MEDICAL GRAND ROUNDS

Chronic Fatigue Syndrome

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August 24, 1989

CHRONIC FATIGUE SYNDROME

A challenging problem frequently encountered by the primary care physician is that of the patient who complains of fatigue. Fatigue is the seventh most common symptom encountered in the primary care setting (1,2). The prevalence of symptoms of fatigue in populations seeking medical care has been noted to be as high as 21 to 24% (2,3).

Definition of the Chronic Fatigue Syndrome

In the March, 1988 issue of the Annals of Internal Medicine, Holmes et. al., characterizing themselves as "an informal working group of public health epidemiologists, academic researchers, and clinicians" proposed a working case definition of the chronic fatigue syndrome (CFS) (4). To be defined as CFS, a case must fulfill two major criteria plus minor criteria to include six or more of eleven symptoms and two or more of three physical criteria; or eight or more of the eleven symptom criteria.

The major criteria for the chronic fatigue syndrome are:

1. The new onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person with no previous history of such symptoms, that does not resolve with bedrest and is severe enough to reduce or impair average daily activity below 50% of the patient's previous activity level for six months or more.

2. Other clinical conditions that may produce such symptoms must be excluded. These include malignancy, autoimmune disease, infection, chronic psychiatric disease, inflammatory disease, neuromuscular disease, endocrine disease, substance abuse, side effects of medications or toxins, or other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal, or hematologic disease.

The minor criteria are of two categories, symptom criteria and physical criteria. The symptom criteria must have begun at or after the onset of fatigue and have persisted or recurred for at least six months. These symptoms include:

1. Mild fever - temperature between 37.5°C and 38.6°C, orally as reported by the patient - or chills.

2. Sore throat.

3. Painful cervical or axillary lymph nodes.

4. Generalized muscle weakness not otherwise explained.

5. Muscle discomfort or myalgia.

6. Prolonged (24 hours or greater) generalized fatigue after levels of exercise that would have been easily tolerated in the patient's premorbid state.

7. Generalized headaches (type, severity, or pattern different from headaches the patient may have had in the premorbid state).

8. Migratory arthralgia without joint swelling or erythema.

9. Neuropsychologic complaints that may include photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, or depression.

10. Sleep disturbance (hypersomnia or insomnia).

11. The main symptom complex initially developing over a few hours to a few days.

The physical criteria must be documented by a physician on at least two occasions, at least 1 month apart and include:

1. Low-grade fever - oral temperature between 37.6°C and 38.6°C, or rectal temperature between 37.8°C and 38.8°C. (Oral temperatures of greater than 38.6°C should prompt studies for other causes of illness, since they are less consistent with CFS.)

2. Nonexudative pharyngitis.

3. Palpable or tender anterior or posterior cervical or axillary lymph nodes. (Lymph nodes greater than two centimeters in diameter suggest other causes, for which further evaluation is warranted.)

Background

This definition of the chronic fatigue syndrome was prompted by reports in the medical literature, beginning in 1985 of a nonspecific syndrome with an unknown cause. It was described in four groups of patients by investigators including Tobi, DuBois, Jones, and Straus (5-8). It quickly became a common subject in both the medical literature and the lay press, earning such names as the "Yuppie flu" and "the malaise of the '80's".

In the four groups of patients originally described, the syndrome consisted of a variety of symptoms including fatigue, weakness, malaise, mild fever, sore throat, painful lymph nodes, decreased memory, confusion, depression, and decreased ability to concentrate, in addition to various other complaints. These symptoms occurred in association with a significant absence of objective physical or laboratory abnormalities. The syndrome was noted to frequently coexist with the presence of Epstein-Barr virus antibody profiles suggesting reactivation of latent infection. Thus prior to the March, 1988 definition of the chronic fatigue syndrome, it was frequently known as the chronic Epstein-Barr virus

syndrome, chronic mononucleosis, or chronic mononucleosis-like syndrome, suggesting a causal relationship to the virus (9).

Is CFS a new syndrome only described since 1985 or is it a more precise definition of several diseases of bygone eras with similar signs and symptoms (10)? I will explore descriptions of such entities from the medical literature, potential etiologies or explanations of these symptom complexes, a prudent approach to patients with these complaints, and potential therapies to improve symptoms.

History

In 1880, George Beard published "A Practical Treatise on Nervous Exhaustion (Neurasthenia)" (11). In it he described a symptom complex of sleep disturbance, musculoskeletal symptoms, fatigue, and mood disturbances in the absence of demonstrable pathology. Neurasthenia was considered to be a "functional disorder in which the demands of civilization predisposed the patient to exhaustion of nervous system energy". The remarkable prevalence of neurasthenia at the end of the 19th century lead Proust and Ballet to call it "the disease of the century"(12,13). It was further subdivided according to the predominant symptoms into entities such as splanchnic neurasthenia, neurocirculatory asthenia, traumatic neurosis, anxiety neurosis, and psychogenic rheumatism.

In 1959, Henderson and Shelekov wrote an article in the New England Journal of Medicine entitled "Epidemic Neuromyasthenia-Clinical Syndrome?"(14). In it they described several outbreaks of an ill defined syndrome that had occurred during the previous two decades (15-48). These cases shared the features of protean symptomatology including fatigue, headache, alterations in emotional state, aching muscular pain, paresis, and paresthesias. They noted that few significant and consistent physical findings or abnormal laboratory values had been found. The cases occurred in young and middle aged adults, with a female predominance. While the outbreaks did affect general communities, those most susceptible seemed to be nurses and physicians.

These illnesses had been called by many different names depending on where they occurred and the predominant symptoms. These included Iceland disease (15), benign myalgic encephalomyelitis (16), Akureyri disease (17-18), epidemic vegetative neuritis (19), acute infective encephalomyelitis (20), encephalomyelitis (21-22), persistent myalgia following sore throat (23), a disease resembling or simulating poliomyelitis (24-25), atypical poliomyelitis (26), encephalomyelitis resembling poliomyelitis (27), and epidemic neuromyasthenia (28-29). In more recent writings they have been termed benign myalgic encephalomyelitis (BME) (49-50).

The first description of BME occurred at the Los Angeles County Hospital during a major poliomyelitis epidemic in Los Angeles (26). Although 210 cases were originally thought to be poliomyelitis, they were eventually diagnosed as BME, because none of the patients developed muscle atrophy or progressive neurologic changes. All had myalgias, paresthesias, headaches, and profound fatigue. None had temperatures above

37.8° C. Loss of concentration, sleep disturbances, and emotional lability were prominent. All laboratory studies were normal. No patients died, but the majority experienced chronic fatigue and relapses.

During the next 20 years, similar outbreaks of illness were reported in Iceland, Australia, Europe, the United States, and South Africa. The primary signs and symptoms associated with each of these outbreaks are summarized in Table 1.

Table 1.

SYMPTOMS AND SIGNS IN 23 OUTBREAKS OF EPIDEMIC NEUROMYASTHENIA

	Fatigue	Sore Throat	Headache	Myalgia	Neuropsych Sx	Paresis	Disability	Recurrences
California, Los Angeles	X	X	X	X	X	X	X	X
Wisconsin, Fon-Du-Lac	X	X	X	X	X		X	
England, Harefield	X	X	X	X			X	X
Iceland	X	X	X	X		X	X	X
Australia, Adelaide	X	X	X	X	X	X	X	X
Kentucky, Louisville		X	X	X		X	X	
New York State		X	X	X		X	X	X
Denmark	X	X	X	X	X	X	X	X
Florida, Lakeland	X	X	X	X		X	X	
England, London	X		X	X		X	X	
Maryland, Rockville	X	X	X	X	X	X	X	X
Florida, Tallahassee	X	X	X	X	X	X	X	
Alaska, Seward	X		X	X	X	X	X	X
Germany, Berlin			X	X	X	X	X	
England, London	X	X	X	X	X	X	X	X
South Africa, Durban	X	X	X	X	X	X	X	
Connecticut, Ridgefield	X	X	X	X	X	X	X	X
Florida, Punta Gorda	X	X	X	X	X	X	X	X
Mass, Pittsfield-Wmstown	X	X	X	X	X	X	X	X
England, London	X		X	X	X	X		
England, Coventry	X	X	X	X	X	X	X	
Greece, Athens	X		X	X	X	X	X	X

Several investigators (51-59) have noted patients with persistent ill health following documented acute infections. These include brucellosis, influenza, schistosomiasis, toxoplasmosis, malaria, upper respiratory infections, varicella, rubella, and infectious mononucleosis. More recently contributors to the medical literature from Great Britain (59-61) have used the term postviral fatigue syndrome in summarizing the illnesses described in Table 1.

There does seem to be an entity described over the past century in the medical literature characterized by the wide array of nonspecific symptoms previously noted, often precipitated by various acute illnesses that causes significant distress and disability to those who experience it. Review of the original descriptions of these illnesses in the literature doesn't determine whether they meet the precise definition of CFS. However, there is strong evidence to believe that this is not a new entity. In fact Lloyd suggests that myalgic encephalopathy and post-viral fatigue syndrome meet the criteria for CFS and should be characterized as such (58). In addition there are various other conditions described in more current literature that have symptoms overlapping CFS.

Fibromyalgia/Fibrositis

One of these is fibromyalgia syndrome, also called fibrositis. It is characterized by generalized wide-spread pain for at least three months, multiple tender points in several anatomic locations, and the absence of underlying disease (62-64). More specifically, to merit the diagnosis of Primary Fibromyalgia Syndrome a case must meet the diagnostic criteria outlined in Table 2 (64). Patients must satisfy the major criteria and at least three minor criteria.

Table 2.

Diagnostic Criteria for Primary Fibromyalgia Syndrome

Major Criteria (required)

1. Widespread pain for at least 3 months.
2. Multiple tender points in at least six specified anatomic sites.
3. Absence of underlying disease as cause for fibromyalgia.

Minor Criteria

1. Alpha intrusion in non REM sleep EEG.
2. Nonresponsive sleep.
3. Overnight increase in morning stiffness and fatigue.
4. Daytime fatigue or tiredness.
5. Subjective swelling or dysesthesias.
6. Aggravation with cold, stress or activities.
7. Improvement with rest, heat, increased level of physical fitness.
8. Chronic headache (migraine, tension).
9. Functional bowel disorder (irritable colon).

The clinical presentation of fibromyalgia has much in common with that of CFS. Symptoms shared by the two syndromes include fatigue, myalgias, arthralgias, headaches, and chronic sleep disturbance. On clinical grounds, there seems to be significant overlap of fibromyalgia and CFS. Buchwald et. al. looked at fifty patients with the diagnosis of fibromyalgia (65). They found that in addition to the above symptoms, many fibromyalgia patients also complained of other symptoms frequently seen with CFS. These included recurrent sore throat (54%), adenopathy (33%), and low-grade fevers (28%). In looking for a common etiology, Buchwald's group did EBV titers on the fibromyalgia patients and found that they were not significantly different from those in age- and sex-matched controls.

Fibromyalgia has been recently fairly well accepted as a specific medical condition. It has been noted to be the second or third most common diagnosis in ambulatory adult rheumatology, accounting for 4% to 20% of new patients (64,66,67). Goldenburg, has

noted striking similarities between the diagnostic criteria for fibromyalgia, benign myalgic encephalomyelitis, chronic fatigue syndrome, and chronic Epstein-Barr Virus syndrome.

Potential Etiologies of CFS

1. Infectious

As previously noted chronic fatigue has been reported following acute illnesses caused by a variety of infectious agents.

Brucella - Beginning in 1903, several groups (68-71) described patients who had persistent ill health with fatigability and inability to carry on normal activities after a documented acute episode of brucellosis. Cluff, et. al. evaluated 10 patients who had chronic symptoms of fatigue, headache, nervousness, depression, and myalgia four to eight years after having acute brucellosis (71). In comparing these patients with those who were asymptomatic after acute brucellosis, they found no abnormalities on physical exam or in serologic testing to brucella. In fact none of the patients in either group had evidence of persistent brucella infection.

Influenza - Imboden and colleagues studied recovery from Asian influenza in a group of military personnel (52). In comparing fourteen persons who were completely recovered at three weeks to twelve persons in whom symptoms persisted longer than three to six weeks, they found no difference in acute symptoms or acute and convalescent viral serologies.

Enterovirus - An association between previous infection with Coxsackie B viruses and symptoms of CFS has been suspected (72). Yousef, et. al. reported on 76 patients with the postviral fatigue syndrome and thirty matched controls (73). Their patients had a history of muscle fatigue, myalgia, difficulty with concentration and short term memory for at least six months, therefore apparently fulfilling the criteria for CFS. They found positive cultures of enteroviruses after dissociation of virus from antibody in seventeen (22%) patients and two (7%) controls. One year later virus of the same serotype was only isolated from five of the original seventeen patients in whom it had previously been found. In addition they found that improvement in clinical symptoms correlated with disappearance of the virus, suggesting a causal relationship in this subset of patients.

Epstein-Barr Virus - The working definition of CFS was prompted by several recent reports in the literature of what was termed the chronic Epstein-Barr syndrome (CEBV). There have been numerous past reports describing chronic mononucleosis syndromes (74-76). A number of recent studies have found abnormal EBV serologic tests in patients with unexplained chronic fatigue (Table 3) (67).

Table 3.

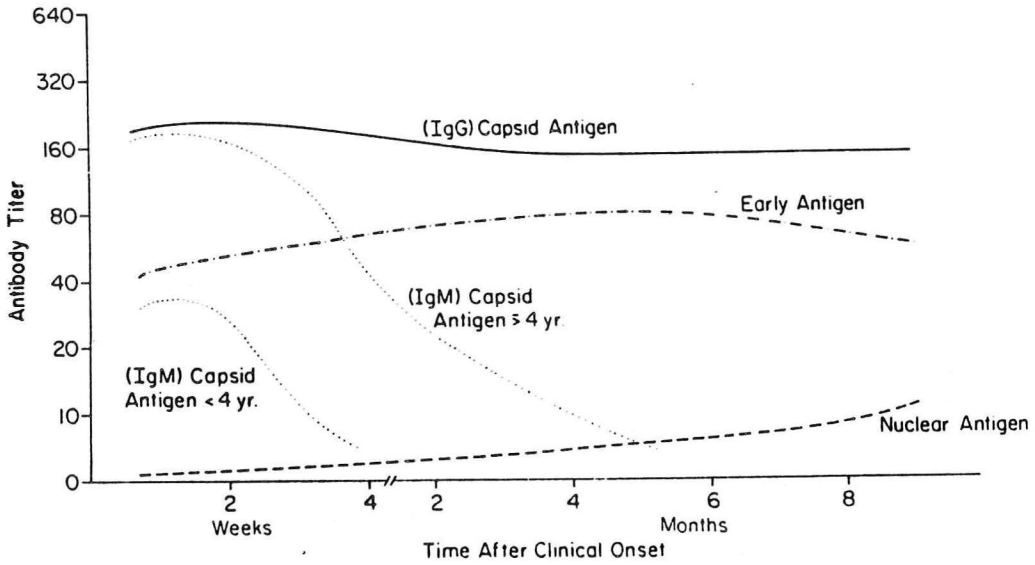
Symptoms and EBV Serologies in Patients with Possible EBV Syndrome and Patients with Fibromyalgia

	Dubois et al.(6) 1984 (N=14)	Straus et al.(8) 1985 (N=23)	Jones et al.(76) (1985 (N=40)	Outpatients with Chronic Fatigue Buchwald et al.(3) 1987 (N=40)	Patients with Fibromyalgia(67) (N=50)
Symptoms*					
Mean Age (Yr)	30	30	24	34	44
% Female	79	52	50	70	92
Fatigue	100	100	74	100	96
Myalgias or arthralgias	93	70	55	80	100
Recurrent headaches	–	35	–	83	90
Recurrent pharyngitis	50	57	64	60	54
History of lymphadenopathy	43	48	59	44	33
Depression, mood changes	71	35	70	78	72
Past history of infectious mononucleosis	43	83	26	26	22
Serologies					
VCA-IgM	Not present	Present in 22%	Present in 8%	Not present	Not present
VCA-IgG	Elevated	Elevated	Elevated	Normal	Normal
EA	Elevated	Elevated	Elevated	Normal	Normal

*All values except mean age and % females are expressed as the percent of patients experiencing the symptom.

Serologic testing for Epstein-Barr virus has been available since the mid-1960's. Several distinct structural and viral-specific antigens and their corresponding antibodies have been identified. These include capsid antigen (VCA), early antigen (EA), and nuclear antigen (EBNA). The usual appearance of the antibodies to these antigens in relation to clinical illness is outlined in Figure 1. (78).

Figure 1.



Dubois et. al. reported fourteen patients with chronic fatigue, weakness, fever, myalgias, and depression (6). Three fourths were women and the average age at onset was 30 years. Forty-three percent had prior infectious mononucleosis. All patients had anti-EA with a wide range of titers. Eight of their patients had temporary remission after an average of 33 months, but only one had a permanent remission. Anti-EA reappeared along with reappearance of symptoms. IgG anti-VCA titers were present, but varied greatly with serial testing over time. Healthy control patients had no anti-EA titers and generally lower anti-VCA titers. Twelve of the fourteen patients also had serologic evidence of cytomegalovirus infection.

Straus, et. al. reported on 31 patients referred to the National Institutes of Health for chronic fatigue of greater than one year's duration after they had infectious mononucleosis (IM) or features suggestive of IM (8). Eight of these 31 patients were found to have other conditions such as Sjögren's syndrome, SLE, lymphoma, and multiple sclerosis. Nineteen of the 23 with no other illness had a history of IM, and eleven had been heterophil-positive in the past. In thirteen of the patients, chronic illness began within one year of acute IM. The predominant symptoms were fatigue, myalgias, arthralgias, mild pharyngitis and low grade fever. EBV serologic findings included intermittently positive VCA-IgM in 5 patients and no controls. Nineteen of 23 patients had anti-EA compared to six of 23 controls.

Jones described 39 highly selected patients with greater than one year of fatigue, headache, paresthesia, depression, pharyngitis, fever, and lymphadenopathy (77). Ten of the patients were heterophil antibody positive. Thirty-one patents had positive VCA-IgG, anti-EA, and EBNA. Three of the patients had positive VCA-IgG and anti-EA, but no EBNA.

The most consistent EBV serologic abnormalities in these reports were the presence of anti-EA and higher titers of anti-EA and IgG-VCA in patients, compared with controls. It has been believed that anti-EA positivity indicates recent onset or reactivation of EBV infection. This may not always be true. Lamy evaluated anti-EA and anti-VCA on 5178 patients referred for EBV serologies (79). By age 35, 45% of these patients had anti-EA titers greater than 1:8. By age 70 to 80, 52% had such titers. IgG-VCA was present at levels of 1:320 to 1:1280 in 56% of patients at ten to fourteen months post IM and in 27% at 40 to 140 months. Therefore high titers of IgG-VCA and anti-EA may persist for years after IM, are present in younger and older age groups, and are found in asymptomatic and immunocompetent individuals.

A methodological problem in the reports of CEBV syndrome was the comparison of a single sample EBV serology in controls versus multiple, serial serologies in the patients with chronic fatigue. For example, Straus had seventeen samples drawn on one patient with anti-EA titers ranging from less than ten to 160 and ten samples from another patient showing a similar range of antibody concentration. In these reports, the highest titer for each patient was compared with the single titer determination in each control.

In addition significant variability in EBV serologies may exist between laboratories as well as within the same laboratory (80). In one laboratory, nineteen EBV-positive sera

were frozen and retested later (81). Fourfold or greater variations between the initial and repeated titers were detected in 18% of the samples tested for anti-EA-D, 26% of those tested for VCA-IgG, and 33% of those tested for anti-EA-R. The currently available indirect immunofluorescence technique for EBV appears to have poor inter- and intra-laboratory reproducibility and must be standardized for quality control.

Holmes et. al. investigated a cluster of 134 cases of mononucleosis like illness thought to represent CEBV in Nevada (81). These cases had been initially diagnosed as CEBV by two internists, based on clinical features of unexplained severe fatigue, associated symptoms such as pharyngitis, and elevated titers of various EBV antibodies as performed by a commercial laboratory. Thirty-three of the original 134 patients had the most severe fatigue lasting for more than two months. Eighteen of these had other explanations for their fatigue. The remaining fifteen patients with chronic fatigue were compared with the other 119 patients. The fifteen case patients were more likely to have splenomegaly on exam. On laboratory testing, they had significantly higher antibody titers against EBV, cytomegalovirus, herpes simplex, and measles. EBV serologies could not reliably differentiate individual case patients from the others. These results suggested that EBV serology is inadequate to diagnose cases which were most likely to fit the CEBV syndrome and that this syndrome may not be caused by EBV. The authors suggested that some patients with such chronic fatigue may have an abnormality of infectious or immunologic origin.

Buchwald, et. al. reported the results of EBV serologies in general medical patients with a history of chronic fatigue (3). In this study 500 patients in a primary care practice were interviewed. Twenty-one percent of these patients reported a chronic fatigue condition for at least 6 months, with a median of 16 months. Patients who had no evidence for chronic illness were asked to participate in the study. EBV tests were obtained on 40 patients who had severe fatigue for at least six months and either recurrent sore throat, myalgias, or headaches. Mean age was 34 years and 70% of the patients were women. A single serum was obtained from each of the 40 patients and age- and sex-matched controls. The mean titers of VCA-IgG, EA-Ab, and EBNA-Ab were not significantly different in patients and controls.

Amsterdam et. al. evaluated 43 depressed patients and 46 controls for CEBV (82). There was no significant difference in titers between these two groups.

Therefore, in unselected patients with chronic fatigue or depression, EBV serologies are not diagnostically useful and should be interpreted cautiously. Rarely, patients may have clinical and laboratory evidence of reactivation or chronic mononucleosis. Only these unusual cases should be termed CEBV syndrome.

Human Herpesvirus Type 6 - In October, 1986, scientists at the National Cancer Institute reported the discovery of a new human herpesvirus released from mitogen-stimulated peripheral blood mononuclear cells (83). The virus replicated efficiently in cord blood B lymphocytes and was initially named human B lymphotropic herpesvirus. It was subsequently noted that the virus replicates well in T cells and other cell lines

(84), leading to the proposal that the virus be renamed human herpesvirus type 6 (HHV6).

The virus has been recovered from many patients with lymphoproliferative disorders. It has also been recovered from the peripheral blood mononuclear cells of some patients with CFS (85). The physical and molecular features of HHV6 are those of a typical herpesvirus. It is a large, enveloped particle whose inner core contains a double-stranded DNA genome of approximately 165,000 kilobase pairs in length. The viral DNA and proteins exhibit little homology to those of other human and animal herpesviruses. Unlike EBV, HHV6 apparently lyses, but does not transform, B lymphocytes.

Early seroepidemiologic studies indicate HHV6 is a fairly ubiquitous agent. Antibodies to HHV6 are found in the serum of between 10 to 40 percent of normal adults. The seroprevalence ranges from 60 to 80 percent among patients with AIDS, B cell lymphomas, sarcoidosis, and the chronic fatigue syndrome.

The higher prevalence in patients with CFS could indicate an association between this syndrome and HHV6 infection. It is more likely, however, an epiphenomenon of the subtle immunologic abnormalities that characterize this syndrome. Either the syndrome permits more frequent reactivation of latent HHV6 that, in turn, stimulates antibody responses or a nonspecific polyclonal activation augments the titers of antibodies to many viruses. Because antibody titers to other viruses are also elevated in CFS, the latter scenario is more likely (81).

HHV6 remains an orphan virus in search of a disease with which it can be associated. There are no clinical syndromes, thus far, that are attributable to primary or reactivated infection with this virus. There is little to link the chronic fatigue syndrome and HHV6, but it is reasonable to presume that infection with this virus could precede the onset of chronic fatigue in the same manner that the syndrome follows infections with other viral and nonviral pathogens (86).

No persistent infection has been found as an etiology for CFS. Greatly stressed individuals may display deficiencies in the immune system of latent viruses, especially the herpesvirus group, which results in reactivation and concomitant elevations in antibody titers. This is likely to be the cause of the observed increases in EBV and HHV6 titers of CFS patients as opposed to ongoing infection.

More work needs to be done in investigating patients who meet the criteria for CFS to rule out previously unidentified infectious agents.

2. Immunologic

A number of studies reveal immunologic abnormalities in patients with CFS (Table 4).

Table 4.

Immunologic Findings in Patients with the Chronic Fatigue Syndrome

Finding	Reference
Humoral immune responses	
Elevated antibodies to viral proteins	5,7,8,80
Low or absent antibodies to EBNA or EBNA-1	8,86
Partial hypogammaglobulinemia	8,87-90
Elevated circulating immune complexes	8
Decreased immunoglobin release in vitro from mitogen-simulated lymphocytes	91
Lymphokine and interleukin responses	
Increased leukocyte 2',5'-oligoadenylate synthetase	8
Decreased interleukin-2 synthesis in vitro by mitogen-stimulated lymphocytes	92
Decreased immune (gamma) interferon synthesis in vitro by mitogen-stimulated cells.	92
Lymphocyte number and function	
Increased helper to suppressor ratios	8
Increased suppression of immunoglobulin synthesis in vitro	93
Decreased natural killer cell activity	92,94
Decreased EBV-specific cytotoxic cell activity	91

In addition to the unusual serologic EBV profiles noted above, there appears to be an uncommon prevalence of partial hypogammaglobulinemia, particularly IgA and IgG deficiencies. Elevated levels of circulating immune complexes are seen in one-fourth to one-third of CFS patients. These levels, however, are below those typically associated with immune complex-mediated disorders (8).

Abnormalities in the cellular immune system have also been seen. An increased ratio of helper to suppressor lymphocytes were noted among patients from the Lake Tahoe area. This apparently reflected a decrease in suppressor cells rather than an absolute increase in the number of helper cells. Hamblin, using a different assay, found a decrease in T helper cells and an increase in T suppressor cells in patients with chronic fatigue following acute infectious mononucleosis (96). Tosato found functional evidence of increased suppressor cell activity, noting that purified T cells from patients with CFS suppressed in vitro immunoglobulin synthesis by cultured B cells (94).

Borysiewicz studied four individuals with symptoms of fatigue for more than two years after documented acute mononucleosis (92). He observed that these patients had normal immunoglobulin levels, T and B cell numbers, T cell proliferative responses, and natural killer cell activity. Their cells, however, did exhibit reduced in vitro immunoglobulin synthesis and reduced EBV-specific cytotoxic T cell activity. Significant reductions in vitro synthesis of interleukin-2 and immune interferon by cultured

lymphocytes were identified in 13 patients with CFS by Kibler et. al. (93). Natural killer cell activity was also deficient as noted by others (95).

Straus found patients with CFS to possess normal levels of circulating interferon, but to show a modest but statistically significant increase in levels of leukocyte 2',5'-oligoadenylate synthetase activity (8). This enzyme is induced during acute viral infections, including acute mononucleosis (97).

Half to three fourths of patients with chronic fatigue syndrome report inhalant, food, or drug allergies (98-101). Straus studied 24 patients with CFS for history or evidence of allergy. All patients were skin tested with extracts from a variety of foods and inhalants. Twelve (50%) of the patients reacted to the food or inhalant extracts, compared to rates of reactivity of 20% to 30% in studies of large unselected adults of similar age. In addition nine of the nonreactive patients gave a history of atopy. Therefore cutaneous reactivity and histories suggestive of atopy occurred in 50% and 83% of CFS patients respectively.

The mechanism of this increased incidence of allergy is unknown. It is possible that individuals with a heightened reactivity to allergens also respond more vigorously to certain infectious antigens. One part of that inherent hyperresponsiveness may be the initiation by certain infectious agents of a level and duration of lymphokine and interleukin release that would in themselves perpetuate the reactive symptoms of the syndrome.

The literature regarding immunologic responses of patients with CFS lacks consistent and reproducible findings. The magnitude and types of abnormalities do not correlate with the severity of symptoms. Immunologic studies of patients with CFS should be undertaken and compared with those of patients who are physically deconditioned or clinically depressed.

3. Psychologic

An early hypothesis regarding the etiology of the chronic fatigue syndrome is that its manifestations represent somatic expressions of psychoneurosis (85). It is impossible to completely dispel the notion that the chronic fatigue syndrome represents a psychoneurotic condition. There are some observations that support this hypothesis.

Reassessment of some outbreaks of epidemic neuromyasthenia indicated a very high prevalence of neurosis in affected individuals. In one of the most famous such epidemics, occurring among staff of the Royal Free Hospital in London in 1955, the progression of the outbreak was argued plausibly to resemble mass hysteria (22,102).

In the 1950's, careful studies were undertaken to assess the validity of Evans' hypothesis that patients with chronic fatigue after acute brucellosis might have a psychologic etiology (69). Imboden compared psychologic profiles of individuals who fully recovered from acute brucellosis and those who manifested continued symptoms, primarily fatigue (51). He found major differences between the groups including a higher incidence of

emotional disturbance, particularly depression, among patients with persisting fatigue. Those retrospective studies could not discern whether the depression was a consequence of lingering symptoms of the disease or whether people with these characteristics might be at risk for the persistent symptoms.

In the 1957 Asian influenza epidemic, Imboden showed a correlation between time to convalescence and preexisting psychoneurotic aberrations (52). It was concluded that certain psychological factors render one vulnerable to postinfectious chronic fatigue. Greenfield studied psychologic attributes that correlate with length of recovery from infectious mononucleosis and concluded that somatic complaints of psychological origin might become established during recovery from an acute infection and merge with those of the resolving physical illness (55).

Kruesi and colleagues at the NIH looked at psychiatric diagnoses in 28 patients who met the case definition criteria for chronic fatigue syndrome (103). They found that a high proportion of patients with CFS possess histories of depression, phobias, or anxiety disorders that frequently predated the onset of their chronic fatigue by several years. Overall psychiatric diagnoses were identified in 75% of their patients upon careful interview with the Diagnostic Interview Schedule (DIS). Over 50% were found to meet criteria for depression (Table 5).

Table 5.

Lifetime Prevalence of Psychiatric Diagnosis by Sex
in 28 Patients with Chronic Fatigue Syndrome

Diagnosis	Women (N=20) N	%	Men (N=8) N	%
Simple Phobia	7	35	1	12.5
Somatization disorder	2	10	0	
Major depressive episode	11	55	2	25.0
Dysthymia	7	35	0	
Panic/agoraphobia	1	5	0	
Alcohol abuse/dependence	2	10	1	12.5
Antisocial personality	2	10	0	
No DSM-III diagnosis	2	10	5	62.5

Manu likewise evaluated 100 adults with a mean duration of fatigue of 13 years (104). Sixty-six of these patients had one or more psychiatric disorders identified by the Diagnostic Interview Schedule (Table 6).

Table 6.

Diagnoses of Attribution of 100 Patients with Chronic Fatigue

	No and % of Patients	95% Confidence Interval,%
Psychiatric diagnoses	64	54.6-73.4
Medical diagnoses	3	0-6.3
Psychiatric and Medical Diagnoses	2	0-4.7
No diagnosis	31	21.9-40.1

Manu suggests that these patients' fatigue is a symptom of their psychiatric diseases. However he did not discern whether the symptoms of psychiatric disease predated the onset of fatigue, or whether the fatigue occurred prior to the onset of psychiatric disease. Komaroff argues that the psychiatric disorders discovered may be a result of the chronic disability these patients experience due to their fatigue, rather than a predisposing factor (105). He further notes that preexisting psychiatric disease should not preclude CFS if a patient meets the diagnostic criteria for CFS.

These findings demonstrate that psychoneurosis does contribute to the chronic fatigue syndrome in many patients. This, however, does not fully explain many of the manifestations noted with CFS.

4. Musculoskeletal/Deconditioning

Intracellular acidosis due to lactic acid occurs with exercise and has been suggested to contribute to the perception of muscle fatigue (106,107). In an effort to determine if intracellular acidosis plays a part in the symptoms of CFS, Arnold, et. al. examined seven patients complaining of general fatigue and weakness persisting for years after an acute viral illness (108). They performed ^{31}P magnetic resonance imaging of the forearm of these patients before and after exercise. Three of the patients demonstrated an abnormally early, severe intracellular acidosis in the forearm muscle during exercise. The intracellular pH decreased to an average of 6.3 during the first five minutes of exercise. This compares with a pH of above 6.8 in healthy controls with similar levels of exercise.

The investigators felt that this was due to excessive glycolytic activity rather than inadequate oxidative metabolism. They noted a predominance of type II fibers. The mechanism by which a viral infection might produce these abnormalities is unknown. However, antibody to mitochondrial ATPase has been found in patients with viral myocarditis (109) and myoadenylate deaminase deficiency has developed after a viral illness (110).

No other studies of muscle in patients meeting the criteria for CFS have been reported. There have, however, been multiple studies of muscle from patients meeting the criteria for primary fibromyalgia which has many characteristics overlapping those of CFS (111).

The muscle changes noted in various studies of patients with fibromyalgia are summarized in Table 7.

Table 7.

Pathophysiology of Fibromyalgia: Recent Investigations

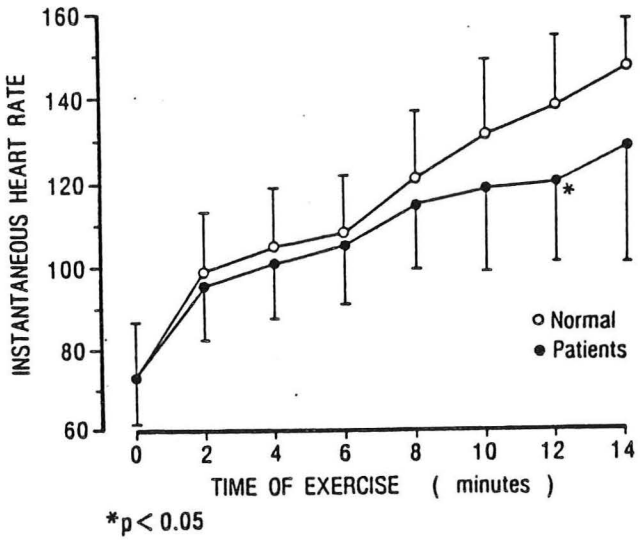
Investigation	Results
Muscle and soft-tissue changes Histopathologic findings	Nonspecific type II fiber atrophy, no inflammation (112-114)
Isokinetic strength, muscle fiber bundles	Isokinetic muscle strength less and threadlike structure around fibromyalgia muscle (115)
Muscle energy metabolism	Marked change in muscle energy metabolism of fibromyalgia tender muscle compared with controls (116)

Biopsy specimens of muscles involved with fibromyalgia have demonstrated minor histopathologic abnormalities but no inflammation. Ultrastructural changes of type II fiber atrophy and increased glycogen have been noted in uncontrolled studies. Muscle energy metabolism studies have revealed a decrease in levels of adenosine triphosphate, adenosine diphosphate, and phosphoryl creatine. An increase in the levels of adenosine monophosphate and creatine were found in the trapezius muscle of patients with fibromyalgia. This has lead to the conclusion that local tissue hypoxia may contribute to the change in muscle energy metabolism in the painful muscles of fibromyalgia.

Montague and his colleagues have noted cardiac abnormalities in patients during the acute phase of community-acquired viral illness (117,118). These include segmental wall motion abnormalities in a few patients, and small pericardial effusions and altered primary ventricular repolarization properties in the majority of patients. These abnormalities largely disappeared by six weeks of follow-up.

They subsequently studied a group of 41 patients who met the criteria for CFS (117). They compared findings from these patients with 41 normal controls matched for age and sex. All subjects underwent 24-hour ambulatory electrocardiographic monitoring, body-surface electrocardiographic mapping, echocardiography, and exercise tolerance testing. All subjects had normal cardiac exams, echocardiograms, and electrocardiograms. Major differences occurred between the two groups with exercise. The CFS patients had significantly less exercise capacity than controls. The CFS patients had a mean duration of exercise of 9 ± 4 minutes compared with 12 ± 4 minutes in controls ($p < 0.01$). Secondly, patients with CFS had a slower acceleration of exercise heart rate, becoming statistically significant ($p < 0.05$) at twelve minutes into the protocol (Figure 2).

Figure 2.



They suggest that these findings are explained by an intrinsic defect in cardiac pacemaker function with exercise or a defect in sympathetic drive to the pacemaker cells. In addition the data suggest a simultaneous dysfunction in working skeletal muscle causing decreased exercise tolerance in these patients. They feel that the peripheral effect actually contributes more to the symptoms than the cardiac effect.

They do not attribute their findings to deconditioning, since poor exercise performance by unfit subjects is usually associated with very rapidly rising heart rates during the exercise.

I have had different findings in two of my own patients who meet the criteria for CFS and have undergone extensive cardiovascular testing by Dr. Drew Gaffney and Lynda Lane at this institution.

Case One

J.B. is a sixteen year old white female who was active and well until March of 1987 when she had a severe case of chicken pox and was completely bedridden for a week and after which she missed six weeks of school due to excess fatigue and inability to keep up with school day activities. She returned to school on a reduced schedule and had negative EBV testing prior to being seen by me in September, 1987. At that time her physical exam revealed her to be orthostatic and have a midsystolic click and murmur, but was otherwise normal. Her laboratory evaluation was similarly normal.

In Dr. Gaffney's lab she underwent two-dimensional echocardiography, measurements of cardiac output, heart rate and blood pressure supine, standing, and during maximal exercise, plasma volume, plasma catecholamines and lactates, and 24 hour urine volume and urine electrolytes. Her echocardiogram revealed a large, redundant mitral valve with prolapse. She had no evidence of vasoconstriction or orthostatic hypotension. She was only able to exercise to 80 watts, half of her predicted maximal workload, reaching a

heart rate of 168. Her maximal oxygen consumption with exercise was 22 ml/kg/min. Her plasma volume was also significantly decreased, consistent with her low fitness state. Her catecholamines and urine electrolytes were within normal limits. She was treated with a slowly progressing exercise program and increased salt and water intake.

Six months later she had repeat exercise testing. She showed improvement in exercising to 120 watts with a maximal heart rate of 175 and oxygen consumption of 26 ml/kg/min. Her symptoms, however, had only improved slightly. After two years of gradual reconditioning , she now is able to function near her premorbid level.

Case Two

L.F. is a 34 year old white female who was well except for palpitations, treated with beta blockers, until September, 1988 when she developed an acute illness characterized by headache, myalgias, and fatigue, that was diagnosed as a viral illness by her physician. She was bedridden for six weeks as a result of this acute illness. She subsequently experienced chronic fatigue and intermittent relapses of the other symptoms, which caused her to be unable to work at her job as a pharmacist.

I first saw her in June, 1988. She had undergone extensive evaluation which included normal serum chemistries, thyroid function tests, vitamin B12 level, chest roentgenogram, urine metanephrine, urine 5 HIAA and electrocardiogram and negative anti-nuclear antibody, rheumatoid factor, lyme antibody, acetylcholine receptor antibody, serologic test for syphilis, and monospot. Her serum protein electrophoresis revealed a polyclonal gammopathy, her hematocrit was persistently borderline low, and her echocardiogram showed slight sagging of the mitral valve with no clear evidence of prolapse.

Upon testing in Dr. Gaffney's lab she had decreased exercise tolerance, biking for one minute at 15 watts, producing a heart rate of 170 beats per minute. Her plasma volume was low and she was "miserably" deconditioned. She was treated with clonidine 0.05 milligrams twice a day, a high salt diet and a slowly progressing exercise program under the direction of a physical therapist. After seven months of training she is able to bike for about 25 minutes with a maximal heart rate of 140 beats per minute. Her exercise tolerance has improved significantly, but is still not back to her baseline.

These two cases demonstrate the fact that marked deconditioning can occur with the chronic fatigue syndrome. This is most likely due to the bedrest with the acute illness which leads to cardiovascular deconditioning. When the patient tries to resume normal activity, they are unsuccessful. They continue resting which exacerbates their cardiovascular deconditioning. Both of these patients developed decreased plasma volume which exacerbated their exercise intolerance. Their previous attempts at resuming normal activity worsened their symptoms. However, they responded well to an exercise program beginning at a very low level and increasing slowly.

Differential Diagnosis of Chronic Fatigue

Very few studies have been done on the presentation and etiologies of the complaint of fatigue. Most of those that have been done are retrospective, anecdotal or focusing on particular underlying diseases (119-122).

In 1944, Allan described a group of 300 patients seen at the Lahey clinic for whom weakness, fatigue or weak spells were the chief complaint (123). In 239 (80%), no physical disorder was identified and the symptoms were attributed to a "nervous state of one kind or another". In 61 patients (20%) a physical disorder was identified. These disorders included chronic infections in thirteen patients, metabolic disorders in twelve, neurologic disorders in sixteen, heart disease in eight, anemia in five, nephritis in three, and vitamin deficiency, lung tumor, Hodgkins disease, and fever of unknown origin in one patient each.

In a retrospective study of 300 patients who volunteered a complaint of lethargy, Jerrett found no organic cause in 62.3%, infection or post-infection in 12.7%, circulatory disorders in 9.3%, and a variety of etiologies including iatrogenic, endocrine disorders, anemia, and uremia in the remaining 15% (Table 8) (119).

Table 8.

Diagnostic Grouping of the 300 Patients Complaining of Lethargy

Diagnostic Group	No of Cases
No organic cause found	187 (62.3%)
Infection or post-infection	38 (12.7%)
Circulatory disorders	28 (9.3%)
Iatrogenic	15 (5%)
Endocrine disorders	15 (5%)
Anemia	11 (3.7)%
Uremia	3 (1%)
Others	3 (1%)

He identified psychosocial problems that he felt contributed to the lethargy in all of the patients in whom he had identified no organic etiology.

Kroenke et. al. recently evaluated patients in a fatigue clinic at Brooke Army Medical Center in San Antonio (2). A survey was done in two primary care clinics to detect those patients who defined fatigue as a major problem for them. This turned out to be 24% of the 1159 patients completing the survey (Table 9).

Table 9.

Prevalence of Fatigue in 1159 Adult Primary Care Patients

	Demographic Subgroup	No of Patients	No (%) of Fatigued Patients
Sex			
	F		
	Age, Y		
	<40	150	44 (25)
	40-64	339	78 (23)
	> 64	187	64 (34)
	M		
	Age,Y		
	<40	62	7 (11)
	40-64	248	52 (21)
	> 64	173	31 (18)
Race			
	White	1033	250 (24)
	Nonwhite	126	26 (21)
Total		1159	276 (24)

Those patients who had fatigue longer than thirty days and had no other illness to explain this on screening were further evaluated in the fatigue clinic. Of the 102 fatigued subjects undergoing evaluation, 72% had been fatigued for more than a year.

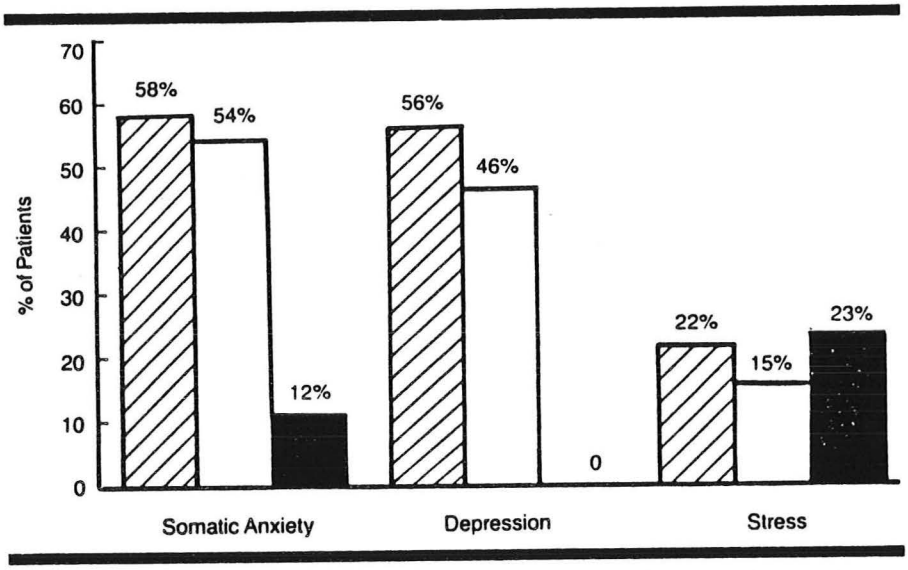
Testing of these patients included exercise index, weight, urinalysis, complete blood count, erythrocyte sedimentation rate (ESR), chemistry panel, chest roentgenogram, monospot, thyroid function tests, and stool for fecal occult blood. A subset of patients had EBV serologic testing. All study participants had psychometric and functional status testing including the Beck Depression Inventory, the Modified Somatic Perception Questionnaire, the Social Readjustment Rating Scale, the Millon Behavioral Health Inventory, and the Sickness Impact Profile.

Laboratory testing was generally not helpful in differentiating between the fatigued patients and a control group. The only significant difference between the two groups was in the number of patients with elevated ESR's. It was elevated in twelve (12%) fatigued patients and one (4%) control. Three fatigued patients had possible causes for their elevated ESR in that two had upper respiratory infections and one had sinusitis. Eleven of the twelve patients had musculoskeletal complaints, but none had evidence of connective tissue disease after one year of follow-up.

Four (3.9%) of the fatigued patients had borderline elevations in serum thyroid stimulating hormone. Three of these had increases in TSH following thyrotropin administration consistent with subclinical hypothyroidism. These patients were all treated with thyroxine, but had no improvement in their symptoms after 6 months.

In contrast to laboratory testing, fatigued patients were more likely than controls to have scores suggestive of depression, somatic anxiety or both on psychometric testing (Figure 3.).

Figure 3.



—Percentages of all fatigued patients (n = 102, hatched bars), matched fatigued patients (n = 26, open bars), and matched controls (n = 26, solid bars) who had scores suggestive of somatic anxiety (≥7 on Modified Somatic Perception Questionnaire), depression (≥10 on Beck Depression Inventory), and stress (>150 on Social Readjustment Rating Scale).

The patients in the fatigue clinic were followed for 12 months to determine clinical outcome. Fatigue improved in only 28% of the patients. Improvement correlated with younger age, lower sickness impact profile score, normal ESR, and fewer clinic visits. Significant fatigue had developed in four (15%) of the control patients during the year of follow-up.

Manu and colleagues undertook a study to determine the frequency of CFS among patients with symptoms of fatigue presenting to the fatigue clinic at the University of Connecticut (l24). They performed a similar set of diagnostic tests as those performed on the patients in San Antonio. Their psychomatic testing included the Diagnostic Interview Schedule to identify psychiatric illness.

Of the l4l patients evaluated only six met the diagnostic criteria for CFS (Table l0).

Table 10.

Application of the Chronic Fatigue Syndrome Criteria in 135 Patients with Fatigue Lasting Longer than Six Months

	Men (n=53) Number (%)	Women (n=82) Number (%)	Total (n=135) Number (%)
Reason for exclusion			
Psychiatric diagnosis	34(64)	57(70)	91(67)
Medical diagnosis	2(4)	2(2)	4(3)
Insufficient minor criteria	14(26)	20(24)	34(25)
Total	50(94)	79(96)	129(95)
With chronic fatigue syndrome	3(6)	3(4)	6(5)

Seven patients had a medical diagnosis causing their chronic fatigue: two had seizure disorder, two had sleep apnea, and one each had panhypopituitarism, bronchial asthma, and polymyalgia rheumatica. Ninety-one of the patients had psychiatric disorders that were clinically active and felt to be the etiology of their fatigue. Thus, in their population, CFS was uncommon if patients presenting with fatigue were carefully evaluated and followed up.

In the working case definition of CFS by Holmes, et. al. several diseases were to be specifically excluded to meet the second major criteria of chronic fatigue (4). These are outlined in Table 11.

Table 11.

Malignancy
Autoimmune disease
Localized infection
    occult infection
Chronic/subacute bacterial disease
    endocarditis
    Lyme disease
    tuberculosis
Fungal disease
    histoplasmosis
    blastomycosis
    coccidioidomycosis
Parasitic disease
    toxoplasmosis
    amebiasis

- giardiasis
- helminthic infestation

Immunodeficiency virus (HIV)

Chronic psychiatric disease
- endogenous depression
- hysterical personality disorder
- anxiety
- neurosis
- schizophrenia
- tranquilizers
- lithium
- anti-depressive medications

Chronic inflammatory disease
- sarcoidosis
- Wegener's granulomatosis
- chronic hepatitis

Neuromuscular disease
- multiple sclerosis
- myasthenia gravis

Endocrine disease
- hypothyroidism
- Addison's disease
- Cushing syndrome
- diabetes mellitus

Drug dependency/abuse
- alcohol
- controlled prescription drugs
- illicit drugs

Side effects of chronic medication
- other toxic agents
- chemical solvents
- pesticides
- heavy metals

Other known or defined chronic disease
- pulmonary
- cardiac
- GI
- hepatic
- renal
- hematologic disease

Evaluation of Patients with Chronic Fatigue

To prove beyond a shadow of a doubt that a particular patient presenting with chronic fatigue does not have any of the diseases mentioned in the differential diagnosis would come close to literally achieving the "million dollar workup". Fortunately most patients do not require such intensive investigation. Certainly, as with most diagnostic dilemmas, especially those with such nonspecific presentation, a detailed history and physical exam is of utmost importance. Any abnormalities that suggest a specific underlying disease should be aggressively pursued.

Since psychiatric illness frequently can be identified in patients with chronic fatigue and/or coexists in patients meeting the criteria for CFS, psychometric testing should be seriously considered early on. As previously mentioned, psychiatric diagnoses do not necessarily conclude a causal relationship to CFS or rule out other etiologies. However identification of these problems and attention to their treatment may improve some of the symptoms of CFS.

Laboratory testing to rule out common illnesses presenting as chronic fatigue should be undertaken in most patients. This would include a hematocrit to rule out anemia, thyroid function tests (primarily thyroid stimulating hormone) to rule out hypothyroidism, and ESR to roughly screen for collagen vascular disease, infection, and malignancy. Normal values do not completely rule these out, however. Further testing should be dictated by the results of the history and physical exam. If the above reveal no underlying illness to explain the chronic fatigue, a provisional diagnosis of CFS can be made.

Once a diagnosis of CFS is made, it is important to continue to follow these patient on a regular basis at least with an interim history and physical exam. Underlying illnesses may subsequently be apparent that were not evident at initial examination.

Treatment of Chronic Fatigue Syndrome

The plight of patients with CFS has encouraged a variety of approaches to treatment. A group at the NIH chose to study acyclovir in the treatment of these patients on the basis of early data suggesting a link to the Epstein-Barr virus (125). They studied 27 adults with criteria for CFS of at least one year's duration who also had titers of antibodies to diffuse or restricted early antigens of Epstein-Barr virus of greater than one to forty. The serologic criteria were chosen to identify a subset of patients who might be more likely to respond to an antiviral agent shown to inhibit the replication of EBV in vitro and in vitro (126,127).

The study was a placebo controlled, double blind crossover trial. The patients were treated in each of two thirty-seven day treatment periods. They received intravenous acyclovir or placebo every eight hours during seven days of hospitalization, followed by 800 mg acyclovir tablets or placebo four times daily for an additional 30 days. Three of

the patients had reversible renal failure with intravenous acyclovir and were withdrawn from the study (128).

Of the 24 patients who completed the study, 21 reported improvement during one treatment phase. The improvement usually lasted for two to three weeks after treatment. Eleven of the patients improved during acyclovir therapy and ten improved during placebo. The patients' EBV serologies and immunologic studies did not change with treatment. Straus' group concluded that clinical improvement could not be attributed to acyclovir.

Adolphe reported an anecdotal case of a patient who met the criteria for CFS in that he had fatigue, recurrent pharyngitis, myalgia, blurred vision, and headaches (129). He was treated with nifedipine ten milligrams three times daily, because his headaches were "migraine-like". He had resolution of all his symptoms with the nifedipine therapy. They recurred when he discontinued nifedipine for 72 hours.

Other pharmacologic therapy reportedly under study for CFS, but not yet reported in the literature include amantadine, adenosine monophosphate, antidepressants, benzodiazepines, nonsteroidal anti-inflammatory drugs, H2 blockers and gamma globulin.

In most patients with CFS continued rest will only prolong the symptomatology. Exercise may serve several roles in treating CFS. As noted in the previous two cases a gradual exercise program can objectively improve the deconditioning associated with the syndrome. Exercise has also been noted to be of benefit in treated some of the psychologic disorders frequently seen with CFS (130). Several studies have documented the benefit of aerobic exercise in treating anxiety (131-136) and depression (137-139). The physical and psychologic mechanisms for this benefit are unknown.

In patients in whom psychiatric illnesses have been identified, specific therapy is indicated regardless of whether the psychiatric illness is a cause or the result of the symptoms of CFS. This may take the form of supportive counselling, antidepressants, or antianxiety medications. Patients must be followed for response of target symptoms rather than placed on such medications indiscriminately without therapeutic goals.

The ultimate goal in treating CFS patients is improvement of symptoms and follow-up to identify potentially treatable etiologies of the chronic fatigue.

Conclusion

Some would suggest that the chronic fatigue syndrome is not a clinical entity, but a diagnostic wastebasket much as the diagnosis of hypoglycemia was in the past. There are several reasons, however, to conclude that CFS is a real disease (140):

1. Several symptoms frequently seen such as pharyngitis, cervical adenopathy, and low-grade fevers are not consistent with a purely psychoneurotic disorder.

2. In most cases the patients give the same description of the start of their illness in that they were healthy and active, then they developed symptoms of a "cold" or "flu" and they were never well again.

3. There are some objective findings in most of these patients, primarily immunologic phenomena.

Many patients who meet the current fairly broad criteria for CFS probably do have underlying disorders, including psychoneurosis. Further study of these groups may reveal infectious diseases that have not previously been identified. However, there will remain a group of patients with CFS in whom nothing else can be found.

Perhaps CFS with its associated symptoms and immunologic findings is a final common pathway of a variety of insults on the body. Certain individuals, maybe linked to psychologic factors, are susceptible to this as a result of any acute illness (usual viral) producing short term disability. Deconditioning as a result of bedrest associated with the acute illness may contribute to the persistence of the disability. There is currently no evidence for ongoing infection in these patients.

The basic tenet in treating these patients is "do no harm". It is prudent to begin a slowly progressive exercise program to overcome the component of deconditioning. Many of these patients will require psychologic support for pre-existing psychiatric illness or those that occur as a result of the disability associated with CFS. Symptomatic treatment with careful followup regarding relief of symptoms is also warranted.

It no longer is appropriate to consider all patients with the chronic fatigue syndrome to be suffering from purely psychoneurotic disorders. On the other hand, we are still struggling to prove an organic basis for this condition. Unfortunately, the present lack of definitive diagnostic and therapeutic tools for assessing and treating individuals with the syndrome leaves both patients and health care providers frustrated (141).

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