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Mycoplasmal Infections in Chronic Illnesses: Fibromyalgia and Chronic Fatigue Syndromes, Gulf War Illness, HIV-AIDS and Rheumatoid Arthritis

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ABSTRACT Invasive bacterial infections are associated with several acute and chronic illnesses, including: aerodigestive diseases such as Asthma, Pneumonia, Inflammatory Bowel Disease; rheumatoid diseases, such as Rheumatoid Arthritis (RA); immunosuppression diseases such as HIV-AIDS; Genitourinary Infections and chronic fatigue illnesses such as Chronic Fatigue Syndrome (CFS), Fibromyalgia Syndrome (FMS) and Gulf War Illnesses (GWI). It is now apparent that such infections could be (a) causative, (b) cofactors or (c) opportunistic agents in a variety of chronic illnesses. Using Forensic Polymerase Chain Reaction we have looked for the presence of one class of invasive infection (mycoplasmal infections) inside blood leukocyte samples from patients with CFS (Myalgic Encephalomyelitis), FMS, RA and GWI. There was a significant difference between symptomatic CFS, FMS, GWI and RA patients with positive mycoplasmal infections of any species (45-63%) and healthy positive controls (~9%) ($P<0.001$). This difference was even greater when specific species *(M. fermentans, M. hominis, M. penetrans, M. pneumoniae*) were detected. Except for GWI, most patients had multiple mycoplasmal infections (more than one species of mycoplasma). Patients with different diagnoses but overlapping signs and symptoms often have mycoplasmal infections, and such mycoplasma-positive patients generally respond to multiple cycles of particular antibiotics (doxycycline, minocycline, ciprofloxacin, azithromycin and clarithromycin). Multiple cycles of these antibiotics plus nutritional support appear to be necessary for successful treatment. In addition, immune enhancement and other supplements appear to help these patients regain their health. Other chronic infections may also be involved to various degrees with or without mycoplasmal infections in causing patient morbidity in various chronic illnesses.

Introduction--Chronic Illnesses

There is growing awareness that many chronic illnesses may have an infectious nature that is either responsible (causative) for the illness, a cofactor for the illness or appears as an opportunistic infection(s) that is responsible for aggravating patient morbidity.[1] There are several reasons for this notion, including the nonrandom or clustered appearance of an illness, often in immediate family members, the course of the illness and its response to therapies based on infectious agents. Since chronic illnesses are often complex, involving multiple, nonspecific, overlapping signs and symptoms, they are difficult to diagnose and even more difficult to treat. Most chronic illnesses do not have effective therapies, and patients rarely recover from their conditions,[2] causing in some areas of the world catastrophic economic problems.

Some chronic illnesses, such as Rheumatoid Arthritis (RA), are well established in their clinical diagnosis,[3] whereas others, such as Chronic Fatigue Syndrome (CFS, sometimes called Myalgic Encephalomyelitis), Fibromyalgia Syndrome (FMS) and Gulf War Syndrome or Gulf War Illnesses (GWI), have rather nonspecific but similar complex, multi-organ signs and symptoms that overlap or are almost identical.[1] In the case of CFS, FMS and GWI these include: chronic fatigue, headaches, muscle pain and soreness, nausea, gastrointestinal problems, joint pain and soreness, lymph node pain, cognitive problems, depression, breathing problems and other signs and symptoms.[4] The major difference between these illnesses appears to be in the severity of specific signs and symptoms. For example, FMS patients have as their major complaint muscle and overall pain, soreness and weakness, whereas CFS patients most often complain of chronic fatigue and joint pain, stiffness and soreness, but otherwise their complaints usually overlap. Often these patients have increased sensitivities to various environmental irritants and enhanced allergic responses. Although chronic fatigue illnesses have been known for several years, most patients with CFS, FMS, GWI and in some cases RA have had few treatment options. This may have been due to the imprecise nature of their diagnoses, which are based primarily on clinical observations rather than laboratory tests, and a lack of understanding about the underlying causes of these illnesses or the factors

responsible for patient morbidity.[1] These illnesses could have different initial causes or triggers but similar cofactors or similar opportunistic infections that cause significant morbidity.

Chronic Illnesses--Overlapping Signs and Symptoms

The multiple signs and symptoms of FMS, CFS and GWI are complex, nonspecific and completely overlapping (Figure 1), suggesting that these illnesses are related and not completely separate syndromes.[1,6] In this figure only differences in the signs and symptoms after the onset of illness are shown, and the data for FMS and CFS have been combined, because previous studies indicated that with the exception of muscle pain and tenderness, there was essentially no difference in patient signs.[4] Illness Survey Forms were analyzed to determine the most common signs and symptoms at the time when blood was drawn from patients. The intensity of patient signs and symptoms prior to and after onset of illness was recorded on a 10-point rank scale (0-10, extreme). The data were arranged by 38 different signs and symptoms and were considered positive if the value after onset of illness was two or more points higher than prior to the onset of illness. The data in Figure 1 indicate that patients diagnosed with CFS or FMS had complex signs and symptoms that were similar to those reported for GWI. In addition, the presence of rheumatoid signs and symptoms in each of these disorders indicates that there are also similarities to RA.[7] Moreover, it is not unusual to find immediate family members who display similar signs and symptoms. For example, there is evidence that GWI has slowly spread to immediate family members,[8] and it is likely that it has also spread to some degree in the workplace.[1] A preliminary survey of approximately 1,200 GWI families indicated that approximately 77% of spouses and a majority of children born after the war had signs and symptoms similar or identical to veterans with GWI.[8]

In the absence of laboratory tests to the contrary, chronic illnesses are often misdiagnosed as somatoform disorders caused by stress and other nonorganic factors.[9] Patients with CFS, FMS and GWI usually have cognitive problems, such as short term memory loss, difficulty concentrating and other problems, and physicians who find psychological or psychiatric problems in these patients often decide that these conditions are caused by somatoform disorders, not organic problems.[1] Stress is often mentioned as an important factor or the important factor in these disorders. Indeed, GWI patients are often diagnosed with Post Traumatic Stress Disorder (PTSD) in veterans' and military hospitals.[10] The evidence that has been offered as proof that stress or PTSD is the source of GWI sickness is the assumption that veterans must have suffered from stress by virtue of the stressful environment in which they found themselves during the Gulf War,[10] but the veterans themselves do not feel that stress-related diagnoses are an accurate portrayal of their illnesses. Most testimony to date refutes the notion that stress is the major factor in GWI,[11] suggesting that stress, albeit important, is not the cause of GWI.[12] But most physicians would agree that stress can exacerbate chronic illnesses and suppress immune systems, suggesting that stress plays a secondary not primary role in chronic illnesses, such as GWI, CFS and FMS.[1] However, in the absence of physical or laboratory tests that can identify possible origins of FMS, CFS or GWI, many physicians accept that stress is the cause of these chronic illnesses. It has been only recently that other causes were seriously considered, including chronic infections.[13]

Mycoplasmal Infections in CFS, FMS and GWI

We have been particularly interested in the association of certain chronic infectious agents with CFS, FMS and GWI, because these microorganisms can potentially cause most or essentially all of the signs and symptoms found in these patients.[1,14] One type of infection that elicited our attention was microorganisms of the class Molecutes, small bacterial mycoplasmas, lacking cell walls, that are capable of invading several types of human cells and are associated with a wide variety of human diseases.[14]

We have examined the presence of mycoplasmal blood infections in GWI, CFS and FMS patients. The clinical diagnosis of these disorders was obtained from referring physicians according to the patients' major signs and symptoms. Since the signs and symptoms of CFS and FMS patients completely overlapped, these patients were therefore considered together (CFS/FMS).[1] Blood was collected, shipped over night at 4°C and processed immediately for PCR after purification of DNA using a Chelex procedure.[1,7] Patients' blood was analyzed for the presence of mycoplasmal infections in blood leukocytes. Positive PCR results were confirmed if the PCR product was 717 base pairs in size using the genus-specific primers (or 850 base pairs for *M. fermentans* specific primers, etc.) along with a positive control of the same size in the same gel, and if a visible band obtained after hybridization with the internal probe.[15] The sensitivity and specificity of the PCR methods were determined by examining serial dilutions of purified DNA of *M. fermentans*, *M. pneumoniae, M. penetrans, M. hominis* and *M. genetalium*. Amounts as low as 10 fg of purified DNA were detectable for all species using the genus primers. The amplification with genus primers produced the expected fragment size in all tested species, which was confirmed by hybridization with an inner probe.[16]

Mycoplasma tests were performed on all patients as described previously [1,7,17] either from Chelex-purified DNA or DNA prepared from whole blood using a commercial kit. The targeted *Mycoplasma spp*. sequence was amplified from DNA extracted from the peripheral blood of 144/203 CFS or FMS patients (~70%). In 70 healthy subjects positive results for *Mycoplasma spp*. were obtained in 6 samples (<9%). The difference between patient and control groups was significant ($p<0.001$).[17] In addition, two of the 70 controls were positive for *M. fermentans*. The ratio between positive and negative patients was comparable in female and male patients. These results are quite similar to the results recently published by others.[18] Similarly, using Nucleoprotein Gene Tracking to analyze the blood leukocytes from GWI patients we found that 91/200 (45%) were positive for mycoplasmal infections.[19,20] In contrast, in nondeployed, healthy adults the incidence of mycoplasmal infections was 4/62 (~6%).[19,20]

Patients with FMS or CFS often have multiple mycoplasmal infections and probably other chronic infections as well. When we examined CFS/FMS patients for *M. fermentans*, *M. pneumoniae, M. penetrans, M. hominis* infections, multiple infections were found in over one-half of 93 patients (Figure 2). CFS/FMS patients had double (over 30%) or triple (over 20%) mycoplasmal infections, but only when one of the species was *M. fermentans* or *M. pneumoniae*.[17] Higher score values for increases in the severity of signs and symptoms were also found in patients with multiple infections. CFS/FMS patients infected with different mycoplasma species generally had a longer history of illness, suggesting that patients may have contracted additional infections with time.[17]

In the course of our studies we found that DNA preparation and blood storage was extremely important in preserving the test samples. Storage of blood frozen or at 0-4°C resulted in reproducible assay results, whereas storage at room temperature resulted in loss of PCR signal over time. Within 1-2 days at room temperature, most of the positive samples reverted to negative results.[1] Also, blood drawn in tubes (blue-top) containing citrate and kept at 0-4°C before the assay yielded better results than other anticoagulants, unless the samples were frozen in EDTA (purple-top) tubes.

Mycoplasmal Infections in Rheumatoid Diseases

The underlying causes of rheumatoid diseases are not known, but RA and other autoimmune diseases could be triggered or exacerbated by infectious agents. It has been known for some time that infectious diseases in some animal species result in remarkable clinical and pathological similarities to RA and other rheumatoid diseases. Aerobic and anaerobic intestinal bacteria, viruses and mycoplasmas have been proposed as important agents in RA.[21] Recently there has been increasing evidence that mycoplasmas may play a role in the initiation or progression of RA.[22] Mycoplasmas have been proposed to interact nonspecifically with B-lymphocytes, resulting in modulation of immunity, autoimmune reactions and promotion of rheumatoid diseases.[23] *M. pneumoniae, M. salivarium* and *U. urealyticum* have also been found in the joint tissues of patients with rheumatological diseases, suggesting their pathogenic involvement.[24]

When we examined RA patients' blood leukocytes for the presence of mycoplasmas, we found that approximately one-half were infected with various species of mycoplasmas.[7] The most common species found was *M. fermentans*, followed by *M. pneumoniae* and *M. hominis* and finally *M. penetrans*. Similar to what we found in CFS/FMS patients, there was a high percentage of multiple mycoplasmal infections in RA patients when one of the species was *M. fermentans*.[7]

Although the precise role of mycoplasmas in RA and other rheumatoid inflammatory diseases remains unknown, mycoplasmas could be important cofactors in the development of inflammatory responses and for progression of the disease. As an example of the possible role of mycoplasmas in rheumatological diseases, *M. arthritidis* infections in animals can trigger and exacerbate autoimmune arthritis.[25] This mycoplasma can also suppress T-cells and release substances that act on polymorphonuclear granulocytes, such as oxygen radicals, chemotactic factors and other substances.[26] Mycoplasmal infections can increase proinflammatory cytokines, such as Interleukin-1, -2 and -6,[27] suggesting that they are involved in the development and possibly progression of rheumatological diseases.

In addition to mycoplasmal infections, other microorganisms have been under investigation as cofactors or causative agents in rheumatological diseases. The discovery of EB virus[28] and cytomegalovirus[29] in the cells of the synovial lining in RA patients suggested their involvement in RA, possibly as a cofactor. There are a number of bacteria and viruses that are candidates in the induction of RA or its progression.[30] In support of bacterial involvement in RA, it has been known for some time that antibiotics like minocycline can alleviate the clinical signs and symptoms of RA.[31] Although this has been proposed to be due to their anti-inflammatory activities, these drugs are likely to be acting to suppress infections of sensitive microorganisms like mycoplasmas.

Mycoplasmal Infections in Immunosuppresive and Autoimmune Diseases

Mycoplasmas have been implicated in the progression of HIV-AIDS. It has been known for some time that some species of mycoplasmas are associated with certain terminal human diseases, such as an acute fatal illness found with certain *Mycoplasma fermentans* infections in non-AIDS patients.[32] Recently, mycoplasmal infections have attracted attention as a major source of morbidity in AIDS patients. For example, *M. fermentans* can cause renal and CNS complications in patients with AIDS,[33] and *M. penetrans* has also been found in the respiratory epithelial cells of AIDS patients.[34] Other species of mycoplasmas have also been found in AIDS patients where they have been associated with disease progression, such as *M. prium* and *M. hominis*.[32] Blanchard and Montagnier[35] have proposed that mycoplasmas are cofactors in HIV-AIDS, accelerating progression and accounting, at least in part, for increased susceptibility of AIDS patients to additional infections. In addition to immune suppression, some of this increased susceptibility may be the result of mycoplasma-induced host cell membrane damage from toxic oxygenated products released from intracellular mycoplasmas.[36] Also, mycoplasmas may regulate HIV-LTR-dependent gene expression,[37] suggesting that mycoplasmas may play an important regulatory role in HIV pathogenicity.

There is some preliminary evidence that mycoplasmal infections could be associated with autoimmune diseases. In some mycoplasma-positive GWI cases the signs and symptoms of Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS or Lew Gehrig's Disease), Lupus, Graves' Disease and other complex autoimmune diseases have been seen. Such usually rare autoimmune responses are consistent with certain chronic infections, such as mycoplasmal infections, that penetrate into nerve cells, synovial cells and other cell types. These autoimmune signs and symptoms could be caused when intracellular pathogens, such as mycoplasmas, escape from cellular compartments and incorporate into their own structures pieces of host cell membranes that contain important host membrane antigens that can trigger autoimmune responses. Alternatively, mycoplasma surface components ('superantigens') may directly stimulate autoimmune responses,[38] or their molecular mimicry of host antigens may explain, in part, their ability to stimulate autoimmunity.[39]

Mycoplasmal Infections in Other Clinical Conditions

Asthma, airway inflammation, chronic pneumonia and other respiratory diseases are known to be associated with mycoplasmal infections. For example, *M. pneumoniae* is a common cause of upper respiratory infections,[40] and severe Asthma is commonly associated with mycoplasmal infections.[41] Recent evidence has shown that certain mycoplasmas, such as *M. fermentans* (incognitus strain), are unusually invasive and often found within respiratory epithelial cells.[34]

Heart infections (myocarditis, endocarditis, pericarditis and others) are often due to chronic infections, such as Mycoplasma,[42, 43] Chlamydia[44] and possibly other infectious agents.

Other species of mycoplasmas are also associated with various illnesses: *M. hominis* infections were first found in patients with hypogammaglobulinemia, and *M. genitalium* was first isolated from the urogenital tracts of patients with nongonococcal urethritis.[45,46] Although mycoplasmas can exist in the oral cavity and gut as normal flora, when they penetrate into the blood and tissues, they may be able to cause or promote a variety of acute or chronic illnesses. These cell-penetrating species, such as *M. penetrans*, *M. fermentans* and *M. pirum* among others, can probably result in complex systemic signs and symptoms. Mycoplasmas are also very effective at evading the immune system, and synergism with other infectious agents may occur.[14] Similar types of chronic infections caused by *Chlamydia, Brucella, Coxiella* or *Boriella* may also be present either as single agents or as complex, multiple infections (see Figure 2) in many of the diseases discussed above.

Mycoplasmal Infections--Treatment Suggestions

Once mycoplasmal infections have been identified in the white blood cell fractions of subsets of CFS, FMS, GWI, RA and other patients, they can be successfully treated. Appropriate treatment with antibiotics should result in patient improvement and even recovery.[6,19,20] The recommended treatments for mycoplasmal blood infections require long-term antibiotic therapy, usually multiple 6-week cycles of doxycycline (200-300 mg/day),[47] ciprofloxacin (1,500 mg/day), azithromycin (500 mg/day) or clarithromycin (750-1,000 mg/day).[48] Multiple cycles are required, because few patients recover after only a few cycles, possibly because of the intracellular locations of mycoplasmas like *M. fermentans* and *M. penetrans*, the slow-growing nature of these microorganisms and their relative drug sensitivities. For example, of 87 GWI patients that tested positive for mycoplasmal infections, all patients relapsed after the first 6-week cycle of antibiotic therapy, but after up to 6 cycles of therapy 69/87 patients recovered and returned to active duty.[19,20] The clinical responses that were seen were not due to placebo effects, because administration of some antibiotics, such as penicillins, resulted in patients becoming more not less symptomatic, and they were not due to immunosuppressive effects that can occur with some of the

recommended antibiotics. Interestingly, CFS, FMS and GWI patients that slowly recover after several cycles of antibiotics are generally less environmentally sensitive, suggesting that their immune systems may be returning to pre-illness states. If such patients had illnesses that were caused by psychological or psychiatric problems or solely by chemical exposures, they should not respond to the recommended antibiotics and slowly recover. In addition, if such treatments were just reducing autoimmune responses, then patients should relapse after the treatments are discontinued.[1]

Patients with CFS, FMS, RA or GWI usually have nutritional and vitamin deficiencies that must be corrected.[48] These patients are often depleted in vitamins B, C and E and certain minerals. Unfortunately, patients with these chronic illnesses often have poor absorption. Therefore, high doses of some vitamins must be used, and others, such as vitamin B complex, must be given sublingual. Antibiotics that deplete normal gut bacteria can result in over-growth of less desirable flora, so *Lactobacillus acidophillus* supplementation is recommended. In addition, a number of natural remedies that boost the immune system are available and are potentially useful, especially during antibiotic therapy or after therapy has been completed.[48] One of us (R.N.) has been involved in the development of ancient African and Chinese natural immune enhancers and cleansers help to restore natural immunity and absorption. Although these products are known to help AIDS patients, their clinical effectiveness in GWI/CFS/FMS/RA patients has not been carefully evaluated. They appear to be useful during therapy to boost the immune system or after antibiotic therapy in a maintenance program to prevent relapses.[48]

Why aren't physicians routinely treating mycoplasmal and other chronic infections? In many cases they are treating these infections, but it has been only recently that such infections have been found in so many unexplained chronic illnesses. These infections cannot be successfully treated with the usual short courses of antibiotics due to their intracellular locations, slow proliferation rates and inherent insensitivity to most antibiotics. In addition, a fully functional immune system may be essential to overcoming these infections, and this is why vitamin and nutritional supplements are so important.

Conclusions

We have proposed that chronic infections are an appropriate explanation for the morbidity seen in a rather large subset of CFS, FMS, GWI and RA patients, and in a variety of other chronic illnesses. Not every patient will have this as a diagnostic explanation or have the same types of chronic infections, and additional research is necessary to clarify the role of such infections in chronic diseases.[1,7] Some patients may have chemical or radiological exposures or other environmental problems as an underlying reason for their chronic signs and symptoms. In these patients, chronic infections may be opportunistic. In others, somatoform disorders or illnesses caused by psychological or psychiatric problems may indeed be important. However, in these patients antibiotics, supplements and immune enhancers should have no lasting effect whatsoever, and they should not recover on such therapies. The identification of specific infectious agents in the blood of chronically ill patients may allow many patients with CFS, FMS, GWI or RA and other chronic diseases to obtain more specific diagnoses and effective treatments for their illnesses. Finally, patients with cardiopathies, AIDS, respiratory illnesses and urogenital infections are often infected with *Mycoplasma, Chlamydia, Brucella* or other chronic, invasive bacterial and parasitic infections, and these patients could benefit from appropriate antibiotic and neutraceutical therapies that alleviate morbidity.

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Figure Legends

Figure 1. Incidence of increase in severity of signs and symptoms in 203 patients with CFS/FMS compared to GWI after the onset of illness. Severity of signs and symptoms was assessed using a Patient Illness Survey Form that included 114 signs and symptoms. The intensity of signs and symptoms were scored by patients on a 10-point scale (0, none; 10, extreme) prior to and after onset of illness. Scores were determined in each category (3-9 questions) as the sum of differences between values prior to and after onset of illness divided by the number of questions in the category. Changes in socre values of 2 or more points were considered relevant.

Figure 2. Incidence of multiple mycoplasmal infections in 93 CFS/FMS patients. Patients were examined for *M. fermentans*, *M. pneumoniae, M. penetrans* or *M. hominis* blood infections by Forensic PCR.