Chronic Fatigue Syndrome

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Continuing Education Activity

Chronic fatigue syndrome, also known as myalgic encephalomyelitis, is a complex multisystem disease commonly characterized by severe fatigue, cognitive dysfunction, sleep problems, autonomic dysfunction as well as post-exertional malaise, which can severely impair a patients' ability to conduct the activities of daily living. Early diagnosis and prompt treatment are critical to prevent the high avoid high morbidity and its overwhelming effect on the quality of life. This activity reviews the evaluation and treatment of chronic fatigue syndrome and highlights the role of the interprofessional team in evaluating and treating patients with this condition.

Objectives:

- Identify the etiology of chronic fatigue syndrome.
- Review the appropriate evaluation of chronic fatigue syndrome.
- Outline the management options available for chronic fatigue syndrome.
- Describe interprofessional team strategies for improving care coordination and communication to and improve outcomes of chronic fatigue syndrome.

Introduction

Chronic fatigue syndrome is a chronic disease that potentially affects about two million Americans.[1] The United States Public Health Services initially described it during an epidemiological study of Los Angeles County during the summer of 1934. Chronic fatigue syndrome, also called myalgic encephalomyelitis, is a complex multisystem disease commonly characterized by severe fatigue, cognitive dysfunction, sleep problems, autonomic dysfunction as well as post-exertional malaise, severely impairing activities of daily living. Things get worsened due to the condition remaining undiagnosed for years secondary to inadequate medical teaching on the subject, provider bias, as well as confusion regarding diagnoses and treatment of the disease.[1]

Etiology

The etiology of chronic fatigue syndrome is controversial, complicated, and incompletely understood. Controversy exists about single versus multiple causations. Theories abound regarding the involvement of infections, immune system as well as genetics in this complex interplay.

Genetics

Increasing evidence supports the role of genetic susceptibility in patients with CFS. Family history study of chronic fatigue syndrome, have shown significantly higher rates of family members of the patient reporting CFS or similar fatigue like symptoms.[2] Studies from the twin registry also have shown increased familial and genetic predisposition of the condition.[2][3][4][5] A study has reported variability in the expression of specific genes in patients with CFS, particularly after exercise, which affects the metabolism and immune responses.[5] At the same time, another study has shown a linkage between CFS, specific genetic mutations, as well as viral infections.[6]

Infection

As stated above, various infectious etiologies, including the Epstein-Barr virus (EBV), the human herpesvirus (HHV)-6, and the human parvovirus B19, are hypothesized to trigger the disease.[7][8][9][10]

Speculations are that in a few patients, acquisition of viral infections like infectious mononucleosis triggers the onset of the disease process.[8][11][12][13]

Researchers have detected anti-HHV-6 IgM antibodies and HHV-6 antigen more commonly in peripheral blood of patients with chronic fatigue syndrome as compared to the general population indicating higher prevalence as well as higher reactivation of the virus in this cohort.[14][15][16][17]

Parvovirus B19, both with and without viremia, has been implicated in the development and triggering of chronic fatigue syndrome.[18] These patients have higher levels of tumor necrosis factor and interferon-gamma.[19]

Alterations in the Immune system

Observations have shown alterations of B cell subsets levels, including those of CD 21+ CD19+ and activated CD5+ cells in patients with chronic fatigue syndrome.[20]

There is also a reported decrease in transitional B cells and plasmablasts, and an increase in the population of CD24+ B cells in these patients.[21][22] Researchers have also found elevations in the levels of immunoglobulins IgG in several studies, again pointing to alteration in the immune functioning of these patients.[23][22][24] Several studies have also described the presence of autoantibodies against nuclear and membrane structure as well as against neurotransmitter receptors.[25][26][27][28]

Epidemiology

Studies have given different prevalence rates for chronic fatigue syndrome based on the type of definition used, the type of population surveyed, and the study design used.[29] Studies have given a current prevalence rate ranging from 0.007% to 2.8% in the general adult U.S. population and from 0.006% to 3.0% in the primary care population.[30][31][32][33][34][35] Studies conducted from 1993 through 1999 reported prevalence of 0.004% to 0.56%, whereas more recent studies have reported prevalence rates of 0.24% to 2.6%.[30][31][33][36] As per the study conducted by Bierl and colleagues in 2004, about 2.2 million American adults suffer from CFS like illness.[37] They estimated that about 1,197 people per 100,000 people suffer from CSF and CFS like illnesses.[37]

Studies have found that the prevalence to be significantly higher in the age group of 40 to 70 years of age group.[30][36][37][38] Women are suffering from it more often than men.[30][36][37][38] The prevalence seems to be higher in the white population rather than the non-whites population.[30] Studies have also reported a markedly higher prevalence in the low-income cohort rather than the higher income and higher educated cohort, suggesting the role of social risk factors such as stress in the causation of CFS.[30][37][38] No regional differences were noticed in the country as far as the prevalence of CFS is concerned.[37]

Pathophysiology

Alterations in the Immune System

The pathophysiological changes which lead to chronic fatigue syndrome are not entirely understood.[39]

The hypothesis state that there is an alteration in the nervous system is occurring secondary to the body's unintended responses to commonly encountered antigens leading to changes in the cell-mediated immunity, activation of oxidative pathways, and alteration in the neuroendocrinal

encountered antigens leading to changes in the cell-mediated immunity, activation of oxidative pathways, and alteration in the neuroendocrinal and autoimmune responses against neurons.[40]

Multiple studies have shown alterations in the functioning of the natural killer (NK) cells, interleukins profile, as well as the decreased response of T cells to certain specific antigens.[39]

There is evidence of ongoing inflammation, as indicated by increased production of various proinflammatory interleukins, which also explains some of the malaise and flu-like symptoms that the patients often complain.[39]

Increased Oxidative Stress

Proposals are that chronic fatigue syndrome patients have a significant increase in oxidative stress, which plays a vital role in the etiopathogenesis of the disease. There is an increase in oxidative stress biomarkers like oxidized LDL and certain prostaglandins and, at the same time, a decrease in the amounts of the antioxidants like glutathione.[41][42]

The oxidative damage transforms the fatty acids and proteins into immunogenic targets.[43]

The free radicals also damage the electron transport chain as well as energy productions and finally cause mitochondrial damage.[44][41]

The proposed mechanism of mitochondrial dysregulation is currently actively researched.[45][46][47]

Oligoadenylate Synthetase/RNase L Pathway

The association between the onset of CFS with a viral infection has always been speculated. One of the interferon-activated antiviral pathways involves the activation of the 2'-5'-oligoadenylate (2-5A) synthetase/RNase L system.[48] Severe deregulation of this antiviral pathway occurs in CFS, which leads to a decrease in the apoptotic activity in the cells.

Alteration of Natural Killer (NK) Cells

Studies have shown a lower number of CD3-CD57 white cells lymphocytes, which are a type of NK cell, whereas the levels of the cytotoxic T cells were not changed.[49][50][51]

B Cell Impairment

The profile of B cell subpopulations may be different in CFS compared with controls. CFS is associated with increased production of the CD20+ CD5+ B cell phenotypes correlating with increased autoantibody production, as well as overexpression of CD21 markers acting as receptors for some viruses.[21][22]

Immunoglobulins

There is also an alteration in the immunoglobulin number and distribution in patients with chronic fatigue syndrome. The total level of immunoglobulin G (IgG), particularly subclasses IgG1 and IgG3, is substantially lower. In contrast, there is an increase in the serum levels of IgA and IgM against the lipopolysaccharides of the normal gram-negative bacteria due to alterations in gut permeability.[52][53] These can also serve as corroborative evidence for the provider about the patient suffering from CFS.

Autoimmunity

Studies have also detected autoantibodies against certain neurotransmitters and neurons, leading to alterations in neurotransmitter response, sleep patterns, and neurocognition.[27][54]

Researchers have found antinuclear antibodies (ANA), anti-dsDNA antibodies, as well as antibodies against neuronal and endothelial cells in these patients.[55] Antibodies against the muscarinic M1 acetylcholine beta-adrenergic receptors have been detected in these patients.[27][10] Disturbance in these receptors could explain symptoms of autonomic dysregulation in these patients.[56]

Alterations in the Central Nervous System

Neuroinflammation and Role of Glial Cells

The presence of proinflammatory changes causes speculation about the involvement of neuroinflammation in the pathogenesis and clinical presentation of the disease process.[57] Multiple studies show that the constant proinflammatory state that occurs in CFS causes activation of glial cells, specifically microglia and astrocytes. These activated glial cells produce the expression of a translator protein, which appears to lead to the activation of inflammation in the central nervous system.[58] The increase in glial activation leads to an increase in neuronal excitation as well as neuronal inflammation, which is supposed to be the leading cause of symptoms of chronic pain in these patients.[59] Studies are currently also evaluating the role of "glial toxins" produced by multiple viruses and bacteria, leading to direct damage to these glial cells.[60]

Neuronal Sensitization

The hypothesis state that there is an exaggerated response to painful stimuli in patients with CFS due to the chemical and structural changes taking place at the level of the central nervous system.[59]

This exaggerated response leads to the formation of sensitized neurons that keep the stimulus going due to the process of "kindling."

Alterations in the Neuroendocrine System

Changes in Serotonin Transmission

The central fatigue, which is a key symptom in patients with chronic fatigue syndrome, is hypothesized to be due to excess levels of serotonin as well as its metabolites in the central nervous system of these patients.[61] The excess serotonin leads to inhibition of the action potential generation and thus reduced motor activity and appears to be a leading contributor to the fatigue symptoms of these patients.[62][63]

Hypocortisolism

It is also theorized that there are low levels of circulating cortisol in patients with chronic fatigue syndrome secondary to dysfunction in the hypothalamic-pituitary axis {HPA}. Cortisol is the principal hormone of the HPA and leads to the cortisol awakening response (CAR). This response is deficient in patients with CFS leading exhibition of post-exertional malaise.[64]

Genetic Predisposition

Studies have shown that there is an interaction between changes in the genes secondary to changes in the environment, leading to epigenetic modification. DNA methylation appears to be the most studied of these epigenetic modifications that can alter the expression of the gene concerning the environmental stimuli and lead to the development of the disease process.[65]

History and Physical

The hallmark symptom is the post-exertional fatigue associated with numerous neurological, cardiovascular, respiratory, as well as gastrointestinal complaints.[65] The fatigue described by patients is not exertional, worsened by low upright posture, not relieved by rest, and no medical reason can be found for it.[66] Patients often state that they have had high fitness levels before the onset of fatigue.[67] Patients describe the beginning of the fatigue rather abruptly, typically associated with a flu-like illness.[68] They also describe post-exertional malaise where the regular activity is followed by symptoms of worsening of discomfort and fatigue, with delayed recovery, usually taking more than one day.[69] Patients also complain of new-onset chronic headaches with varied weekly fluctuations.[69] Muscle pain is seen more commonly more in pediatric patients and also could be a feature of comorbid fibromyalgia.[70] Patients can also report joint pains, and there could be an associated autoimmune rheumatological condition.[70] Patients state that sleep is disturbed and not refreshing, as well as there is day time hypersomnolence and nighttime insomnia.[69] There are also complaints of cognitive decline with slowed mental processing speed, poor learning abilities, impaired processing of new information, memory decline and decreased attention span, and multitasking ability.[71] Besides, these patients can also manifest autonomic manifestations, including nausea, vomiting, drenching night sweats, dizziness, intolerance to alcohol, and other medications.[72][73] Patients can also exhibit symptoms of uncontrolled anxiety, panic attacks, and impaired social functioning.[72][74][75] Most of these patients have decreased ability to work.[76]

Evaluation

Chronic fatigue syndrome is a diagnosis made on clinical examination and after exclusion of other possible etiologies.

Initially, when the etiological considerations were was considered to be mainly viral in origin, the Center for Disease Control and Prevention (CDC) U.S.A. in the year 1988 came up with the criterion for the same with the primary focus on the physical symptoms. The Oxford criterion was developed in the year 1991 and defined a case of chronic fatigue syndrome if mild to severe symptoms of fatigue, myalgias, and tiredness were present.[74] The Oxford criterion considered fatigue to be the primary symptom and should have a definite beginning and should be severe, disabling, and affecting mental and physical functions. These symptoms should have been present for a minimum of six months and should be affecting the patient more than fifty percent of the time. There was a need for other symptoms like myalgias, mood, and sleep disturbances to be present as well. Exclusion criteria included those with a known medical condition known to cause fatigue as well as those with the diagnosis of mental health disorders like schizophrenia, mania, depression, eating disorders, substance abuse, or known organic brain pathology.[74]

Subsequent conclusions stated that the Oxford criterion was over-inclusive as well as had a low threshold that recruited patients with milder symptoms, leading to the generalization of treatments for all patients. Hence, the treatment guidelines could not be generalized to those with severe symptoms, patients with chronic pain, post-exertional malaise, and other conditions that mimicked chronic fatigue syndrome.[77][78][79]

Considering the need for revision of the diagnostic criterion, the CDC, in the year 1994, came up with a broader definition for chronic fatigue syndrome developed by Fakuda and colleagues.[80] As per these criteria, the patient should have severe fatigue for more than six months as well as at least four of the following symptoms- a new type of headache or a change in the pattern or severity of the headache, myalgias, pain in multiple joints, post-exertional malaise lasting more than one day, sore throat, tender lymph nodes, unrefreshing sleep and lastly a significant impairment in short term memory or concentration.

The modified CDC criterion was in extensive usage until the year 2015 when the Institute of Medicine (IOM) came up with the criterion to diagnose chronic fatigue syndrome.[81] The current IOM criterion developed after reviewing the 1994 CDC guidelines by Fakuda and colleagues, the 2003 Canadian clinical case definition for CFS, the 2007 Clinical Guidelines for CFS from the British National Institute for Health and Clinical Excellence (NICE) along with the 2010 revised Canadian Consensus Criteria for CFS (Revised CCC).[81]

2015 IOM Diagnostic Criteria for CFS

Diagnosis requires the presence of the following three symptoms for more than six months as well as the intensity of the symptoms should be moderate or severe for at least 50% of the time.

The three main symptoms include:

- **Fatigue** - A noticeable decrease or impairment in patient's ability to engage in activities which they would enjoy before the onset of the illness, and this impairment continues for more than six months and is associated with new-onset severe fatigue, unrelated to exertion, and not relieved by rest.

- **Post-exertional malaise** - Patients experience worsening symptoms and function after exposure to physical or cognitive stressors, which they previously well tolerated.
- **Unrefreshing sleep**-patients feel that tired after a night's sleep.

Criterion fulfillment for diagnosis requires the three above stated symptoms, **plus one of the additional** below mentioned symptom.

- **Cognitive impairment -** Problems with the thought or executive function worsened by exertion, effort, or stress or time pressure
- **Orthostatic intolerance** - Worsening of symptoms upon assuming and maintaining an upright posture. Symptoms are improved, although not necessarily abolished, by lying back down or elevating the feet.[81]

The typical approach to a patient with chronic fatigue should begin with a history and physical examination, focusing on identifying the underlying symptoms and ruling out any underlying serious illnesses. The providers should use a validated clinical questionnaire like the DePaul symptom questionnaire or the Center for Disease Control Symptom Inventory.[82][83]

There are no pathognomonic or diagnostic tests or single biomarkers of CFS. Tests to rule out other etiologies and undertaken in the context of the particular patient. The standard laboratory tests include urinalysis, complete blood count with differential, blood chemistries, thyroid function tests, muscle enzymes like creatine kinases, and C- reactive protein.[80] The National Institute for Clinical Excellence (NICE) also conducting tests for gluten sensitivity recommends using immunoglobulin A endomysial antibodies, urine drug screening, and rheumatological antibodies as indicated and recommend against using viral titers unless required by the patient's clinical examination.[84]

Treatment / Management

Non-Pharmacologic Management

The primary treatment modalities are cognitive behavior therapy (CBT) and graded exercise therapy (GET).

A randomized control trial conducted in 2011 in the United Kingdom compared the effectiveness and safety CBT, GET, adaptive pacing therapy (APT), and specialist medical care in the management of chronic fatigue syndrome. Overcoming fatigue and improvement of physical function were taken as measures of effectiveness while safety assessment comprised of recording all adverse effects. The results showed that both CBT and the GET improved outcomes when added to, whereas APT was not a useful addition.[77]

Treatment for any comorbid condition should be undertaken to minimize symptom burden.[80][85]

Cognitive Behavior Therapy (CBT)

During the CBT sessions, the therapist emphasizes the role of thought process and its impact on the patient's actions and feelings as well as recognize behaviors which cause them to feel more tired and hence minimize them. Multiple trials, as well as Cochrane reviews, have shown the positive benefits of CBT on improving the fatigue, mood, and post-exertional malaise in both the adolescent and adult patients.[77][85][86][87][88] Studies have also shown lower school absences when CBT is provided to the adolescent population.[89]

Graded Exercise Therapy (GET)

GET involves a supervised, gradual increase of physical activity intensity and duration. This therapy got much publicity after the PACE trial, which showed effectiveness for fatigue and functional impairment with the GET.[77] The trial encouraged the participants to gradually increase the timing of their physical activity to a final goal of 30 minutes, spread over 52 weeks to a final goal of 30 minutes of light exercise five days per week while trying to avoid overexertion. Other studies have also supported its efficacy.[90][91][92]

Pharmacologic Management

Pain Medications

Nonsteroidal, including COX-2 inhibitors, are used due to their action in relieving pain and associated inflammation.[93][94] Opioid medications are addictive and hence only used for very severe cases for the shortest possible duration.[95]

Tricyclic Antidepressants

Multiple tricyclic antidepressants have shown varying degrees of success in improving sleep, pain levels, as well as the severity of fatigue.[93] Doses used here are typically lower than the doses used for use in the treatment of depression.[96]

Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

Many SSRIs like fluoxetine, sertraline, paroxetine have been used for treating depression and anxiety, which either accompany the disease process or occur as a consequence of it.

SNRIs have the added benefit of providing neuropathic pain relief besides the antidepressant effect. However, neither SSRIs nor SSNRIs has any direct action on the underlying pathophysiology of the disease process.[77]

Antiviral Therapy

The hypothesis regarding viral etiologies, including Epstein Barr virus, for chronic fatigue syndrome, several antiviral medications have been tried in these patients, but most of these studies have been inconclusive.[97][98]

Randomized control trials comparing the effect of nucleotide analog inhibitors like acyclovir, valacyclovir, and ganciclovir, versus placebo, have shown no difference in symptom control.[99]

Studies with the use of interferons versus placebo on chronic fatigue syndrome also did not show evidence of clear benefit.[100]

Immunoglobulin

A systemic review conducted by Whiting et al. in 2001 evaluated the effect of the five RCT's on the use of immunoglobulins in patients of chronic fatigue syndrome, and four RCTs showed positive results.[77] Unfortunately, other studies did not report any benefit and, in fact, concluded the potential dangers of the immunoglobulins.

Corticosteroids

Multiple RCTs and systemic reviews performed with steroids in 2005 showed varying responses. One systemic review conducted in 2015 showed a weak benefit from low dose hydrocortisone, but the effect was only short-lived and was associated with adverse effects.[101]

Complementary and Alternative Medicines

Systemic reviews of the studies using essential fatty acids, magnesium, acetyl -l-carnitine, vitamin B12, and antioxidants have shown only partial response and require further studies to decipher a definitive relation.[102]

Newer Treatments and Trials

Rintatolimod

Rintatolimod is a newly approved immunomodulator, and an antiviral drug for the treatment of chronic fatigue syndrome, in Canada and Europe.[103] An RCT published in the Journal of American Medical Association (JAMA) in 2001, showed the medication to be of some benefit in these patients.[104] The U.S. FDA rejected the drug to be marketed in the U.S. for the treatment of CFS, citing insufficient safety and efficacy data.

Rituximab

Rituximab is an anti-CD20 monoclonal antibody causing the depletion of B cells. An initial small double-blind, placebo-controlled trial of 30 patients with CFS receiving rituximab showed some benefit, leading the researchers to hypothesize that B cells might have a significant role in the pathogenesis of some of the patients of chronic fatigue syndrome.[105] A more extensive study, however, showed no fatigue difference between patients who received rituximab versus who did not receive it.[106] Also, patients receiving rituximab showed more adverse effects, including neutropenia and infections.[106]

Fecal Microbiota Transplantation

Alteration in gastrointestinal (GIT) microbiota in patients of CFS has been hypothesized as one of the etiologies as well. Trials of fecal microbiota transplantation is an exciting, relatively safe, and rapidly growing treatment modality that is currently undergoing experimentation for the management of multiple medical conditions, including CFS. The process involves the transfer of feces from a healthy donor into the gut of a patient. Numerous studies in recent years have shown significant symptom relief in these patients after the fecal microbiota transfer providing some promising therapeutic insights.[107][108][109][110][111][112][113]

Even though currently there has been some success with the fecal microbiota, it is still too early to conclude but opens doors for future research in this direction.

Differential Diagnosis

Chronic fatigue syndrome can potentially affect the instrumental activities of daily living (IADLs), which comprise activities like cleaning, laundry, driving, and managing finances.[114] Hence, the clinicians must be able to diagnose this condition but, at the same time, also be able to differentiate it from other commonly encountered disorders in clinical practice, which can have overlapping presentations.

Chronic Fatigue

Even though chronic fatigue syndrome has fatigue as one of the three mandatory symptoms, it is a complex multisystem neurological disease with evidence of inflammation at the brain and hence the term myalgic encephalomyelitis.[115] Chronic fatigue, on the other hand, lacks the associated post-exertional malaise, unrefreshing sleep, as well as cognitive impairment.[115] To minimize the confusion with the terminology, the Institute of Medicine (IOM) has even suggested switching the terminology from chronic fatigue syndrome to systemic exertion intolerance disease (SEID)" instead of CFS.[1]

Rheumatological Disorders

Fibromyalgia, polymyalgia rheumatica, polymyositis, as well as autoimmune disorders like systemic lupus erythematosus [116], rheumatoid arthritis [117], Sjogren syndrome [118] can present a significant diagnostic dilemma for the provider. It requires proper history, clinical examination, laboratory testing for autoantibodies before arriving at the correct diagnosis.

Psychiatric Disorders

Roughly 20% of the patients presenting to primary care clinics that have an underlying undiagnosed depressive illness and a targeted mental health history is critical.[119] There could be a range of undiagnosed or underdiagnosed disorders like major depressive disorder, bipolar disorder, eating disorder, schizophrenia somatoform disorders as well as substance abuse. It is the utmost importance to remember that in the elderly symptoms of fatigue, unrefreshing sleep, as well as cognitive changes, can be very much part of the symptom complex of late-onset depression.[120]

Endocrine Disorders

There could be adrenal abnormalities (Addison disease, adrenal insufficiency, Cushing disease), thyroid abnormalities (both hypothyroidism and hyperthyroidism) as well as diabetes mellitus, which can mimic symptoms of chronic fatigue syndrome.

Hematological and Oncologic Disorders

Undiagnosed malignancies can present with symptoms of fatigue and mandates a search for underlying cancer which as well as age-appropriate screening. However, age alone should not be the only determining criterion for ordering these screenings.[121]

Anemia from any cause can present with excessive tiredness and fatigue.[122][123][124][125]

Infectious Diseases

Infectious diseases like Human immunodeficiency virus, tuberculosis, chronic hepatitis can have ongoing fatigue as their initial presentation.

Gastrointestinal Disorders

Inflammatory bowel disease can present with chronic fatigue symptoms.[126] Celiac disease can present with fatigue and without sometimes even without gastrointestinal symptoms.

Neurological Disorders

Fatigue is the main presenting feature of multiple sclerosis.[127] Dementia, which has cognitive impairment as its major presentation, can cause a diagnostic dilemma, as can pseudodementia.

Age-related Orthostatic Hypotension

It is again imperative to recognize that there are age-related changes in blood vessels, causing decreased autonomic responsiveness, which gets worsened with lack of adequate fluid intake as well as polypharmacy.[128]

Respiratory Disorders

Chronic respiratory conditions like chronic obstructive pulmonary disease (COPD) and sarcoidosis can present with chronic fatigue.[129]

Sleep Apnea

Undiagnosed obstructive sleep apnea can present with fatigue as well as unrefreshing sleep, which are two of the main diagnostic criteria for chronic fatigue syndrome. This is diagnosed by polysomnography.[130]

Enhancing Healthcare Team Outcomes

Chronic fatigue syndrome frequently poses a diagnostic dilemma. The hallmark symptom is the post-exertional fatigue associated with numerous neurological, cardiovascular, respiratory, as well as gastrointestinal complaints. Patients can also exhibit symptoms of uncontrolled anxiety, panic attacks, and impaired social functioning. Chronic fatigue syndrome is a diagnosis made on clinical examination and after exclusion of other possible etiologies. Considering the need for revision of the diagnostic criterion, the CDC, in the year 1994, came up with a broader definition for chronic fatigue syndrome developed by Fakuda and colleagues. As per these criteria, the patient should have severe fatigue for more than six months and also have at least four of the following symptoms- a new type of headache or a change in the pattern or severity of the headache, myalgias, pain in multiple joints without any swelling or redness, post-exertional malaise lasting more than one day, sore throat, tender lymph nodes, unrefreshing sleep and lastly a significant impairment in short term memory or concentration.

It is important to consult with an interprofessional team of specialists that include a pain specialist, a psychiatrist, a psychotherapist, and possibly a physical therapist. Even though chronic fatigue syndrome has fatigue as one of the three mandatory symptoms, it is a complex multisystem neurological disease with evidence of inflammation at the brain. Hence, the term myalgic encephalomyelitis, a neurology consultation can be useful when indicated. The main non-pharmacological treatment modalities are cognitive behavior therapy and graded exercise therapy. There is a wide range of medications that can be used for CFS. They range from NSAIDs to antidepressants. A broad range of differential diagnoses should be considered before diagnosing chronic fatigue syndrome. However, to improve outcomes, consultation with an interprofessional group of specialists is recommended.

References

[1] Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Military medicine. 2015 Jul [PubMed PMID: 26126237]

[2] Hickie I,Bennett B,Lloyd A,Heath A,Martin N, Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: a twin study. Psychological medicine. 1999 Mar; [PubMed PMID: 10218918]

[3] Hickie I,Kirk K,Martin N, Unique genetic and environmental determinants of prolonged fatigue: a twin study. Psychological medicine. 1999 Mar; [PubMed PMID: 10218917]

1999 Mar; [PubMed PMID: 10218917]

[4] Buchwald D,Herrell R,Ashton S,Belcourt M,Schmaling K,Sullivan P,Neale M,Goldberg J, A twin study of chronic fatigue. Psychosomatic medicine. 2001 Nov-Dec [PubMed PMID: 11719632]

[5] Whistler T,Jones JF,Unger ER,Vernon SD, Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. BMC physiology. 2005 Mar 24; [PubMed PMID: 15790422]

[6] Zhang L,Gough J,Christmas D,Mattey DL,Richards SC,Main J,Enlander D,Honeybourne D,Ayres JG,Nutt DJ,Kerr JR, Microbial infections in eight genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis. Journal of clinical pathology. 2010 Feb; [PubMed PMID: 19955554]

[7] Myalgic encephalomyelitis: International Consensus Criteria. Journal of internal medicine. 2017 Oct; [PubMed PMID: 28929634]

[8] DuBois RE,Seeley JK,Brus I,Sakamoto K,Ballow M,Harada S,Bechtold TA,Pearson G,Purtilo DT, Chronic mononucleosis syndrome. Southern medical journal. 1984 Nov; [PubMed PMID: 6093268]

[9] Jacobson SK,Daly JS,Thorne GM,McIntosh K, Chronic parvovirus B19 infection resulting in chronic fatigue syndrome: case history and review. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1997 Jun [PubMed PMID: 9195056]

[10] Ortega-Hernandez OD,Shoenfeld Y, Infection, vaccination, and autoantibodies in chronic fatigue syndrome, cause or coincidence? Annals of the New York Academy of Sciences. 2009 Sep [PubMed PMID: 19758205]

[11] Manian FA, Simultaneous measurement of antibodies to Epstein-Barr virus, human herpesvirus 6, herpes simplex virus types 1 and 2, and 14 enteroviruses in chronic fatigue syndrome: is there evidence of activation of a nonspecific polyclonal immune response? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1994 Sep; [PubMed PMID: 7811864]

[12] Loebel M,Strohschein K,Giannini C,Koelsch U,Bauer S,Doebis C,Thomas S,Unterwalder N,von Baehr V,Reinke P,Knops M,Hanitsch LG,Meisel C,Volk HD,Scheibenbogen C, Deficient EBV-specific B- and T-cell response in patients with chronic fatigue syndrome. PloS one. 2014; [PubMed PMID: 24454857]

[13] Loebel M,Eckey M,Sotzny F,Hahn E,Bauer S,Grabowski P,Zerweck J,Holenya P,Hanitsch LG,Wittke K,Borchmann P,Rüffer JU,Hiepe F,Ruprecht K,Behrends U,Meindl C,Volk HD,Reimer U,Scheibenbogen C, Serological profiling of the EBV immune response in Chronic Fatigue Syndrome using a peptide microarray. PloS one. 2017; [PubMed PMID: 28604802]

[14] Ablashi DV,Eastman HB,Owen CB,Roman MM,Friedman J,Zabriskie JB,Peterson DL,Pearson GR,Whitman JE, Frequent HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2000 May; [PubMed PMID: 10738137]

[15] Chapenko S,Krumina A,Kozireva S,Nora Z,Sultanova A,Viksna L,Murovska M, Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2006 Dec; [PubMed PMID: 17276369]

[16] Frémont M,Metzger K,Rady H,Hulstaert J,De Meirleir K, Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients. In vivo (Athens, Greece). 2009 Mar-Apr; [PubMed PMID: 19414405]

[17] Aoki R,Kobayashi N,Suzuki G,Kuratsune H,Shimada K,Oka N,Takahashi M,Yamadera W,Iwashita M,Tokuno S,Nibuya M,Tanichi M,Mukai Y,Mitani K,Kondo K,Ito H,Nakayama K, Human herpesvirus 6 and 7 are biomarkers for fatigue, which distinguish between physiological fatigue and pathological fatigue. Biochemical and biophysical research communications. 2016 Sep 9; [PubMed PMID: 27396623]

[18] Kerr JR, The role of parvovirus B19 in the pathogenesis of autoimmunity and autoimmune disease. Journal of clinical pathology. 2016 Apr; [PubMed PMID: 26644521]

[19] Kerr JR,Barah F,Mattey DL,Laing I,Hopkins SJ,Hutchinson IV,Tyrrell DAJ, Circulating tumour necrosis factor-alpha and interferon-gamma are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. The Journal of general virology. 2001 Dec; [PubMed PMID: 11714978]

[20] Barker E,Fujimura SF,Fadem MB,Landay AL,Levy JA, Immunologic abnormalities associated with chronic fatigue syndrome. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1994 Jan; [PubMed PMID: 8148441]

[21] Bradley AS,Ford B,Bansal AS, Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls. Clinical and experimental immunology. 2013 Apr; [PubMed PMID: 23480187]

[22] Mensah F,Bansal A,Berkovitz S,Sharma A,Reddy V,Leandro MJ,Cambridge G, Extended B cell phenotype in patients with myalgic encephalomyelitis/chronic fatigue syndrome: a cross-sectional study. Clinical and experimental immunology. 2016 May; [PubMed PMID: 26646713]

[23] Guenther S,Loebel M,Mooslechner AA,Knops M,Hanitsch LG,Grabowski P,Wittke K,Meisel C,Unterwalder N,Volk HD,Scheibenbogen C, Frequent IgG subclass and mannose binding lectin deficiency in patients with chronic fatigue syndrome. Human immunology. 2015 Oct; [PubMed PMID: 26429318]

[24] Löbel M,Mooslechner AA,Bauer S,Günther S,Letsch A,Hanitsch LG,Grabowski P,Meisel C,Volk HD,Scheibenbogen C, Polymorphism in COMT is associated with IgG3 subclass level and susceptibility to infection in patients with chronic fatigue syndrome. Journal of translational medicine. 2015 Aug 14; [PubMed PMID: 26272340]

[25] Konstantinov K,von Mikecz A,Buchwald D,Jones J,Gerace L,Tan EM, Autoantibodies to nuclear envelope antigens in chronic fatigue syndrome. The Journal of clinical investigation. 1996 Oct 15; [PubMed PMID: 8878441]

[26] Nishikai M,Tomomatsu S,Hankins RW,Takagi S,Miyachi K,Kosaka S,Akiya K, Autoantibodies to a 68/48 kDa protein in chronic fatigue syndrome and primary fibromyalgia: a possible marker for hypersomnia and cognitive disorders. Rheumatology (Oxford, England). 2001 Jul; [PubMed PMID: 11477286]

[27] Loebel M,Grabowski P,Heidecke H,Bauer S,Hanitsch LG,Wittke K,Meisel C,Reinke P,Volk HD,Fluge Ø,Mella O,Scheibenbogen C, Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. Brain, behavior, and immunity. 2016 Feb; [PubMed PMID: 26399744]

[28] von Mikecz A,Konstantinov K,Buchwald DS,Gerace L,Tan EM, High frequency of autoantibodies to insoluble cellular antigens in patients with chronic fatigue syndrome. Arthritis and rheumatism. 1997 Feb; [PubMed PMID: 9041942]

[29] Richman JA,Flaherty JA,Rospenda KM, Chronic fatigue syndrome: have flawed assumptions been derived from treatment-based studies? American journal of public health. 1994 Feb; [PubMed PMID: 8296954]

[30] Jason LA,Richman JA,Rademaker AW,Jordan KM,Plioplys AV,Taylor RR,McCready W,Huang CF,Plioplys S, A community-based study of chronic fatigue syndrome. Archives of internal medicine. 1999 Oct 11; [PubMed PMID: 10527290]

[31] Steele L,Dobbins JG,Fukuda K,Reyes M,Randall B,Koppelman M,Reeves WC, The epidemiology of chronic fatigue in San Francisco. The American journal of medicine. 1998 Sep 28; [PubMed PMID: 9790487]

[32] Fukuda K,Dobbins JG,Wilson LJ,Dunn RA,Wilcox K,Smallwood D, An epidemiologic study of fatigue with relevance for the chronic fatigue syndrome. Journal of psychiatric research. 1997 Jan-Feb; [PubMed PMID: 9201644]

[33] Wessely S,Chalder T,Hirsch S,Wallace P,Wright D, The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. American journal of public health. 1997 Sep; [PubMed PMID: 9314795]

[34] Reyes M,Gary HE Jr,Dobbins JG,Randall B,Steele L,Fukuda K,Holmes GP,Connell DG,Mawle AC,Schmid DS,Stewart JA,Schonberger LB,Gunn WJ,Reeves WC, Surveillance for chronic fatigue syndrome--four U.S. cities, September 1989 through August 1993. MMWR. CDC surveillance summaries : Morbidity and mortality weekly report. CDC surveillance summaries. 1997 Feb 21; [PubMed PMID: 12412768]

[35] Buchwald D,Umali P,Umali J,Kith P,Pearlman T,Komaroff AL, Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system. Annals of internal medicine. 1995 Jul 15; [PubMed PMID: 7778839]

[36] Lawrie SM,Pelosi AJ, Chronic fatigue syndrome in the community. Prevalence and associations. The British journal of psychiatry : the journal of mental science. 1995 Jun; [PubMed PMID: 7663830]

[37] Bierl C,Nisenbaum R,Hoaglin DC,Randall B,Jones AB,Unger ER,Reeves WC, Regional distribution of fatiguing illnesses in the United States: a pilot study. Population health metrics. 2004 Feb 4; [PubMed PMID: 14761250]

[38] Vincent A,Brimmer DJ,Whipple MO,Jones JF,Boneva R,Lahr BD,Maloney E,St Sauver JL,Reeves WC, Prevalence, incidence, and classification of chronic fatigue syndrome in Olmsted County, Minnesota, as estimated using the Rochester Epidemiology Project. Mayo Clinic proceedings. 2012 Dec; [PubMed PMID: 23140977]

[39] Lorusso L,Mikhaylova SV,Capelli E,Ferrari D,Ngonga GK,Ricevuti G, Immunological aspects of chronic fatigue syndrome. Autoimmunity reviews. 2009 Feb; [PubMed PMID: 18801465]

[39] Lorusso L,Mikhaylova SV,Capelli E,Ferrari D,Ngonga GK,Ricevuti G, Immunological aspects of chronic fatigue syndrome. Autoimmunity reviews. 2009 Feb [PubMed PMID: 18801465]

[40] Marshall-Gradisnik S,Huth T,Chacko A,Johnston S,Smith P,Staines D, Natural killer cells and single nucleotide polymorphisms of specific ion channels and receptor genes in myalgic encephalomyelitis/chronic fatigue syndrome. The application of clinical genetics. 2016; [PubMed PMID: 27099524]

[41] Kennedy G,Spence VA,McLaren M,Hill A,Underwood C,Belch JJ, Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. Free radical biology [PubMed PMID: 16085177]

[42] Kennedy G,Khan F,Hill A,Underwood C,Belch JJ, Biochemical and vascular aspects of pediatric chronic fatigue syndrome. Archives of pediatrics [PubMed PMID: 20819963]

[43] Maes M, Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Current opinion in psychiatry. 2009 Jan; [PubMed PMID: 19127706]

[44] Morris G,Maes M, Mitochondrial dysfunctions in myalgic encephalomyelitis/chronic fatigue syndrome explained by activated immuno-inflammatory, oxidative and nitrosative stress pathways. Metabolic brain disease. 2014 Mar; [PubMed PMID: 24557875]

[45] Schoeman EM,Van Der Westhuizen FH,Erasmus E,van Dyk E,Knowles CV,Al-Ali S,Ng WF,Taylor RW,Newton JL,Elson JL, Clinically proven mtDNA mutations are not common in those with chronic fatigue syndrome. BMC medical genetics. 2017 Mar 16; [PubMed PMID: 28302057]

[46] Billing-Ross P,Germain A,Ye K,Keinan A,Gu Z,Hanson MR, Mitochondrial DNA variants correlate with symptoms in myalgic encephalomyelitis/chronic fatigue syndrome. Journal of translational medicine. 2016 Jan 20; [PubMed PMID: 26791940]

[47] Finsterer J,Zarrouk-Mahjoub S, Is chronic fatigue syndrome truly associated with haplogroups or mtDNA single nucleotide polymorphisms? Journal of translational medicine. 2016 Jun 18; [PubMed PMID: 27317438]

[48] Nijs J,De Meirleir K, Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. In vivo (Athens, Greece). 2005 Nov-Dec; [PubMed PMID: 16277015]

[49] Michel T,Poli A,Cuapio A,Briquemont B,Iserentant G,Ollert M,Zimmer J, Human CD56bright NK Cells: An Update. Journal of immunology (Baltimore, Md. : 1950). 2016 Apr 1; [PubMed PMID: 26994304]

[50] Poli A,Michel T,Thérésine M,Andrès E,Hentges F,Zimmer J, CD56bright natural killer (NK) cells: an important NK cell subset. Immunology. 2009 Apr; [PubMed PMID: 19278419]

[51] Brenu EW,Huth TK,Hardcastle SL,Fuller K,Kaur M,Johnston S,Ramos SB,Staines DR,Marshall-Gradisnik SM, Role of adaptive and innate immune cells in chronic fatigue syndrome/myalgic encephalomyelitis. International immunology. 2014 Apr; [PubMed PMID: 24343819]

[52] Maes M,Twisk FN,Kubera M,Ringel K,Leunis JC,Geffard M, Increased IgA responses to the LPS of commensal bacteria is associated with inflammation and activation of cell-mediated immunity in chronic fatigue syndrome. Journal of affective disorders. 2012 Feb; [PubMed PMID: 21967891]

[53] Maes M,Mihaylova I,Leunis JC, Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability. Journal of affective disorders. 2007 Apr; [PubMed PMID: 17007934]

[54] Sotzny F,Blanco J,Capelli E,Castro-Marrero J,Steiner S,Murovska M,Scheibenbogen C, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome - Evidence for an autoimmune disease. Autoimmunity reviews. 2018 Jun; [PubMed PMID: 29635081]

[55] Ortega-Hernandez OD,Cuccia M,Bozzini S,Bassi N,Moscavitch S,Diaz-Gallo LM,Blank M,Agmon-Levin N,Shoenfeld Y, Autoantibodies, polymorphisms in the serotonin pathway, and human leukocyte antigen class II alleles in chronic fatigue syndrome: are they associated with age at onset and specific symptoms? Annals of the New York Academy of Sciences. 2009 Sep; [PubMed PMID: 19758204]

[56] Reynolds GK,Lewis DP,Richardson AM,Lidbury BA, Comorbidity of postural orthostatic tachycardia syndrome and chronic fatigue syndrome in an Australian cohort. Journal of internal medicine. 2014 Apr; [PubMed PMID: 24206536]

[57] Nakatomi Y,Mizuno K,Ishii A,Wada Y,Tanaka M,Tazawa S,Onoe K,Fukuda S,Kawabe J,Takahashi K,Kataoka Y,Shiomi S,Yamaguti K,Inaba M,Kuratsune H,Watanabe Y, Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(R)-PK11195 PET Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2014 Jun; [PubMed PMID: 24665088]

[58] Chen MK,Guilarte TR, Translocator protein 18 kDa (TSPO): molecular sensor of brain injury and repair. Pharmacology [PubMed PMID: 18374421]

PMID: 18374421]

[59] Glassford JA, The Neuroinflammatory Etiopathology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Frontiers in physiology. 2017; [PubMed PMID: 28261110]

[60] Svahn KS,Göransson U,Chryssanthou E,Olsen B,Sjölin J,Strömstedt AA, Induction of gliotoxin secretion in Aspergillus fumigatus by bacteria-associated molecules. PloS one. 2014; [PubMed PMID: 24705440]

[61] Yamashita M,Yamamoto T, Tryptophan circuit in fatigue: From blood to brain and cognition. Brain research. 2017 Nov 15; [PubMed PMID: 28893581]

[62] Cotel F,Exley R,Cragg SJ,Perrier JF, Serotonin spillover onto the axon initial segment of motoneurons induces central fatigue by inhibiting action potential initiation. Proceedings of the National Academy of Sciences of the United States of America. 2013 Mar 19; [PubMed PMID: 23487756]

[63] Liu JZ,Yao B,Siemionow V,Sahgal V,Wang X,Sun J,Yue GH, Fatigue induces greater brain signal reduction during sustained than preparation phase of maximal voluntary contraction. Brain research. 2005 Sep 28; [PubMed PMID: 16129419]

[64] Hall DL,Lattie EG,Antoni MH,Fletcher MA,Czaja S,Perdomo D,Klimas NG, Stress management skills, cortisol awakening response, and post-exertional malaise in Chronic Fatigue Syndrome. Psychoneuroendocrinology. 2014 Nov; [PubMed PMID: 25049069]

[65] Wallis A,Ball M,McKechnie S,Butt H,Lewis DP,Bruck D, Examining clinical similarities between myalgic encephalomyelitis/chronic fatigue syndrome and D-lactic acidosis: a systematic review. Journal of translational medicine. 2017 Jun 7; [PubMed PMID: 28592308]

[66] Vermeulen RC,Kurk RM,Visser FC,Sluiter W,Scholte HR, Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. Journal of translational medicine. 2010 Oct 11; [PubMed PMID: 20937116]

[67] MacDonald KL,Osterholm MT,LeDell KH,White KE,Schenck CH,Chao CC,Persing DH,Johnson RC,Barker JM,Peterson PK, A case-control study to assess possible triggers and cofactors in chronic fatigue syndrome. The American journal of medicine. 1996 May; [PubMed PMID: 8644768]

[68] Salit IE, Precipitating factors for the chronic fatigue syndrome. Journal of psychiatric research. 1997 Jan-Feb; [PubMed PMID: 9201648]

[69] Rowe PC,Underhill RA,Friedman KJ,Gurwitt A,Medow MS,Schwartz MS,Speight N,Stewart JM,Vallings R,Rowe KS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer. Frontiers in pediatrics. 2017; [PubMed PMID: 28674681]

[70] Clauw DJ, Perspectives on fatigue from the study of chronic fatigue syndrome and related conditions. PM [PubMed PMID: 20656623]

[71] Cockshell SJ,Mathias JL, Cognitive functioning in chronic fatigue syndrome: a meta-analysis. Psychological medicine. 2010 Aug; [PubMed PMID: 20047703]

[72] Bested AC,Marshall LM, Review of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: an evidence-based approach to diagnosis and management by clinicians. Reviews on environmental health. 2015; [PubMed PMID: 26613325]

[73] Komaroff AL,Fagioli LR,Geiger AM,Doolittle TH,Lee J,Kornish RJ,Gleit MA,Guerriero RT, An examination of the working case definition of chronic fatigue syndrome. The American journal of medicine. 1996 Jan; [PubMed PMID: 8579088]

[74] Sharpe MC,Archard LC,Banatvala JE,Borysiewicz LK,Clare AW,David A,Edwards RH,Hawton KE,Lambert HP,Lane RJ, A report--chronic fatigue syndrome: guidelines for research. Journal of the Royal Society of Medicine. 1991 Feb; [PubMed PMID: 1999813]

[75] Afari N,Buchwald D, Chronic fatigue syndrome: a review. The American journal of psychiatry. 2003 Feb; [PubMed PMID: 12562565]

[76] Bombardier CH,Buchwald D, Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. Medical care. 1996 Sep; [PubMed PMID: 8792781]

[77] White PD,Goldsmith KA,Johnson AL,Potts L,Walwyn R,DeCesare JC,Baber HL,Burgess M,Clark LV,Cox DL,Bavinton J,Angus BJ,Murphy G,Murphy M,O'Dowd H,Wilks D,McCrone P,Chalder T,Sharpe M, Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet (London, England). 2011 Mar 5; [PubMed PMID: 21334061]

[78] Larun L,Brurberg KG,Odgaard-Jensen J,Price JR, Exercise therapy for chronic fatigue syndrome. The Cochrane database of systematic reviews. 2016 Jun 24; [PubMed PMID: 27339435]

[79] Sharpe M,Goldsmith KA,Johnson AL,Chalder T,Walker J,White PD, Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. The lancet. Psychiatry. 2015 Dec; [PubMed PMID: 26521770]

[80] Fukuda K,Straus SE,Hickie I,Sharpe MC,Dobbins JG,Komaroff A, The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Annals of internal medicine. 1994 Dec 15; [PubMed PMID: 7978722]

[81] Clayton EW, Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness. JAMA. 2015 Mar 17; [PubMed PMID: 25668027]

[82] Jason LA,Sunnquist M, The Development of the DePaul Symptom Questionnaire: Original, Expanded, Brief, and Pediatric Versions. Frontiers in pediatrics. 2018; [PubMed PMID: 30460215]

[83] Wagner D,Nisenbaum R,Heim C,Jones JF,Unger ER,Reeves WC, Psychometric properties of the CDC Symptom Inventory for assessment of chronic fatigue syndrome. Population health metrics. 2005 Jul 22; [PubMed PMID: 16042777]

[84] Baker R,Shaw EJ, Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE guidance. BMJ (Clinical research ed.). 2007 Sep 1; [PubMed PMID: 17762037]

[85] 2007 Aug; [PubMed PMID: 21563329]

[86] O'Dowd H,Gladwell P,Rogers CA,Hollinghurst S,Gregory A, Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health technology assessment (Winchester, England). 2006 Oct; [PubMed PMID: 17014748]

[87] Deale A,Husain K,Chalder T,Wessely S, Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. The American journal of psychiatry. 2001 Dec; [PubMed PMID: 11729022]

[88] Vos-Vromans DC,Smeets RJ,Huijnen IP,Köke AJ,Hitters WM,Rijnders LJ,Pont M,Winkens B,Knottnerus JA, Multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome: a randomized controlled trial. Journal of internal medicine. 2016 Mar; [PubMed PMID: 26306716]

[89] Nijhof SL,Bleijenberg G,Uiterwaal CS,Kimpen JL,van de Putte EM, Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet (London, England). 2012 Apr 14; [PubMed PMID: 22385683]

[90] Powell P,Bentall RP,Nye FJ,Edwards RH, Patient education to encourage graded exercise in chronic fatigue syndrome. 2-year follow-up of randomised controlled trial. The British journal of psychiatry : the journal of mental science. 2004 Feb; [PubMed PMID: 14754826]

[91] Moss-Morris R,Sharon C,Tobin R,Baldi JC, A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. Journal of health psychology. 2005 Mar; [PubMed PMID: 15723894]

[92] Li SH,Sandler CX,Casson SM,Cassar J,Bogg T,Lloyd AR,Barry BK, Randomised controlled trial of online continuing education for health professionals to improve the management of chronic fatigue syndrome: a study protocol. BMJ open. 2017 May 10; [PubMed PMID: 28495811]

[93] Castro-Marrero J,Sáez-Francàs N,Santillo D,Alegre J, Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome. British journal of pharmacology. 2017 Mar; [PubMed PMID: 28052319]

[94] Theoharides TC,Asadi S,Weng Z,Zhang B, Serotonin-selective reuptake inhibitors and nonsteroidal anti-inflammatory drugs--important considerations of adverse interactions especially for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome. Journal of clinical psychopharmacology. 2011 Aug; [PubMed PMID: 21694612]

[95] Degenhardt L,Gisev N,Cama E,Nielsen S,Larance B,Bruno R, The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. Pharmacoepidemiology and drug safety. 2016 May; [PubMed PMID: 26781123]

[96] Clemons A,Vasiadi M,Kempuraj D,Kourelis T,Vandoros G,Theoharides TC, Amitriptyline and prochlorperazine inhibit proinflammatory mediator release from human mast cells: possible relevance to chronic fatigue syndrome. Journal of clinical psychopharmacology. 2011 Jun; [PubMed PMID: 21532369]

[97] Sanders P,Korf J, Neuroaetiology of chronic fatigue syndrome: an overview. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2008; [PubMed PMID: 17853290]

[98] Jason L,Benton M,Torres-Harding S,Muldowney K, The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient education and counseling. 2009 Nov; [PubMed PMID: 19356884]

[99] Strayer DR,Carter WA,Brodsky I,Cheney P,Peterson D,Salvato P,Thompson C,Loveless M,Shapiro DE,Elsasser W, A controlled clinical trial with a specifically configured RNA drug, poly(I).poly(C12U), in chronic fatigue syndrome. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1994 Jan; [PubMed PMID: 8148460]

[100] Brook MG,Bannister BA,Weir WR, Interferon-alpha therapy for patients with chronic fatigue syndrome. The Journal of infectious diseases. 1993 Sep; [PubMed PMID: 8354926]

[101] Cleare AJ,Reid S,Chalder T,Hotopf M,Wessely S, Chronic fatigue syndrome. BMJ clinical evidence. 2015 Sep 28; [PubMed PMID: 26415100]

[102] Chambers D,Bagnall AM,Hempel S,Forbes C, Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. Journal of the Royal Society of Medicine. 2006 Oct; [PubMed PMID: 17021301]

[103] Smith ME,Haney E,McDonagh M,Pappas M,Daeges M,Wasson N,Fu R,Nelson HD, Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Annals of internal medicine. 2015 Jun 16; [PubMed PMID: 26075755]

[104] Whiting P,Bagnall AM,Sowden AJ,Cornell JE,Mulrow CD,Ramírez G, Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. JAMA. 2001 Sep 19; [PubMed PMID: 11560542]

[105] Fluge Ø,Bruland O,Risa K,Storstein A,Kristoffersen EK,Sapkota D,Næss H,Dahl O,Nyland H,Mella O, Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PloS one. 2011; [PubMed PMID: 22039471]

[106] Fluge Ø,Rekeland IG,Lien K,Thürmer H,Borchgrevink PC,Schäfer C,Sørland K,Aßmus J,Ktoridou-Valen I,Herder I,Gotaas ME,Kvammen Ø,Baranowska KA,Bohnen LMLJ,Martinsen SS,Lonar AE,Solvang AH,Gya AES,Bruland O,Risa K,Alme K,Dahl O,Mella O, B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Annals of internal medicine. 2019 May 7; [PubMed PMID: 30934066]

[107] Brüssow H, Biome engineering-2020. Microbial biotechnology. 2016 Sep; [PubMed PMID: 27471167]

[108] Smits LP,Bouter KE,de Vos WM,Borody TJ,Nieuwdorp M, Therapeutic potential of fecal microbiota transplantation. Gastroenterology. 2013 Nov; [PubMed PMID: 24018052]

[109] Bibbò S,Ianiro G,Gasbarrini A,Cammarota G, Fecal microbiota transplantation: past, present and future perspectives. Minerva gastroenterologica e dietologica. 2017 Dec; [PubMed PMID: 28927251]

[110] Giloteaux L,Goodrich JK,Walters WA,Levine SM,Ley RE,Hanson MR, Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome. 2016 Jun 23; [PubMed PMID: 27338587]

[111] Frémont M,Coomans D,Massart S,De Meirleir K, High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. Anaerobe. 2013 Aug; [PubMed PMID: 23791918]

[112] Navaneetharaja N,Griffiths V,Wileman T,Carding SR, A Role for the Intestinal Microbiota and Virome in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)? Journal of clinical medicine. 2016 Jun 6; [PubMed PMID: 27275835]

[113] Wallis A,Butt H,Ball M,Lewis DP,Bruck D, Support for the microgenderome invites enquiry into sex differences. Gut microbes. 2017 Jan 2; [PubMed PMID: 27808584]

[114] Guo HJ,Sapra A, Instrumental Activity of Daily Living (IADL) . 2020 Jan [PubMed PMID: 31985920]

[115] Treisman R, Identification and purification of a polypeptide that binds to the c-fos serum response element. The EMBO journal. 1987 Sep; [PubMed PMID: 3119326]

Lee HM,Sugino H,Nishimoto N, Cytokine networks in systemic lupus erythematosus. Journal of biomedicine [PubMed PMID:

[116] 20414360]

[117] Davis MC,Zautra AJ,Younger J,Motivala SJ,Attrep J,Irwin MR, Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. Brain, behavior, and immunity. 2008 Jan; [PubMed PMID: 17706915]

[118] Harboe E,Tjensvoll AB,Vefring HK,Gøransson LG,Kvaløy JT,Omdal R, Fatigue in primary Sjögren's syndrome--a link to sickness behaviour in animals? Brain, behavior, and immunity. 2009 Nov; [PubMed PMID: 19560535]

[119] Stadje R,Dornieden K,Baum E,Becker A,Biroga T,Bösner S,Haasenritter J,Keunecke C,Viniol A,Donner-Banzhoff N, The differential diagnosis of tiredness: a systematic review. BMC family practice. 2016 Oct 20; [PubMed PMID: 27765009]

[120] Sekhon S,Patel J,Sapra A, Late Onset Depression . 2020 Jan [PubMed PMID: 31855351]

[121] Budh DP,Sapra A, Cancer Breast Screening . 2020 Jan [PubMed PMID: 32310510]

[122] Bower JE,Ganz PA,Irwin MR,Arevalo JM,Cole SW, Fatigue and gene expression in human leukocytes: increased NF-κB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. Brain, behavior, and immunity. 2011 Jan; [PubMed PMID: 20854893]

[123] Kwak SM,Choi YS,Yoon HM,Kim DG,Song SH,Lee YJ,Yeom CH,Koh SJ,Park J,Lee MA,Suh SY, The relationship between interleukin-6, tumor necrosis factor-α, and fatigue in terminally ill cancer patients. Palliative medicine. 2012 Apr; [PubMed PMID: 21807751]

[124] Thornton LM,Andersen BL,Blakely WP, The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2010 May; [PubMed PMID: 20496988]

[125] Bower JE,Ganz PA,Tao ML,Hu W,Belin TR,Sepah S,Cole S,Aziz N, Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009 Sep 1; [PubMed PMID: 19706826]

[126] Jelsness-Jørgensen LP,Bernklev T,Henriksen M,Torp R,Moum BA, Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. Inflammatory bowel diseases. 2011 Jul; [PubMed PMID: 21674713]

[127] Gold SM,Krüger S,Ziegler KJ,Krieger T,Schulz KH,Otte C,Heesen C, Endocrine and immune substrates of depressive symptoms and fatigue in multiple sclerosis patients with comorbid major depression. Journal of neurology, neurosurgery, and psychiatry. 2011 Jul; [PubMed PMID: 21296901]

[128] Sapra A,Malik A,Bhandari P, Vital Sign Assessment . 2020 Jan [PubMed PMID: 31985994]

[129] Al-shair K,Kolsum U,Dockry R,Morris J,Singh D,Vestbo J, Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. Respiratory research. 2011 Jan 5; [PubMed PMID: 21208443]

[130] Mills PJ,Kim JH,Bardwell W,Hong S,Dimsdale JE, Predictors of fatigue in obstructive sleep apnea. Sleep [PubMed PMID: 18516635]

Multicenter Study Further Debunks Link Between Chronic Fatigue Syndrome, Murine Viruses

GenomeWeb, 2012