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Chronic Intestinal Candidiasis as a Possible Etiological Factor in the Chronic Fatigue Syndrome

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Abstract — The chronic candidiasis syndrome, also known as the *Candida*-related complex, putatively caused by the overgrowth of *Candida albicans* in the gastrointestinal tract and secondarily in the genital organs, is briefly described. Patients with this disorder have many of the same symptoms as those with the chronic fatigue syndrome, except for the recurrent flu-like symptoms of the latter disorder. The positive response of a large number of patients with the chronic fatigue syndrome (CFS) to an oral antifungal agent and a diet for intestinal candidiasis has been described by another clinician. There is evidence that *Candida albicans* infection of the mucous membranes depresses T cell and natural killer (NK) cell function. Similar abnormalities of immune function are found in the CFS. The function of cytotoxic T cells, T helper cells, and NK cells is important in preventing reactivation of infections from Epstein–Barr virus, cytomegalovirus, and other herpesviruses. Reactivation of one or more of these viruses could lead to the expression of the flu-like symptoms in the CFS. Yet the immune dysfunction found in this disorder has been considered the primary underlying causal factor. It is proposed that chronic intestinal candidiasis may be an agent which leads to immune depression in many CFS patients and therefore that it could be a causal factor in CFS.

Introduction

The chronic candidiasis syndrome (CCS), also known as the chronic candidiasis sensitivity syndrome (CCSS) or the *Candida*-related complex (CRC) is a polysymptomatic disorder involving multiple bodily systems, putatively caused by mucous membrane overgrowth of *Candida albicans*, most frequently in the gastrointestinal tract and also in the genital tract. Several of the symptoms in distant body areas have been ascribed to immunologic or allergic reactions. Many of the symptoms or signs in the complex have individually been associated with gastrointestinal candidiasis in past and recent medical literature. The disorder primarily affects women who often have a history of and/or ongoing recurrent vaginal candidiasis. Other frequent genital symptoms include premenstrual symptoms, painful menstruation, excessive bleeding, infertility, ovarian failure, and sexual function difficulties. Gastrointestinal complaints are among the most frequent, and include symptoms of irritable bowel syndrome such as chronic recurring diarrhea and/or constipation and cramping abdominal pain, as well as gas and bloating, and nausea. Central nervous system symptoms are also common and include fatigue (often severe and incapacitating), depression (either premen-

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strual or on-going), headaches (often severe and recurring), anxiety symptoms and panic attacks, and reduced cognitive efficiency with reduced ability to concentrate and to remember. Other common systemic manifestations include musculoskeletal and joint pains, urinary burning, frequency, and dysuria, transient or long-standing neurological dysfunctions (occasionally mimicking multiple sclerosis), skin diseases such as urticaria or psoriasis in addition to local fungal infections of the skin, various problems in the oral, nasal, and pharyngeal passages from both local *Candida* infection of the mucous membranes and from the increased inhalant allergies often found in the syndrome, especially to volatile chemicals and to molds, food intolerances (frequently yeast-containing), and cravings for certain foods, especially those high in simple carbohydrates.

Predisposing factors include prolonged or repeated exposure to broad spectrum antibiotics, immunosuppressant or corticosteroid medications, and multiple pregnancies. Diagnosis is made primarily from the typical history and from a 1–2 month treatment trial which consists of a special diet of avoiding simple carbohydrates, reducing total carbohydrate intake, and avoiding yeast containing foods (for some this is not necessary), of using oral antifungal agents such as nystatin, and of avoiding the predisposing factors, if possible.

A previous paper (1) relating somatization disorder to this syndrome gives a more extensive discussion of the syndrome itself and of its validity. A recent review (2) provides an even more thorough consideration of the syndrome and its validity, especially from the standpoint of allergy.

The chronic fatigue syndrome (CFS) also known as the chronic fatigue and immune dysfunction syndrome (CFIDS) has only recently been investigated. Severe incapacitating fatigue, often made worse by exercise or exertion which is persistent or relapsing, along with a flu-like illness resembling a low-grade viral infection are the hallmarks of the disorder. The characteristics of the flu-like syndrome are a relapsing low-grade fever, sore throat with non-exudative pharyngitis on exam, and cervical lymphadenopathy which is often tender. Other symptoms include generalized muscle weakness and myalgia, inco-ordination, arthralgias, headaches, cognitive difficulties including difficulties in concentrating, remembering, and thinking, and confusion, and emotional disturbances including depression, anxiety, and irritability. In many cases, patients experience the onset of their symptoms over a brief period of time after a flu-like illness. Early reports of this syndrome found elevated antibody titers against early antigen and viral capsid antigen of the Epstein–Barr virus (EBV) suggesting that a low-grade relapsing infection from this virus was the cause of the disorder (3, 4). Evidence has been found which has brought into question EBV as the primary etiologic agent of CFS (5), and most now believe that EBV is not causal for the disorder, although one investigator has continued to support EBV as a major factor in some who have the illness (6).

Many investigators believe there is probably some underlying factor such as an infectious or environmental agent whose presence is necessary for the illness to occur, the so-called 'Agent X'. This agent may cause an immunologic dysfunction (perhaps in the presence of a genetic predisposition) which allows viral infections to trigger CFS, or the immune dysfunction may allow a reactivation of previously latent or dormant viruses, especially those of the herpes group, and this viral reactivation, along with other secondary immune responses, leads to the syndrome (7).

The recent report of a marked positive response of a large number of patients with chronic fatigue syndrome to an oral antifungal agent has suggested a possible etiologic role for chronic intestinal candidiasis in the chronic fatigue syndrome (8). Since chronic candidiasis results in many disturbances in immune function as outlined in a previous article (1), the possibility that intestinal candidiasis may be a predisposing factor for the immunological dysfunction allowing the chronic fatigue syndrome to appear and progress, at least in some patients with the syndrome, becomes evident. The purpose of this communication is to explore how chronic candidiasis might lead to the chronic fatigue syndrome and, more specifically, how chronic *Candida* mucous membrane infection might lead to depression of T cell function, allowing reactivation of latent viruses and the appearance of the symptoms of the chronic fatigue syndrome.

The recent positive response of CFS to oral antifungal therapy

Dr Carol Jessop reported her findings in 1100 patents with chronic fatigue syndrome at the Chronic Fatigue Syndrome Conference, April, 1989 (8). 84% of the patients had a favorable response to oral ketoconazol along with a special diet forbidding sugar, alcohol, fruit, and fruit juice, with a major reduction of their chronic fatigue symptoms after 3–12 months of treatment. The more objective criterion of disability status before and after treatment provides a striking contrast. In September of 1987, 685 of the 1100 patients were on disability; in April of 1989 only 12 of the 1100 were on disability.

Many of these patients had predisposing factors or symptoms suggesting the presence of chronic candidiasis. 80% of the patients had recurrent antibiotic treatment as a child, adolescent, or adult. 95% had serious sugar addictions or alcohol abuse prior to the onset of their chronic fatigue syndrome, often several years before. Premenstrual syndrome, irritable bowel syndrome, vaginal yeast infections, and headaches were very common in these patients. 80% had stopped alcohol because of the negative reaction (in many cases resembling an allergic response) they developed after taking the substance.

Others have also observed symptoms classically associated with the chronic candidiasis syndrome to be frequently present in chronic fatigue syndrome patients, including irritable bowel symptoms, severe premenstrual symptoms (70% according to one authority), and allergic manifestations including increased and severe nasal allergies and rhinitis (9). Many of the symptoms which are classical for each disorder are common to both, including the fatigue, the headaches, the myalgias, the arthralgias, the emotional disturbances (depression, anxiety, panic disorder, and irritability), and the cognitive dysfunction with difficulties in concentrating, thinking, and remembering. Whereas there is an overlap of many of the common symptoms of each disorder with the symptoms of the other disorder, the relapsing flu-like symptoms which are classical in CFS have not been mentioned as commonly present in the *Candida*-related complex or chronic candidiasis syndrome. Perhaps a viral reactivation is not a prominent or necessary component of the latter syndrome, and the intestinal candidiasis is sufficient to cause most of the other symptoms of the syndrome.

Immunological findings

The immunological findings in chronic candidiasis and CFS have striking similarities and could suggest an interrelationship between the two disorders. The immunological mechanisms for the precipitation of viral reactivation provide a link in explaining how the immunological depression from *Candida* infection might be the underlying cause of CFS in some patients.

Findings in chronic candidiasis

Suppression of the T cell response in intestinal candidiasis was observed by the clinician who first described the chronic candidiasis syndrome (10) and was proposed as the explanation for the self-perpetuating and chronic course of this illness. More extensive immunologic investigation has been done in patients with chronic recurrent vaginal candidiasis, a problem which is present in a high frequency in patients with the chronic candidiasis syndrome. Macrophages of recurrent vaginal candidiasis patients produce PGE_2 (and suppress the production of IL-1) in response to *Candida* antigen, and the PGE_2 stimulates T suppressor function, which in turn inhibits the production of Interleukin-2 (IL-2) by T helper cells. The macrophages from these patients will suppress both their own lymphocyte proliferation as well as lymphocyte proliferation in controls in response to *Candida* stimulation (11, 12).

The finding of increased IgE, both in serum and in vaginal washings of chronic vaginal candidiasis (CVC) patients suggests another way T cells might be suppressed in these patients (13). Since the IgE was directed mostly toward *Candida*, a hypersensitivity toward *Candida* and increased release of histamine in response to *Candida* was likely. Histamine release, in turn, leads to release of histamine-induced suppressor factor (HSF) by H_2 receptor-bearing T suppressor lymphocytes. HSF stimulates the macrophage to produce PGE_2 which raises T suppressor cell function which in turn inhibits T cell proliferation by inhibiting the production of IL-2 as noted before (14, 15). Because allergy to *Candida* as well as sensitivity to other environmental agents plays such a major role in the chronic candidiasis syndrome, this mechanism may be a significant factor in the immune suppression induced by chronic *Candida* overgrowth.

An immune mechanism which may have relevance to the promotion of viral reactivation has been suggested by in vitro experimental data and has similarities to the mechanism discussed above. A non-specific inhibitor substance is produced when human T cells are cultured with *C. albicans*-purified polysaccharide (MPPS). This non-specific suppressor substance was produced by T suppressor cells and blocked the production of interleukin-1 (IL-1) as well as IL-2. The function of cytotoxic cells as well as that of natural killer (NK) cells was reduced, probably secondary to the reduced production of IL-2 (16). The function of both of these cell types will be seen later to be of great importance in the defense against the reactivation of EBV and other herpesvirus infections. It is interesting that the cellular system used to demonstrate suppression of cytotoxic activity in this investigation was the response against EBV-transformed B cells which highlights the relevance of this mechanism to herpesvirus group reactivation. The non-specific suppressor substance also inhibited the expression of IL-2 receptors, as well as the production of gamma interferon which could well have been from its reduced production by NK cells and T cells from

the decreased stimulation by IL-2 (16). Gamma interferon also has important effects for inhibiting viral attack on uninfected cells and will be discussed further in relationship to EBV. The non-cellular suppressor factor may be related to the serum factor in CVC patients which inhibits proliferative lymphocyte response to *Candida* antigen (17).

It is important to emphasize that, whereas all of the above suppressor mechanisms are specific with respect to *Candida* stimulation, they are non-specific with respect to their effects on T cell immune function. Since the chronic candidiasis syndrome involves a more long-standing and widespread antigenic stimulation, some degree of general suppression of lymphokine production, along with a consequent reduction of T cell and NK cell function, is to be expected. This concept will become important when considering possible secondary effects of chronic intestinal candidiasis.

Another important effect of intestinal *Candida* is the suppression of delayed hypersensitivity responses as measured by skin tests. A large majority of patients with chronic mucocutaneous candidiasis have anergic responses to skin tests (18), and many of these patients maintain regression of the disorder and of the accompanying immune disturbances after treatment with oral antifungal agents (19). That suppression of delayed hypersensitivity reactions could commonly be caused by intestinal *Candida* overgrowth is supported by studies in which delayed type hypersensitivity (DTH) skin test reactions were reduced in animals after the oral administration of killed *Candida* organisms (20), or after the injection of mannan, a *Candida* cell wall component (21), and this suppression is probably induced by macrophages (22), which again may be conveyed by the production of PGE_2 in conjunction with antigen presentation to suppressor cells.

There are studies which suggest that the afferent mechanism inducing the macrophages to initiate the antigen non-specific suppressive response may be a generalized release of migration inhibitory factor (MIF) by the DTH effector cells subsequent to the widespread exposure of these cells to antigen (23, 24). In the localized DTH response, the suppressive response by macrophages would serve to signal the DTH effector cells of their arrival and that no further release of MIF was necessary.

Since the DTH effector cells (T_D) responding to *Candida* antigen are probably T helper 1 (T_H1) cells which produce IL-2 and gamma interferon (whereas T helper 2 (T_H2) cells interact exclusively with B cells and produce IL-4) (25), the suppression of this response could induce a more generalized immune suppressive response because of the consequent suppression of IL-2 and gamma interferon production. (On the other hand, some DTH responses, especially to viruses, can be mediated by cytotoxic (T8) T_D cells (26, 27)).

Taking the delayed hypersensitivity response as an example of the immune suppression by chronic candidiasis, and considering the end organ effects of this response in which the lymphokines released by the effector lymphocytes attract macrophages and other inflammatory cells and prime these cells for attack against invading organisms and for phagocytic activity, it is not surprising that suppression becomes necessary in the low-grade chronic widespread *Candida* overgrowth, since the cost of prolonged and widespread inflammation would be greater in harmful effects to the host than the benefits of the defensive response in the face of a relative ineffectiveness in removing the *Candida* organisms which are less easily distinguished because of their eukaryotic nature.

Viral reactivation

The reactivation of viruses, especially of those in the herpesvirus group, probably plays a major role in the chronic fatigue syndrome. A major factor that might allow viral reactivation is immune depression, especially the depression of the function of cytotoxic T lymphocytes (CTL), of T helper cells, and of natural killer cells. Cytotoxic lymphocytes play a primary role in suppressing the recurrence of active infection of Epstein–Barr virus by reacting against B cells expressing a membrane antigen associated with the virus (28), but T helper cells are also important, because in one study of growth regression of EBV-infected B cells by specific autologous lymphocyte populations, T8 cytotoxic cells were required for growth regression, but T8 cells alone gave a weak or absent proliferative response of the cytotoxic effector cells, and T8 cells alone produced no growth regression of the EBV-infected B cell outgrowths (29). In another study, T4 cells were not required for activation of the EBV-specific cytotoxic cells, but the presence of IL-2 was required, and the cytotoxic cells in this study probably made small amounts of IL-2 (30). The contradictory findings of these two studies could be explained by differences in the numbers of stimulating and responding cells in the two experimental systems. The second study might be less similar to the in vivo situation in which the specialized cytotoxic cells have a lower exposure to the infected cells and therefore need T cell help.

It has been shown that many individuals with past EBV infection continue shedding infectious virus into the throat, and it has been postulated that viral replication continues to occur in pharyngeal epithelial cells

after the active phase of infection and that this site acts as a continual source of infected B cells since lymphocytes circulate in high numbers through this region (28, 31). This suggests that persistent infection at specific sites (pharyngeal cells and B cells) rather than dormancy is a more accurate picture of the state of the virus–host interaction in those with past EBV infection, and that the balance between the ongoing subclinical infection and the immune function of the host takes on a greater importance.

The findings of one study suggest that NK cells may also play a central role in killing infected B cells in acute EBV infections before the cytotoxic cells have become differentiated and responsive in their specialized functions, as well as possibly in helping to prevent viral reactivation (32). T helper cells are important for the production of IL-2 which stimulates NK cell function and cytotoxic T cell function. Gamma interferon, which blocks EBV-induced B cell transformation, and is therefore important in preventing the spread of infection, is produced mainly by T lymphocytes in acute EBV infection and the presence of IL-2 is required for its production (33). For this reason, T helper functions assume another important role in controlling EBV viral reactivation.

Added support for the importance of T helper function in controlling EBV reactivation is provided by a study of the generation of cytotoxic T cells to EBV-infected cells in men with AIDS. There was a progressive reduction of specific cytotoxic function in those seropositive for HIV, those with ARC, and those with AIDS which paralleled the reduction of IL-2 production in the same cellular response systems, and which also paralleled the relative proportion and absolute number of T4 cells in the same individuals. The amount of gamma interferon was also closely related to the amount of IL-2 produced. Adding recombinant IL-2 was able to restore cytotoxic function to the cells of many with severe deficiencies from HIV (34).

Another virus which has received attention as a candidate for bringing on the symptoms of CFS is the human herpesvirus type 6 (HHV-6). This virus can cause EBV negative infectious mononucleosis in teenagers and young adults. In one group of cases of infectious mononucleosis, 12% were associated solely with HHV-6 and 58% were associated with active HHV-6 along with active EBV (primary double infection or primary EBV with reactivated HHV-6). Although most people have been exposed to this virus and carry antibodies against it, one study of post-infectious CFS patients found average titers above 1:3000 and average titers above 1:3800 in the patients with neurologic disorders. A large percentage of the CFS patients were observed to grow large HHV-6 positive blasts from their peripheral blood and to have CNS 'plaques' demonstrable on ESR studies. Similar to EBV and CMV, latent HHV-6 may become reactivated in patients with immune suppressive illnesses such as HIV infection and incipient AIDS, and double infection of T cells with both viruses has been demonstrated suggesting that HHV-6 may aggravate the lymphocytolysis from HIV (35).

Since the virus infects a wide spectrum of lymphocytes including T helper cells, T suppressor cells, cytotoxic T cells, and B cells with a higher frequency of T cell infection, similar immune defense mechanisms are probably operative as in EBV, with NK and cytotoxic cells reacting against other lymphocytes early in the infection, gamma interferon reducing the spread of the virus, and a possible development of more specific cytotoxic cells later in the infection.

Similar mechanisms are important in controlling cytomegalovirus (CMV). Cell-mediated immunity is the major factor in curbing this infection, especially cytotoxic T cell responses, natural killer (NK) cells, and antibody dependent cytotoxic cell responses. These immune defenses have been shown to be important in bone marrow transplant and renal transplant recipients receiving immunosuppressants in reducing CMV infections and in determining the survival of patients who acquire new CMV infections or have a reactivation of dormant infection (36).

Although most investigators of the chronic fatigue syndrome believe that reactivated Epstein–Barr virus infection is not, per se, the cause of the disorder, the recurrent flu-like symptoms could very well be caused by viral reactivation of some type, and the herpesviruses are primary suspects. Among the herpesviruses, EBV is one of the major suspects because of its characteristic of causing persistent infection. Two studies have often been cited to discount the role of EBV in CFS and to discredit the use of EBV antibody titers as adjuncts to diagnosing this disorder (5, 37).

In the first study (5), which was mentioned previously, significant elevations were found of antibody titers to other viruses (cytomegalovirus, herpesvirus types 1 & 2, and measles virus) in addition to EBV, and this result was used to question any relationship of EBV to CFS. What the investigators were possibly unaware of and failed to mention is that primary EBV infection itself causes an elevation in antibody titers to cytomegalovirus, measles virus, and HHV-6, probably from the polyclonal B cell stimulation by EBV, and that these antibodies do not cross-react with EBV antigens (38).

In the second study (37) chronic fatigue symptoms associated with either sore throats, myalgias, or headaches were present in a large percentage of medical patients (21% of 500). Although significant elevations of EBV titers were not found in patients with positive

symptoms, the lack of adequate numbers giving a weak power to recognize real numerical differences along with the trend toward significance should have given the investigators pause in emphasizing their finding of a non-significant difference and implies that a type II statistical error (the non-detection of a difference that does exist and concluding that it does not exist) could well have been made. Also the criteria used to suggest a 'chronic Epstein–Barr virus infection' – one of the three symptoms plus fatigue – are weak compared to current standards for diagnosing CFS.

On the other hand, since other viruses have been implicated in the syndrome and since the usefulness of EA antibody titers has been questioned by another study (39), EBV is probably not the only virus involved in viral reactivation symptoms in CFS. Even though antibody studies may not be able to accurately differentiate those with viral reactivation from those without, certain individuals appear to have chronic active viral infection and specialized cellular studies may demonstrate this to be the case. Antibody titers in these individuals are often very high. In those with lower antibody titers, viral reactivation may not be as prominent a factor in their CFS and other environmental stressors may assume more importance.

One question that might come to mind is whether the herpesviruses themselves could cause an immune depression leading to their own reactivation. Certainly, acute EBV infections have been observed to cause suppression of immune function, especially of antibody production which is a defense against polyclonal activation and the production of inappropriate antibodies (40). However, suppression of T cell function also occurs in acute EBV, but this disappears when the acute infection resolves (41). Some immune disturbance may be present also in HHV-6 because of its predilection for T cells. On the other hand, since viral reactivation does not occur in most individuals having normal immune function but frequently occurs in many individuals with immune depressive disorders such as AIDS, we can assume that some immune system suppression is probably necessary for viral reactivation to occur in most patients with CFS. In patients with severe ongoing viral infection, the immune suppression by the virus itself may be all that is necessary for continued infection.

Immunologic abnormalities in CFS

Several diverse and some apparently conflicting immunologic abnormalities have been found in the CFS. The major findings have been a reduction of T cell function, T cell numbers, and of natural killer (NK) cell function and numbers. A recent study of CFS in Australia found a reduction of delayed-type hypersensitivity (assessed by skin testing with seven antigens) in 88% of the patients, providing very strong evidence for disordered T cell function. A statistically significant reduction in the absolute numbers of total T lymphocytes, helper/inducer T cells (CD4), and suppressor/cytotoxic T cells (CD8) was also observed in the patients as well as a reduced response of T cells to phytohemagglutinin stimulation. IgG_1 and IgG_3 subclass deficiencies occurred in some of the patients (42).

In a study of CFS using the older criteria for chronic active EBV infection, reduced natural killer (NK) cell function was found, especially when these cells were not separated from other lymphocytes and their cytokines (43). A more recent study found a total reduction of NK cells with a specific reduction in the $NKH1^+T3^-$ subset in CFS patients which represents the great majority of NK cells in normals, but a normal number of the $NKH1^+T3^+$ subfraction cells which is a small fraction (about 20%) of NK cells in normals. Also the NK cells of CFS patients had low levels of killing against a variety of different targets. After activation with IL-2, the NK cells had increased activity against certain targets, but were still unable to lyse EBV-infected B cell targets. The $NKH1^+TK3^-$ subfraction showed little activity in CFS patients and most of the killing activity came from the $NKH1^+T3^+$ subfraction in these patients (44).

Another recent study found a deficient display of the surface membrane marker CD3 in some patients with CFS. CD3 is intimately associated with the T cell antigen receptor Ti and is probably crucial in the transduction of the T cell activation signal after stimulation of the Ti antigen receptor has taken place (45). However, this defect probably cannot account for the majority of T cell functional problems observed in CFS patients. Whether this defect is familial and contributes to the expression of CFS, or whether triggering factors which reduce immune function can contribute to this defect is unknown.

Another immunological finding of interest in CFS is related to the manifestation of increased allergic responses in CFS including allergic rhinitis, asthma, drug reactions, and food reactions (9, 46). Allergic patients identified as having chronic active EBV infections were found to have higher numbers of IgE positive T and B cells, responsiveness to greater numbers of allergens, and higher responses to individual allergens than other allergy patients without the syndrome (46). Allergic manifestations are a prominent feature of chronic candidiasis as mentioned before, and immune suppression may predispose to atopic

illness in both disorders. Atopic illness may also be a predisposing factor in immune suppression by the mechanism of HSF mentioned previously.

The last finding distributed over a large group of CFS patients to be mentioned is that of significant elevations of interleukin-2 (IL-2) in over 100 CFS patients (mean 56 μ/mL versus 1.4 μ/mL in normals) (47). Since increased IL-2 is associated with increased T helper stimulation, this result appears somewhat contradictory to the other findings of depressed T cell function in CFS. Although elevated IL-2 may be important in causing some of the symptoms of the disorder, since the use of IL-2 in high doses to treat cancer often causes fatigue and some other symptoms of CFS, its presence by definition must be a response to another stimulant, and it may be a response to chronic active infection from recurrent viral reactivation, and this would be consistent with the increased IL-2 produced in infectious mononucleosis (33). On the one hand, T helper cells may be overstimulated intermittently, but the capacity for an effective cellular response to specific agents, especially involving cytotoxic T cells and NK cells, may still be reduced because of overall T helper suppression or because of lack of specific helper factors. This reduced reactivity may be reflected in the decreased capacity to mount delayed hypersensitivity responses in CFS patients. On the other hand, a recent finding in 25 CFS patients may shed some light on the findings of elevated IL-2 levels in the previously mentioned study. In the more recent study, the range of IL-2 levels found in both CFS patients and controls was quite broad, from 0–500 and, in this light, a median level of 56 μ of the prior study does not appear so high. The median for IL-2 in CFS patients was 5.7 compared to a median of 12.3 in controls (48). Also, a child with a syndrome consistent with chronic EBV infection (remittent fever, lymphadenopathy, hepatosplenomegaly, and diarrhea for 4 years, as well as extremely elevated EBV VCA and EA(D) IgG titers) was successfully treated with recombinant IL-2 (49), suggesting that the need for the immune stimulation by this lymphokine may outweigh its intermittent elevation in the disorder. So the finding of elevated IL-2 in CFS may be an epiphenomenon secondary to intermittent viral reactivation, rather than central to the pathogenesis of the disorder. At any rate, by definition, elevated IL-2 is a response to another stimulus, and so the finding could not be explanatory in a primary sense.

Correlations and implications

Looking over the many studies of the immune suppression by chronic candidiasis, the overall picture is one of T cell suppression which can be initiated by macrophage production of PGE_2. This non-specific T cell suppression inhibits the production of IL-1 by macrophages, and reduced IL-1 leads to significant reductions in IL-2 and T helper cell function which in turn leads to reduced function of cytotoxic T cells and NK cells as well as a reduced capacity to produce interferon. T cell suppression also leads to reduction in delayed type hypersensitivity responses and a relative anergy to batteries of skin tests. Increased allergic responses to *Candida* and other environmental antigens may also lead to immune suppression via HSF. Similar findings consistent with reductions of T cell function are present in CFS patients, including reduced responses of T cells to phytohemagglutinin stimulation, reduced numbers and function of NK cells, and reduced delayed hypersensitivity responses. Also there is increased proneness to allergic responses in CFS patients, with increased IgE-positive cells in these patients. The depression of cytotoxic T cell function and NK cell function, along with T helper cell function and interferon production may be significant factors in allowing viral reactivation in the CFS, and since infection from *Candida* has been shown to lead to all of these problems from its non-specific T cell suppression, chronic candidiasis of the intestine and other mucosal sites may be a causal factor for this immune dysfunction in a significant percentage of patients with CFS.

Conclusion

The positive response of a large group of chronic fatigue syndrome patients to an oral antifungal agent along with a diet to reduce intestinal candidiasis has suggested that chronic candidiasis of the intestinal mucosa may be an important causal agent of CFS. The similarity of the symptoms of the two disorders has also suggested an interrelationship. A similar depression of T cell function and of NK cell function in both disorders also suggests an interconnection. It appears that in chronic candidiasis the infection leads to the immune disturbance, whereas in CFS, the immune disturbance may be necessary for the disorder to express itself. Reduced function of cytotoxic T cells, of T helper cells, and of natural killer cells, as well as reduced interferon production, may be important predisposing factors for viral reactivation to take place. By its suppression of T cell function, and consequently of cytoxic lymphocyte function, NK cell function, and interferon production, chronic candidiasis of the intestinal mucosa and other mucous membranes may be an important predisposing factor,

and in some cases a necessary precursor, for the expression of the chronic fatigue syndrome.

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