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Infectious Causes of Chronic Fatigue Syndrome

Numerous studies have demonstrated a high incidence of chronic infections in chronic fatigue syndrome and fibromyalgia. These include viral infections of Epstein bar (EBV), cytomegalovirus (CMV), human herpes virus-6, (HHV-6), and bacterial infections such as mycoplasma, chlamydia pneumonia (CP) and Borrelia burgdorferi (Lyme disease). There is controversy regarding the presence of active infection in these conditions because physicians, including infectious disease specialists, do not understand that the standard way to diagnose acute infections, an elevation of IgG and IgM antibodies, is not a sensitive means of detecting chronic infections in these patients (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21). With an acute infection, the body will start producing IgM antibodies against that infection and then start producing IgG antibodies after a few weeks so there is an elevation of both IgG and IgM antibodies. Chronic reactivating infection, such as those mentioned above, do not stimulate IgM antibodies as they are not new infections but rather intracellular reactivating infections, so most doctors, again including infectious disease specialists, will tell patients who have elevated IgG antibodies that they had an old infection or previous exposure and that there is no evidence of or they do not have an active infection because that is what they learned in medical school. This standard way of detecting active infections has clearly been shown to be inaccurate and miss the overwhelming majority of patients with active infections (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21).

Polymerase chain reaction (PCR) testing is much more sensitive in a research setting than in the clinical setting because if the blood sits for more than a few hours, the infectious organism's DNA degrades and often goes undetected. In a clinical setting, it is a specific test (if it is positive you know you have an active infection), but suffers from low sensitivity (often negative despite an active chronic infection). Additionally limiting sensitivity is the fact these infections are not concentrated in the blood or serum but rather in the tissues, especially nerves, brain and the white blood cells. Physicians must have a high incidence of suspicion and look for elevated IgG or early antigen (EA) antibodies along with other signs of chronic infections including low natural killer cell activity, high RNAse-L activity, high ACE (> 35), coagulation activation, high tumor necrosis factor (TNF), low melanocyte stimulation hormone (MSH), high interleukin-6 (IL-6), low WBC, increased 1-25 vitamin D/1-25 vitamin D ratio and elevated or decreased total IgA, IgM or IgG levels. Chronic infections are almost always present in those whose symptoms started very acutely, especially with an infection, those who's symptoms were ever associated with swollen lymph nodes or sore throat and those with significant cognitive dysfunction or flu-like symptoms. It must be remembered that in order to have the highest probability of successful treatment, a multi-system approach should be initiated (see new standard of treatment).

Herpes Viruses (Epstein Bar, Cytomegalovirus and HHV-6)

EBV, CMV and HHV-6 cause or contribute to the symptoms of a large percentage of CFS and FM patients. As stated previously, the presence of active infections correlate with an elevated IgG antibody, despite the lack of IgM antibodies (10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21). These infections are generally not acute but rather intracellular reactivation of an old infection, an elevation of IgM antibodies is typically not seen with active infections of EBV, CMV, HHV-6, (10-21). Due to the immune dysfunction seen in CFS, in addition to a lack of IgM antibody formation, there may also be a lack of IgG antibodies present despite the presence of an active infection in CFS patients (22,17,23). This has also been demonstrated to be the case with AIDS patients, as demonstrated in the study published in the New England Journal of Medicine entitled Absence of detectable IgM antibodies during cytomegalovirus disease in patients with AIDS (22). It has also been shown that the presence of antithyroid antibodies in CFS patients has a significant correlation with active HHV-6 infection (24).

A study published in Acta Pathologica, Microbiologica et Immunologica Scandinavica entitled Multiple co-infections (Mycoplasma, Chlamydia, human herpes virus-6) in blood of Chronic Fatigue Syndrome Patients: Association with Signs and Symptoms found 52% of CFS patients had active mycoplamsa infection, 30.5% had active HHV-6 infection, and 7.5% had Chlamydia pneumonia infections vs. only 6%, 9% and 1% of controls, respectively. They conclude, "The results indicate that a large subset of CFS patients show evidence of bacterial and/or viral infection(s), and these infections may contribute to the severity of signs and symptoms found in these patients (25)."

A study entitled A Chronic Illness Characterized by Fatigue, Neurological and Immunological Disorders, and Active Human Herpes virus Type 6 Infection published in the Annals of Internal Medicine found 70% of patients with CFS had active HHV-6 infection through the use of primary cell cultures and confirmation using assays of monoclonal antibodies specific for HHV-6 proteins and by PCR. Again, an elevation of IgM antibodies is generally not seen (26).

As summarized below, when specialized testing is used to detect active vs. past infection of HHV-6, the overwhelming number of studies demonstrate a high incidence of active herpes virus infections. These reactivation infections often do not illicit an IgG and especially not an IgM response, so standard serologic testing is specific but not sensitive for such infections. As mentioned before, PCR testing in a research setting is much more reliable, sensitive and useful than in the clinical setting when the blood is usually not processed for 12-48 hours.

Wagner et al, found that 61% of CFS patients with elevated IgG antibodies and 81% with immune deficiency, had confirmed active HHV-6 infection vs only 19% of those patients who did not (15). This is regardless of whether or not IgM antibodies were elevated.

Below in ***figure 1*** is a summary of studies that have looked at the incidence of active HHV-6 infection in CFS/FM patients vs. controls, with 83% of the studies demonstrating a large portion of CFS/FM patients have and active HHV-6 infection.

A study by Lerner found that treating patients with 6 months of Valtrex resulted in a significant improvement in symptoms (46). In a separate study, Lerner et al found that in CFS patients with elevated IgG antibody against CMV, treatment with the intravenous antiviral ganciclovir, which has a more broad spectrum coverage than Valtrex and anti-CMV activity, resulted in 72% of patients returning to their premorbid health states (total resolution of symptoms)(47). A randomized, placebo controlled study published in Clinical Infectious Diseases, demonstrated that in CFS patients with an elevated IgG antibodies against CMV, a combination of oral Valtrex and intravenous ganciclovir resulted in dramatic improvements with almost complete resolution of symptoms (27).

Montoya et al at Stanford University treated chronic fatigue syndrome patients with 6 months of valganciclovir (Valcyte) if they had elevated IgG tests for HHV-6 and EBV and had at least 4 of the following symptoms: impaired cognitive functioning, slowed processing speed, sleep disturbance, short-term memory deficit, fatigue and symptoms consistent with depression. Nine of the twelve treated patients (75%) "experienced near resolution of their symptoms, allowing them all to return to the workforce or full time activities." In the nine patients with a symptomatic response to treatment, EBV VCA IgG and HHV-6 IgG titers significantly dropped. (21)

We have been using Valcyte in our center for the treatment of chronic fatigue syndrome for over 4 years and have found it to be effective, especially in patients with the flowing: flu-like symptoms or symptoms started with a flu-like illness; elevated IgG or EA against Epstein bar virus, cytomegalovirus and/or HHV-6; low natural killer cell activity; high RNAse-L activity; high ACE (> 35); coagulation activation; high tumor necrosis factor (TNF); low melanocyte stimulation hormone (MSH); high interleukin-6 (IL-6); low WBC; increased 1-25 vitamin D/25 vitamin D ratio and/or elevated or decreased total IgA, IgM or IgG levels.

This study contributes more confirmatory evidence that IgM antibodies are not typically elevated in chronic reactivating infections so most patients are incorrectly told they do not have an active infection based on such testing. This study also demonstrated the lack of sensitivity of standard PCR testing.

There is also evidence that CFS may be due to the above discussed infections with "stealth adaptation" (28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38). This is primarily due to the deletion of the genes coding for the major antigenic components normally targeted by the cellular immune system. "Stealth viral adaptation" results in replication that is less efficient than conventional viruses, but has a distinct advantage over conventional viruses in not having to confront the body's cellular immune defense mechanisms. They can, therefore, evade the immune system and create persistent ongoing infections in spite of an individual's intact immune system (28-38).

A number of studies have also shown dramatic improvement in patients with interferon treatments, especially those with low natural killer cell function, (39,40,41). While ganciclovir and interferon may be effective, their toxicity precludes their use and there are less toxic means of eradicating these infections.

figure 1

Assays that differentiated between active and latent virus: 83% positive						
Author	Year	CFS+	Controls+	Method used	Result	Size of study
Nicolson	2003	31%	9%	PCR on serum or plasma	Positive	200 CFS, 100 controls
Koelle	2002	0%	0%	PCR on serum or plasma	Negative	22 CFS, 22 controls (twins)
Ablashi	2000	54%	8%	IgM Early Antigen antibodies	Positive	35 CFS, 25 controls
Ablashi	2000	+++	+	Lymphocyte response	Positive	10 CFS, 6 controls
Ablashi	2000	57%	16%	IgM Early antigen antibodies	Positive	35 CFS, 25 controls
Reeves	2000	0%	0%	Viral isolation	Negative	26 CFS, 52 controls
Zorzenon	1996	73%	0%	CPE/IFA positive	Positive	52 CFS, 51 controls
Wagner	1996	39%	-	Primary culture/isolation	Positive	107 CFS
Patnaik	1995	77%	12%	IgM Early antigen antibodies	Positive	119 CFS, 165 controls
Secchiero	1995	3%	0%	PCR on Serum or plasma	Positive*	39 patients, 37 controls
Buchwald	1992	70%	20%	Primary cell culture	Positive	113 CFS, 40 controls
Josephs	1991	43%	0%	Short term culture	Positive	7 CFS, 2 controls

Mycoplasma

Numerous studies have demonstrated a high incidence of active Mycoplasma infection in CFS and FM (1,44,45,46,47,48, 49,50,51,52). Nijs et al published a study in the Journal Immunology and Medical Microbiology entitled High Prevalence of Mycoplasma infections among European Chronic Fatigue Syndrome Patients demonstrated that 68% of CFS patients had an active mycoplasma infection as diagnosed with specialized polymerase chain reaction (PCR) testing where the red and white cells were immediately lysed and centrifuged to concentrate and collect the DNA (1). Being predominantly intracellular, there is typically not a significant serologic antibody response or just an isolated IgG response with this number of other intracellular infections so IgG and especially IgM antibodies are almost always in the normal range despite the presence of an active infection (1, 2, 3, 4, 5, 6, 7, 8, 9).

This study and others discussed below demonstrated that IGM antibodies are not helpful in the diagnosis of an active infection in CFS and FM. Nijs et al stated, "Mycoplasma detection based on antibody testing is characterized by a very high specificity [if IGG and IGM positive], but extremely low sensitivity [active infection almost always present without elevated IgG and IgM antibodies] renders it useless as a diagnostic tool (1)." A study by Dylewski et al in the New England Journal of Medicine demonstrates that in immune compromised patients, such as this patient, active infections correlate with elevations in IgG antibodies without elevations of IgM antibody and that a lack of elevation of IgM is not useful in these patients as a way to rule-out active infection. A high clinical suspicion must be maintained and implementation of anti-infective treatment should be based on elevated IgG levels (9).

A study entitled Diagnosis and Treatment of Chronic Mycoplasmal Infections in Fibromyalgia and Chronic Fatigue Syndrome: Relationship to Gulf War Illness published in Biomedical Therapy investigated the presence of active mycoplasmal infection by forensic PCR in patients with CFS and/or FM vs. controls. They found that 63% of CFS/FM patients had active mycoplasmal species infection compared to 9% of normals and more specifically the incidence of active Mycoplasma fermentans infection was 50% in CFS/FM patients vs. 0% of controls (2).

A study published in the International Journal of Medicine Biology Environment tested the blood of 565 CFS and/or FM patients vs. 71 healthy controls. They found 53.1% of patients were positive for mycoplasmal infection vs. only 7 out of 71 controls and 24.6% of patients had an M. fermentans infection vs. 2.8% of normals (42).

In a study published in the International Journal of Occupational Medicine, Immunology and Toxicology found that through specialized testing over half of Gulf War Syndrome/CFS patients had active mycoplasma infections that would not have been detected by standard serological IgG and IgM testing and that 78% of the patients completely recovered with appropriate treatment. Additionally, all of recovered patients that were subsequently retested no longer had evidence of infection (7).

A study and review published in the Antimicrobics and Infectious Disease Newsletter discussed the high incidence of mycoplasma infections in CFS. They discuss the fact that the culturing procedures and serological testing are insensitive for detecting intracellular infections due to the fact that there is usually a lack of hormonal response with these infections resulting in "normal" antibody titers or an isolated elevation of IgG antibodies with a lack of IgM antibodies (8). Sophisticated PCR testing found multiple species of mycoplasma in the majority of CFS patients. They found of the 87 gulf war illness-chronic fatigue syndrome patients treated with antibiotics, most relapsed after the first 6 week trial and most felt worse, but after up to 6 cycles of 6 weeks of therapy approximately 80% of these patients recovered and were able to return to their normal functional capacity. This was not a placebo controlled trial, but they discuss the fact that it is unlikely a placebo effect that most patients felt worse during treatment. They conclude stating that in order to be successful in the treatment of gulf war illness-chronic fatigue syndrome, a comprehensive treatment approach must be used that addresses the numerous physiological abnormalities, including chronic infections (8).

A study by Nasralla et al published in the European Journal of Clinical Microbiology & Infectious Disease entitled Multiple Mycoplasmal Infections Detected in Blood of Chronic Fatigue Syndrome and Fibromyalgia Syndrome Patients investigated the presence of different mycoplasmal species in blood samples from mycoplasma positive patients with chronic fatigue syndrome and/or Fibromyalgia. They found that the majority of patients had multiple species of mycoplasmal infections, with 59% of patients having active M. Pneumonia infections, 48% having active M fermentans infection, 31% having an active M. hominis and 20% having M pentrans (43).

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