁻⁸ With an environmental perspective in mind and considering work exposure or the exposure to other causes, a review of the literature has been elaborated, related to the development of rheumatic diseases, pointing to the main evidence and generating some hypothesis about these interesting facts.

General Aspects

The study of the health-disease process, in the context of environmental and work exposure, attempts to characterize and quantify associations for the exposure to dangerous substances, toxins, infectious agents, food pollutants, common-use items, such as beauty and food products, and others risk factors such as the quality of water, noise and its effect on populations and urban conditions.^{6,8} Most acute and chronic diseases described as consolidated clinical entities have, among their possible etiologies, some environmental agent; the work environment can also play an important role. In addition, in rheumatic diseases there are possible environmental agents that act on a genetic predisposition on a given host (a patient, for all clinical purposes). Rheumatic disease constitute a group of more than 150 well-characterized diseases,⁹ universal in their distribution and, especially present in the most productive stages of life of the subjects, making their appearance something that affects not only the quality of life of the subjects, but also their work productivity and self-esteem, with an impact on social health systems by constituting the first cause of temporal and permanent work disability.^{10,11} For a country such as México, with recurring economical crisis and a varying health budget according to each administration, their importance is more than evident.

Specific Diseases, Environment, and Exposure to Infectious Agents

For diseases such as Systemic Lupus Erythematosus (SLE), there are reports of different environmental and work factors that can contribute to its development. Sunlight and ultraviolet radiation unfold DNA and, on occasion, are triggering factors for SLE and generally increase this and other diseases' activity. However, results from recent studies¹² contradict, albeit partially, these

facts. The study by Hasan et al,¹² with 1 year of follow-up on patients with SLE, did not show any increase in the exacerbations of SLE between a group of patients with usual sunlight exposure and no photo-protection, and another that employed adequate solar-blockage. Cold is related to the development of capillary vasospasm in Raynaud's phenomenon¹³; against many years of inertia in which there was little to offer patients with Raynaud's phenomenon, there is now evidence to support the use of sildenafil for its complications,^{14,15} and another novelty would be the relationship between Raynaud's phenomenon and infections.¹⁶ Specific working situations that expose the subjects to changes in temperature, sunlight and poor protection can contribute to the development of rheumatic disease. A recent, interesting study on the development of rheumatoid arthritis related to work exposure has been published by the group led by Stolt,¹⁷ which analyzes the relationship between the risk of developing rheumatoid arthritis and 2 specific factors: working with silica, found in rocks and dust, and smoking. Their study is done in cases and controls, adequately paired by their characteristics (except the exposure to silica and tobacco for controls), and groups are of similar size (267 patients and 267 controls). Exposure to silica or silica dust for prolonged periods of time showed an increase in the risk for rheumatoid arthritis of 2.2 and up to 3, as mean values, but the absolute range was 1.2-7.617, showing an overbearing elevation in risk if one considers that the normal risk is 1 and any of the relative risk values found (RR) is above double the normal risk. Several autoantibodies, such as antinuclear antibodies (ANA) and anti-universal antibodies, such as rheumatoid factor (RF) among others, have been demonstrated not only in immediate consanguine family members of patients with rheumatic disease, but also in spouses and work colleagues, allowing for the assumption of some mechanism, undetermined as of yet, for the development of these reactants. Although other auto-antibodies have also been found on laboratory workers manipulating serum samples from rheumatic patients.¹⁸⁻²⁰ The environmental relationship between the positivity for antinuclear antibodies, in those first studies, permitted the inference of a link to food products such as alfalfa and, later, with more specific substances such as concanavaline.²¹ Although those first reports did show a relationship of these substances to the development of SLE and other illnesses, in other situations there was only a simulation of the autoimmune diseases, such as in the report by Hodkivassilion et al,²² who described 3 patients who erroneously were diagnosed with SLE for years and were treated with glucocorticoids and immunosuppressants, showing a poor response to these drugs, until a diagnosis of hypersensitivity to gluten was done. In the 3 cases studied and in similar ones, it is possible for a deficiency in immunoglobulin A (IgA) to favor the production of anti-dsDNA. In a recent study

presented by Cainelli et al,²³ antinuclear antibodies are found to be common and do not necessarily predict the development of an autoimmune disease such as SLE. In that study a great prevalence of ANA is informed, ranging from 3.5% to 27% in healthy subjects (with no autoimmune disease) and the highest prevalence of ANA are related to repeated infections. Now, when talking specifically of documented infections and changes in the patterns of rheumatic disease, we will mention that a few studies and case reports recently published, which associate changes in different diseases with some infectious agent. The environmental factors in these reports seem to be microbial agents. For example, for seronegative spondyloarthropathies, Martínez et al,²⁴ find a relationship with gastrointestinal infections. The most frequently related infections are enteral (36%) and genito-urinary (21%). Antiphospholipid syndrome is associated, with varying frequencies, to infectious agents. A recent case-report presents it as secondary to an infection by *Klebsiella pneumoniae*.²⁵ Behçet's disease can also be caused by an infectious agent,²⁶ with pathology lesions not always having a sterile content and not being quite aseptic, though many organisms have been isolated from them. What is relevant and new is that the same antimicrobial treatment employed to treat agents potentially related to reactive arthritis, such as *Chlamydia*, can induce reactive arthritis.²⁷ One of the possible mechanisms for this effect is the induction of antibodies through the drugs used to fight *Chlamydia*. On the other hand, in bio-security studies and in work health forums, the role of pathologic residues has been discussed, as well as the ecotoxicology conditions and measures to minimize the biologic risks for an adequate work and environmental situation.²⁸

Diseases, Environment, and Other Exposures

Rheumatoid arthritis has a frequency between 1%-3% in the general population, with a predominance of the female gender and is mostly seen from the third to the sixth decades of life. Several factors have been implicated in its etiology, without identifying one, unique cause.⁵ The most plausible and consistent are genetic predisposition, the influence of hormonal changes that are acted upon by bacterial and viral agents, as well as affective disorders,³⁻⁵ which cause an altered immunity and the production of anomalous antibodies. A possible explanation for the fact that a given work environment can develop into a determined illness (rheumatic or other), among workers (a situation that would be similar to what happens at home and other sites of prolonged interaction), is the exchange of virus in a non-evident form. Virus would then lead to disease through molecular mimicry with cell receptors.^{6,7} Another possible mechanism is the immunosuppression that favors the expression of B cells and their production

of antibodies, and another is favoring the expression of latent autoimmune disease.

One study,²⁹ which analyzed 1424 patients regarding the seasonal variations of their diseases, with a mean follow-up of 24 years, showed that in addition to seasonal variations, with December and January being the months with worsening and July the month associated with improvement, socialization was one of the factors associated to worsening. A larger fraternization at work and social circles led to a greater possibility of relapse. Another study³⁰ found a high prevalence (3%-19%) of arthritis among the resident nurses in certain community centers. The study also mentions that research into this disease among health workers is seldom investigated.

Social interaction and the specific work group may possibly be associated to a role that has not been analyzed and discussed by the authors of that study,³⁰ as well as in literature in general, finding only a few reports. In these studies, the environment-work relationship is beginning to be established, though the discussion on their results in these and other, similar studies can still generate new hypothesis and lines of research.

Systemic progressive sclerosis (SPS), a rheumatic disease which is characterized by skin fibrosis, esophageal and lung alterations, and great contractures, can develop as a result of food poisoning, as happened in Spain, leading to a new approach of SPS and a new term: "human adjuvant disease."^{31,32} As for Raynaud's phenomenon that accompanies SPS, we have pointed out its relationship to cold, infections and abnormal reactivity of the blood vessels and endothelial lesions.¹³⁻¹⁵

It is recognized that health workers have an increased risk due to a larger exposure to biologic and chemical products, anesthetics, laboratory residue, radiation, and microbial agents.²⁷ This work and environmental exposure probably has a role in the genesis of rheumatic disease in predisposed subjects, though there is a subgroup of the same health personnel that, even while exposed, do not develop these diseases.

In a preliminary report,³³ our group did not find any conclusive evidence of rheumatic disease due to prolonged work exposure (mean, 5-7 years). One might ask what happens in order to develop the autoimmune disease and though, in first place, we consider that the lack of an appropriate genetic background limits the complete development of an autoimmune rheumatic disease, this review allows us to postulate some hypothesis to explain these interesting facts. Only well documented studies (cohorts, cases-controls, contrasted series) can provide conclusive information. Statistical methodology and clinical epidemiology are strong enough to allow us to know the magnitude of these numbers. Therefore we propose the following hypothesis:

1. It is possible that microbial agents have a more relevant function in the development of specific rheumatic diseases.

2. Treatments employed for infectious and rheumatic disease can lead to the development of an autoimmune disease.
3. The immune response can be altered in an opposed sense to the one expected by immunosuppressant or antibiotic treatment.
4. Work environments and socialization also play a part in the development of rheumatic disease, which has been underestimated, with insufficient reports in the scientific literature.
5. Seasonal variations in presentation, the exacerbation and improvement of rheumatic disease is something that has not been thoroughly studied, which would allow us to have adequate prognostic factors and modify autoimmune diseases.

In summary, there is evidence in diverse rheumatic disease of the possibility that they are caused by environmental and work factors. Microbial agents, viruses, and work-related risk factors have been implicated. The possibility of developing a rheumatic disease due to environmental and work-related factors is also present in health workers and some studies indicate that socialization can be a trigger for rheumatic and autoimmune disease. All in all, more studies with overwhelming conclusions through statistical tests and methodology are needed to establish valid inferences.

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