CHRONIC CO-INFECTIONS IN RHEUMATOID ARTHRITIS AND OTHER CHRONIC ILLNESSES

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Patients with Rheumatoid Arthritis (RA), Chronic Fatigue Syndrome/Myalgic Encepthalomyelitis (CFS/ME), Fibromyalgia Syndrome (FMS), and Gulf War Illnesses (GWI) often present with similar chronic signs and symptoms. One of the most common of these is sore and painful joints and loss of joint mobility. This is why we originally proposed that GWI is a CFS/ME or in some patients a RA- or FMS-like illness [1].

INFECTIONS CAUSE MORBIDITY IN MANY CHRONIC ILLNESS PATIENTS

Although the causes of chronic illnesses, including autoimmune illnesses, are for the most part unknown, the complex signs and symptoms that evolve in many, perhaps even a majority of patients, may be due, in part, to systemic chronic infections (bacteria, viruses, fungi). These can follow acute or chronic chemical or other insults (viral, environmental, trauma, etc.) that have the potential to modify the immune system and cause endocrine dysfunction [2]. Chronic illnesses probably evolve over time as a multi-step process that may require multiple toxic exposures, including infections that can be causative for illness in some patients, cofactors for illness (not cause the illness but important to morbidity), or they can be opportunistic if they can avoid immune surveillance and penetrate and hide in various tissues and organs, including cells of the Central and Peripheral Nervous Systems and synovial cells in the joints.

Autoimmune signs and symptoms can be caused when intracellular pathogens, such as mycoplasmas and other bacteria, escape from cells and are identified as "foreign" by the immune system [3]. Microorganisms like mycoplasmas can incorporate into their own structures pieces of host cell membranes that contain important host membrane antigens that can trigger autoimmune responses, and they can also 'mimic' host cell antigen structures. Thus patients with such infections may respond immunologically to microorganism antigens as well as their own membrane antigens, producing unusual autoimmune signs and symptoms. For example, when these infectious agents colonize synovial cells in the joints and are released from these cells, they can stimulate chronic inflammation and immune responses.

BACTERIAL AND VIRAL INFECTIONS IN CHRONIC ILLNESSES

Bacterial infections have been commonly found in RA, CFS/ME, FMS and GWI patients [2-5], and when certain infections are found they are thought to be important factors in the illness that require physicians' attention. These microorganisms, principally *Mycoplasmas* and other primitive bacteria (*Chlamydia, Brucella, Borrelia*, etc.) are now considered important emerging pathogens in various chronic diseases. In our recent studies on CFS/ME, FMS and RA patients, most patients had multiple bacterial infections [4,5]. These infections invade the vascular system and cause coagulation problems, and they can cause or increase the risk of coronary diseases, such as endocarditis and myocarditis. Most Lyme Disease patients (with *Borrelia burgdorferi* infections) show some RA signs and symptoms. Although few urban patients have *Brucella* infections, these are more commonly found in rural chronic illness patients. *Chlamydia pneumoniae* infections were found in approximately 7% of CFS/ME patients and one control subject out of 100 that also did not have other bacterial or viral infections [6].

Viruses also play an important role in various chronic illnesses. One of the most common viral infections found is Human Herpes Virus-6 or HHV-6 [7]. Although several studies have associated HHV-6 with CFS/ME [8,9], there are also reports that could not find a HHV-6 association with CFS/ME [10]. When we studied CFS/ME patients we found that approximately 31% had HHV-6 infections [6]. In control subjects without evidence of signs or symptoms we found HHV-6 infections in 9 of 100 subjects. None of these HHV-6-positive control subjects had other infections [6]. In addition to HHV-6, cytomegalovirus or CMV has been found in chronic illness patients [11].

MULTIPLE CO- NFECTIONS IN CHRONIC ILLNESSES

When we examined the incidence of active HHV-6 infections in mycoplasma-positive and –negative CFS/ME patients, we found that the incidence of HHV-6 in mycoplasma-positive patients was 30.7%, whereas in mycoplasma-negative patients HHV-6 infections were found in 30.2% of patients. There was also no preference for particular *Mycoplasma* species in HHV-6 co-infections [6]. In addition, we examined the incidence of *C. pneumoniae* infections in mycoplasma-positive and –negative patients and found that there was no co-infection preference among mycoplasma-positive or -negative patients, In mycoplasma-positive patients *C. pneumoniae* infections were found in 7.7% of patients, whereas in mycoplasma-negative patients *C. pneumoniae* infections were found in 7.3% of patients [6]. Although we expected to find chronic illness patients infected with different types of infectious microorganisms, an unexpected finding in our study was that *Mycoplasma* species, *Chlamydia pneumoniae* and HHV-6 infections were not clustered together in most patients. Although patients that had multiple infections had on the average more severe signs and symptoms, we did not find differences between the types of infections and signs and symptoms.

POSSIBLE SOURCE OF MICROORGANISMS FOUND IN CHRONIC ILLNESS PATIENTS

Most microorganisms like mycoplasmas are not considered as important human pathogens when they are found at superficial sites, such as the oral cavity or gut, but some species have the capacity to penetrate into the blood circulation and colonize various tissues, and these cell-penetrating microorganisms have been closely associated with various human diseases [3]. Similarly, infections such as HHV-6 also penetrate the blood vascular where they colonize blood vessel endothelial cells. Do such infectious agents actually cause chronic illnesses? Probably not on their own, but microorganisms like *Mycoplasma, Chlamydia* and other bacteria and some viruses, HHV-6 and CMV, appear to be important in causing chronic illness *progression* and patient morbidity, exacerbating the major signs and symptoms. How do patients contract the bacterial and viral infections? Many patients may already have these infections in dormant or latent forms, and their triggering of illness may be associated with a decline in the ability of the immune system to hold them in check. For example, many chronic illness patients report prior severe trauma or acute infections preceded their chronic illness. In these patients, infections may occur by a variety of routes, including airborne transmission, fluid exchange (such as blood transfusions), or in contaminated vaccines. Only rarely are vaccines contaminated, and most vaccinations would not be expected to cause illness, but in some commercial vaccines contamination (up to 6%) has been documented [12].

ANTIBIOTIC AND ANTIVIRAL TREATMENTS FOR CHRONIC ILLNESSES

When microorganism infections are identified in blood fractions of subsets of patients with chronic illnesses, these patients can be treated as medical not psychological or psychiatric patients, just like any other patients with blood bacterial infections. Long-term treatment is required for the types of bacterial infections found in RA, CFS/ME, FMS, GWI and other chronic illnesses [13]. Few patients recover after only a few cycles of therapy, possibly because of the intracellular locations of the infections and the slow-growing nature of most of these microorganisms. We now recommend that patients who have been diagnosed with blood infections receive continuous antibiotics for at least 6 months before using 6-week cycles of treatment [14] Although patients starting such therapy usually have Herxheimer reactions and feel initially worse due to die-off or release of toxic materials from damaged microorganisms, they eventually stabilize and then slowly begin to recover. Unfortunately, the treatment requires long-term therapy and recovery is usually very slow. Patients that have been sick for many years are unlikely to recover within a year of therapy. We are also examining oxygen therapy using hyperbaric oxygen treatment.

The clinical responses with antibiotics that are seen are not due to placebo effects, because administration of some antibiotics, such as penicillins, resulted in patients becoming more not less symptomatic. In addition, they are not due to immunosuppressive effects of some of the antibiotics, because other antibiotics that do not cause immune suppression are also effective but only if they suppress the chronic infections. Some patients recover to a certain point and then fail to continue to respond to the recommended antibiotics, suggesting that other problems, such as viral infections, environmental exposures and other toxic events also play an important role in these illnesses, and may even play a predominant role in some patients [13].

Since many patients also have viral (HHV-6, CMV, etc.) infections, these must also be treated. For severe infections, there are some antivirals that can help, but most patients do well on immune enhancement and nutritional supplements (see www.immed.org for further information).

FOR FURTHER INFORMATION

The Institute for Molecular Medicine studies bacterial and viral infections of the types that are associated with chronic diseases like RA, CFS/ME, FMS, GWI and other autoimmune diseases. The website for further information is: www.immed.org.

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