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A Comprehensive Update of the Current Understanding of Chronic Fatigue Syndrome

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Abstract

This is a comprehensive literature review of chronic fatigue syndrome (CFS). We provide a description of the background, etiology, pathogenesis, diagnosis, and management regarding CFS. CFS is a multifaceted illness that has many symptoms and a wide array of clinical presentations. As of recent, CFS has been merged with myalgic encephalomyelitis (ME). Much of the difficulty in its management has stemmed from a lack of a concrete understanding of its etiology and pathogenesis. There is a potential association between dysfunction of the autoimmune, neuroendocrine, or autonomic nervous systems and the development of CFS. Possible triggering events, such as infections followed by an immune dysregulation resulting have also been proposed. In fact, ME/CFS was first described following Epstein Barr virus (EBV) infections, but it was later determined that it was not always preceded by EBV infection. Patient diagnosed with CFS have shown a noticeably earlier activation of anaerobic metabolism as a source of energy, which is suggestive of impaired oxygen consumption. The differential diagnoses range from tick-borne illnesses to psychiatric disorders to thyroid gland dysfunction. Given the many overlapping symptoms of CFS with other illnesses makes diagnosing it far from an easy task. The Centers for Disease Control and Prevention (CDC) considers it a diagnosing of exclusion, stating that self-reported fatigue for at minimum of six months and four of the following symptoms are necessary for a proper diagnosis: memory problems, sore throat, post-exertion malaise, tender cervical or axillary lymph nodes, myalgia, multi-joint pain, headaches, and troubled sleep. In turn, management of CFS is just as difficult. Treatment ranges from conservative, such as cognitive behavioral therapy (CBT) and antidepressants, to minimally invasive management. Minimally invasive management involving ranscutaneous electrical acupoint stimulation of target points has demonstrated significant improvement in fatigue and associated symptoms in a 2017 randomized controlled study. The understanding of CFS is evolving before us as we continue to learn more about it. As further reliable studies are conducted, providing a better grasp of what the syndrome encompasses, we will be able to improve our diagnosis and management of it.

Keywords: Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, Systemic Exertion Intolerance Disease, Chronic Fatigue Immune Disorder

1. Context

Chronic fatigue syndrome (CFS) is a multifaceted illness with a wide array of symptoms, potential etiological causes and prognoses. Similarly, naming of the condition has proven to be equally as complex with multiple accepted alternatives such as myalgic encephalomyelitis (ME), chronic fatigue immune disorder syndrome (CFIDS) and systemic exertion intolerance disease (SEID) (1).

CFS alone tends to oversimplify the complexity of the disease and undermine the constellation of symptoms experienced by patients. Thus, more recent merging of CFS

and ME, also known as ME/CFS has been described to better encompass the complexity of the disease and its neuroinflammatory components (2). Individual criteria for CFS and ME share overlapping symptoms of fatigue, neurocognitive dysfunction, disturbed sleep and autonomic dysfunction. In contrast, a required infective agent is unique to ME and is a major criteria component. However, this is considered a minor symptom/optional criteria for joint ME/CFS and further proves the merged term to be more encompassing than either CFS or ME alone (3). At the core of ME/CFS is a persistent and disabling fatigue that results in a significant reduction in activity for greater than six months. Furthermore, worsening of symptoms after mild physical and/or mental exertion is a key feature of ME/CFS and referred to as post-exertional malaise (4). Unrefreshing sleep, cognitive dysfunction including attention or concentration difficulties as well as orthostatic intolerance are further findings common to ME/CFS patients (1).

In addition to potential trivialization of the disease, the term chronic fatigue syndrome (CFS) complicates its distinction from idiopathic chronic fatigue (ICF). Fatigue is a common complaint and can be idiopathic or a symptomatic component of various illnesses. An individual's perception of fatigue is subjective and can be perceived differently in relation to not only physical stress, but also psychological and social stress (5). For the same reason that detection and quantification of fatigue is difficult, finding an accurate diagnostic test for ME/CFS has been complicated, as well. Despite seemingly similar features, there are clinical distinctions between experiencing fatigue (ICF) and suffering from chronic fatigue syndrome (ME/CFS). According to the Institute of Medicine Diagnostic Criteria, ME/CFS requires the presence of one or more of the following: cognitive impairment and/or orthostatic intolerance (6). In contrast, little to none of these symptoms are reported in ICF (2). This suggests that CFS is likely of different etiology with additional clinical features and not simply located on the upper spectrum of general fatigue or ICF.

Research into ME/CFS etiology and potential treatment management is important due to its ability to extend beyond the effects on a patient's body. ME/CFS takes a toll on social, family and work life of the individuals affected. A study of middle school-aged students with ME/CFS were reported to have characteristic symptoms such as irritability and being afraid to go to school (7). Extending into adulthood, individuals report economic difficulties due to the loss or inability to attain manageable employment (5). Without more discussion and acceptance in medical research and practice, further misconception, unawareness and misdiagnoses will persist. The goal of this paper is to advocate for better awareness, discussion and provide an up-to-date review on ME/CFS. The evolving history of ME/CFS and the lack of a universally accepted name, criteria, and etiology fuels an already present hesitancy to make the diagnosis. Awareness of the controversial and somewhat subjective definition of ME/CFS and its diagnostic criteria is important in allowing physicians to appreciate the complexity of the disease and its wide array of presentations.

2. Epidemiology

ME/CFS has long left researchers not only questioning its etiological origin, but also the best approach to diagnoses and management. Whilst the cause of CFS remains unknown, popular hypotheses include infectious triggers, microbiome disruption, immune response dysregulation, endocrine abnormalities and intracellular dysfunction such as in the mitochondria (8). However, these various hypotheses hold the common belief that the onset of dysfunction leading to ME/CFS occurs in an already genetically susceptible population (6). It is possible that all of these hypotheses play a role in the etiology of ME/CFS and perhaps there are further subsets of ME/CFS that have yet to be described.

2.1. Gender & Age Risks

Research into sex and age-specific incidence rates has demonstrated two distinct age peaks of ME/CFS. The first peak incidence occurs in the age group 10- to 19-year-olds, and the second in the 30- to 39-year-olds (9). Separate studies of men and those of women demonstrated these two peaks in incidence. However, the pattern was described as more distinct in women, while the second peak was less pronounced in men (9). Similar to many disorders of immune dysregulation, women appear to be more affected than men and represent the majority of the ME/CFS research participants. A study compared gender differences in ME/CFS and despite the smaller male sample size, gender differences were reported. Data showed the age of onset to be younger in males in comparison to females and was often triggered by an infectious process (10). Males also reported less muscle, immunological and neurovegetative symptoms, as well as a better overall quality-of-life in regard to pain and physical functioning. Despite certain differences, both sexes reported similar symptoms of unrefreshing sleep, a core manifestation of ME/CFS (10). Due to the small sample size and overall small male population with ME/CFS, it is difficult to accurately determine whether females are truly more at risk of ME/CFS or whether the disease manifests differently in males, and therefore goes undescribed.

2.2. Infectious Triggers & Immune Dysregulation

Infectious triggering of a chronic inflammatory response has long been a hypothesized risk factor for the development of ME/CFS due to the large number of individuals with a history of infection prior to the onset of symptoms. In fact, ME/CFS was first described in reference to a post-Epstein Barr fatigue (11). However, infection prior to its onset is not true of all ME/CFS patients, thus its etiological significance remains uncertain. Infectious triggers are suggested to contribute to development of ME/CFS through disruption of not only the immune response, but also mitochondrial functioning and other cellular processes (12). A wide range of microorganisms have been described in relation to CFS with varying mechanisms of pathogenesis. However, a shared ability to establish persistent infections and often be detected in healthy individuals provides further clues on ME/CFS etiology (12, 13). For this reason, the risk of ME/CFS is likely more so related to the presence of an underlying genetic predisposition that upon infection, allows for a dysregulated response and impaired clearance, suggesting ME/CFS etiology is more likely a result of the host's dysregulated immune response rather than the infection itself (6). Individuals with inflammatory bowel disease (IBD) have been shown to be at increased risk of ME/CFS compared to the general population (14). The specific pathogenesis of IBD remains uncertain; however, the theorized abnormal immune response to intestinal flora mirrors the dysregulation seen in ME/CFS. With this, research has placed focus on regulation abnormalities in pathways of the immune response. However, a recent systematic review of research regarding circulating cytokines in ME/CFS has highlighted inconclusive results among studies. Inconsistent and contradictory data suggest circulating cytokine levels may be more so indicative of coexisting inflammatory processes rather than ME/CFS itself (15). Perhaps dysfunction at the level of the immune cells themselves should be further researched as an alternative. Reduced natural killer (NK) cell function and cytotoxicity has been demonstrated to play a role in the immune dysregulation aspect of ME/CFS. NK cells play an important role in contributing to the elimination of infected cells, cytokine production, and immune activation (16). Cellular processes crucial to NK cell cytotoxicity and immune function rely on regulation of intracellular calcium through transient receptor potential (TRP) channels. While TRP channels can be found on many different tissues of the body, the melastatin-3 subfamily (TRPM3) is specifically expressed on NK and B lymphocytes (16). Compared to healthy controls, ME/CFS immune NK and B cells were found to have reduced expression of TRPM3, and therefore reduced calcium influx (17). TRPM3 gene associated single nucleotide polymorphism SNPs have also been reported in ME/CFS patients compared to controls (18). These findings demonstrate impaired immune NK cell cytotoxicity due to reduced surface receptor expression and its role in immune dysregulation. Furthermore, suggesting a genetic variation predisposing individuals to impaired clearance and increased risk of dysregulation in response to stressors.

2.3. Altered Energy Metabolism

Lipid and energy metabolism dysfunction are also thought to contribute to the etiology of ME/CFS. With exercise, ME/CFS patients have shown early activation of anaerobic metabolic pathways, suggesting impaired oxygen consumption (19). A recent study induced a ME/CFS-like fatigue in mice through repeated forced swimming. When compared to control groups, swim induced fatigue mice were found to have a decrease in pyruvate dehydrogenase (PDH) enzyme activity, a crucial enzyme for oxidative metabolism. PDH is responsible for converting pyruvate into acetyl-CoA under standard aerobic conditions. In contrast, under anaerobic conditions, PDH activity and, therefore linking of glycolysis to the Krebs cycle and oxidative phosphorylation is inhibited. This impairment leads to the accumulation of pyruvate and shunting towards anaerobic metabolism with an increased production of lactate (20). Impaired activity of essential metabolic enzymes such as PDH has been suggested to increase the risk for development of ME/CFS. Early conversion to less efficient anaerobic metabolism may also explain the characteristic post-exertional malaise reported in ME/CFS. Disruption in host intracellular function is another method infectious triggers can contribute in the development of ME/CFS. Viruses such as Epstein-Barr virus (EBV) can decrease mitochondrial DNA replication through direct protein interactions and promote the replication of viral DNA replication. While other viruses, such as HHV-6B and CMV influence mitochondrial functioning by increasing oxidative damage (12). Dysfunction in mitochondrial function and increased reactive oxygen species damage similarly contribute to symptoms of post-exertional malaise in ME/CFS.

2.4. Differential Diagnosis

Diagnosis of ME/CFS is difficult not only due to lack of diagnostic testing, but also due variability in its presentation and shared clinical symptoms with many conditions. Common differential diagnoses include Lyme disease and other tick-borne illnesses, psychiatric disorders, including depression, thyroid and adrenal gland dysfunction, various sleep disorders and other autoimmune diseases (19). Further complicating diagnosis is comorbid diseases which are common in ME/CFS and often co-exist with

overlapping symptoms. Many comorbid diseases have been reported, a few of which include mood disorders, irritable bowel syndrome, headaches, chronic pain, hypermobility and autonomic dysfunction (8). Fibromyalgia is another relatively common comorbid condition and was once thought to be a part of a shared spectrum of disease with ME/CFS. However, studies comparing CFS only patients to comorbid CFS and fibromyalgia patients, have demonstrated a distinct difference between the two conditions. Comparisons of patterns of sleep architecture show that patients with comorbid CFS and fibromyalgia experience additional symptoms of sleep disturbance that are not experienced in CFS only patients (4). Major depressive disorder (MDD) is another differential of psychiatric origin, which may present very similarly to ME/CFS. It is easy to understand how one could be mistaken for the other due to not only shared symptoms, but also shared risk factors and comorbidities (5). In fact, at one time ME/CFS itself was thought to be a psychosomatic illness and an atypical form of MDD. High rates of depression are seen in ME/CFS; however, it is not seen in all ME/CFS patients. Thus categorization as a purely psychiatric illness was dismissed in 2015 by the Institute of Medicine (IOM) (21). Whether high rates of depression are a result of one disorder affecting the other or simply due to a shared etiological pathway remains controversial. Nevertheless, recent research has shown that despite being closely interrelated ME/CFS and MDD are distinct disorders and should be clinically treated as such (22). Distinguishing between ME/CFS and other comorbid conditions is important for the best approach to management in order to address all underlying causes. Due to the vast variation in clinical presentation of CFS and lack of diagnostic test, the ability to recognize common comorbidities may be the only indication of potential disease presence itself.

3. Pathogenesis

The cause of CFS is unknown and likely multifactorial. Some questioned whether CFS is psychological in origin given its symptomatology and lack of diagnostic testing (23). However, there is a growing body of evidence supporting the role of dysfunction in immune, neuro-endocrine, and autonomic systems (23-25). Several biologically based theories are currently being pursued. It has been hypothesized that circulating cytokines may contribute to symptoms of CFS (26, 27). However, support for this notion is inconsistent and needs to be further explored (26, 27). Obstruction of the lymphatic system may produce low grade inflammation in the central nervous system (CNS) precipitating symptoms of CFS (23). Hypothalamic-pituitary-adrenal axis impairment may contribute to symptoms of fatigue and low mood (28). Alterations in methylation patterns have also been implicated as a potential mechanism in the susceptibility to or development of CFS (29).

3.1. Clinical Presentation and Implications

The clinical presentation of CFS is heterogeneous with the most common symptoms being mental and physical fatigue, cognitive dysfunction, and mood disturbances. Cognitive dysfunction has been subjectively reported and objectively measured in experiments (30, 31). Orthostatic hypotension is also common and may be debilitating (32). CFS may share similarities in presentation with idiopathic intracranial hypertension, and given that these are both diagnoses of exclusion affecting a similar patient population, it has been postulated that they may be related (33). Consequently, there is a need to develop objective measures rather than reliance on subjective reporting of symptoms (34). Understanding the pathogenesis of CFS is important in making accurate diagnoses and improving treatment and management. Children and adolescents with CFS have higher rates of school absenteeism, resulting in missed educational opportunities as well as valuable psychosocial experiences (35). Given the trend of recent data pointing towards a biological basis of CFS, novel treatments will likely be similarly directed (36).

4. Diagnosis

Diagnosis of CFS is difficult due to a lack of exposure in medical training resulting in missed diagnoses, variability in clinical diagnostic criteria, and fatigue being a common complaint in approximately twenty-five percent of primary care visits (1). CFS is a diagnosis of exclusion where it is important to rule out active diseases that share similar symptoms (1). Common presenting medical symptoms include pathological fatigue, malaise after exertion, muscle weakness, cramps, defective stress tolerance, sleep disturbances, autonomic dysfunction, pain, and neuroendocrine abnormalities (6). Diagnosing CFS is further complicated due to symptoms overlap with mental conditions such as anxiety and depression, which can become more intense with duration of time (5). Guidelines for diagnosing CFS vary across countries with differences including application of diagnosing criteria, excluding criteria, symptom treatment and management (7).

4.1. Clinical Criteria

Presence of disabling fatigue for a minimum duration of 6 months in adults and 3 months in children and adolescents that affects both physical and mental functioning is an important indicator in diagnosis (1, 4) The Centers for Disease Control and Prevention established that

after discounting any other links for chronic fatigue, self-reported fatigue for at least 6 months and four of the following symptoms are necessary for proper diagnosis: memory problems, sore throat, post-exertion malaise, tender cervical or axillary lymph nodes, myalgia, multi-joint pain, headaches, and troubled sleep (4). The heterogeneity of the disease symptoms underlies personalized patient treatments with differences in fatigue severity and physical and mental disorders guiding patient-centered approaches (8).

4.2. Biomarkers and Immune Pathways

Using machine learning and innovative procedures, researchers can combine biomarkers and clinical phenotypes to examine the underlying mechanism of action for a more accurate diagnosis (3). Although there are no established biomarkers of disease, CFS is observed to have activated immune pathways involving inflammation, intracellular signaling, nfkb pathways, autoimmune responses, oxidative stress pathways, decreased level of antioxidants, mitochondrial function impairment, increased systemic and cerebral lactate production, Gram-negative bacteria translocation causing gut dysbacteriosis, decreased B-acetyl aspartate metabolism, and atrophy of gray matter (37). Comparing blood samples from patients with CFS against healthy controls, new diagnostic biomarkers can be developed for objective monitoring of immune, endocrine, and metabolic dysfunction (9). Due to the prominent role of immune-inflammatory pathways in pathogenesis of CFS, normal cytokine levels of TNF-α, Interferons (interferon gamma), Interleukins (IL-6 and IL-1), TGF-β, CSF cytokines and aberrant expression of these agents can potentially guide detection and diagnosis of CFS (38).

4.3. Myalgic Encephalomyelitis

An international panel of physicians adapted a newly accepted diagnostic criteria claiming the 6-month time frame was unnecessary and preferred the name myalgic encephalomyelitis (ME) to associate the widespread inflammation and multisystemic neuropathology of the disease (36). A patient needed to meet the criteria for post-exertional neuroimmune exhaustion, one of three neurological impairment categories, one of three gastrointestinal impairment categories, and one symptom minimum of metabolic/transport impairments to be diagnosed with ME (36). Chronic Fatigue syndrome and myalgic encephalomyelitis being separate and independent diagnoses is controversial (39).

5. Treatment and Management

5.1. Conservative Management

At present, treatment of chronic fatigue syndrome (CFS) is directed at symptom management rather than curative intent. Therefore, treatment should be tailored to patient needs given the heterogeneity of symptoms in this patient population (40-42). Topics to be discussed when planning appropriate treatment include sleeping patterns, level of physical activity, and psychological symptoms (42). Treatments may be designed with respect to the biopsychosocial model and address all aspects which may precipitate, predispose, and perpetuate illness (42, 43). Possible treatments to be discussed in the management of CFS may be broadly categorized into the following groups: behavioral therapy, pharmacological therapy, complementary or alternative medicine, and dietary recommendations.

Current recommendations for treatment of CFS include cognitive behavioral therapy (CBT) and graded exercise therapy (GET). CBT challenges patients' thoughts and provides coping strategies with the intent to reduce stress and prevent exacerbation of symptoms (44). The efficacy of CBT via telemedicine is currently being explored and may expand accessibility and cost effectiveness of care (45). CBT may provide short term benefit but has not been associated with remission of symptoms (46). GET has been demonstrated to reduce fatigue and improve physical functioning through conditioning exercises of varying intensity (44, 47). Moderate exercise has been shown to decrease fatigue as well as improve sleep quality, physical function and view of health (48). Some have expressed frustration with the dominance of CBT and GET in literature regarding the treatment of CFS as it undermines the results of alternative treatments and may indirectly blame the patient for symptoms (43, 49). Additionally, this recommendation is often rejected by CFS patients due to feelings of being unheard or dismissed (50). Adaptive pacing therapy (APT), characterized by the avoidance of known triggers of fatigue and daily activity goals, has demonstrated inconsistent results in terms of symptomatic improvement (39, 51). Additionally, research is being conducted to assess the effect of individualized relaxation techniques, mindfulness, and heart rate variability on sleep quality and functioning in CFS (52).

Pharmacological treatment with antidepressants may seem intuitive given frequent comorbid psychological symptoms such as anxiety and depression, but its efficacy in CFS remains unclear (53). Likewise, given the association between CFS and viral illness, antiviral treatments have been suggested (53). Patients with known history of Epstein-Barr virus (EBV) showed improvement when

treated with valacyclovir but not acyclovir (53). Immune modulating agents have also been proposed as therapy given the association with CFS and immune dysfunction (53). These agents have been directed at various immune markers and shown inconsistent results (53). Additionally, management with stimulants, melatonin and acetylcholinesterase inhibitors have been inadequate (51).

The use of alternative medicine has been explored in patients with CFS due to lack of effective symptom control with traditional Western medicine. Traditional acupuncture techniques have been shown to be effective in reducing symptoms of fatigue (54, 55). Additionally, traditional acupuncture techniques have demonstrated decreased levels of stress and depressive symptoms (54). Jin's three-needle acupuncture technique (JTN) is currently being studied in the treatment of CFS as it has been previously used to promote wellness and treat depression (56). JTN varies from traditional acupuncture techniques in that it is more deliberate in the selection of acupoints (56). Qigong, a form of exercise with a concurrent emphasis on breath-work and meditation, has been shown to reduce symptoms of mental and physical fatigue as well as depression (57). Additionally, traditional Japanese medicine (shosaikoto-based treatment) has been reported to provide effective treatment of CFS in a pediatric patient (58). However, the efficacy of alternative medicine in CFS should be further explored as study design oftentimes could be improved (59).

Several dietary recommendations have been proposed in the management of CFS. Probiotic treatment has shown decreased gastrointestinal symptoms, levels of inflammatory markers, and anxiety but failed to alter levels of depression (60) However, these studies are limited and further research is needed to determine efficacy (60). Other hypotheses include supplementation with a variety of substances such as selenium, vitamin B12, NADH, coenzyme Q and folic acid (39, 61, 62). It is difficult to draw conclusions on the effectiveness of introducing dietary modifications in the management of CFS due to frequent poor study design and inconsistent findings (61). More information needs to be acquired on the pathogenesis of CFS before being able to make definitive dietary recommendations (61). Healthy diet and supplementation may be advised in the setting of inflammation and malabsorption (39).

The treatment of CFS is complex and requires frequent dialogue between physicians, patients, and other practitioners to be optimized to patient needs. Self-management interventions, requiring patient education and frequent self-assessment, may be effective in reducing fatigue (63). Further research is needed, particularly in the pediatric population, to make adequate treatment recommendations (64). Given the variety of treatment options, it appears that a personalized, multidisciplinary approach offers the greatest potential for effective symptom management and the possibility of remission.

6. Medical Management of CFS

Although there is no curative therapy for CFS, certain management options are available to reduce the severity of symptoms the patient experiences. Medical management is patient-dependent and targeted to balance rest and activity, which vary greatly depending on the patient's age, medical history, and background (19). Sleep, professional counseling, exercise, medications, supplements, and cognitive behavioral therapy have all proven to help treat patients with persistent CFS (39).

6.1. Pharmacological Treatment and Supplements

Pharmacological treatments have been shown to decrease rates of common CFS symptoms such as chronic fatigue, depression, and anxiety, while improving quality of life and physical performance variables (maximal oxygen consumption, anaerobic threshold, load time to failure) (65). Proper supplementation of nutrients such as Vitamin B12, Folic Acid, Supradyn (multivitamin), $NADH^{+}$ coenzyme Q, and D-ribose are safe treatment options (61). Replacing deficient lipid content and using antioxidant therapy have shown efficacy in patients who present with moderate to severe CFS symptoms (61).

The monoclonal antibody Rituximab, which is used for autoimmune diseases such as rheumatoid arthritis, showed no difference in comparison of effectiveness to controls when examining fatigue and functional status in CFS patients (66). Rintatolimod, a double stranded RNA compound, operates as an activating ligand for Toll-Like Receptor 3 in the innate immune system and provides relief of symptoms in 30 - 40% of CFS/ME patients (67). Urits et al. describe the importance of understanding what the cause of the fatigue, such as hypomagnesemia so that it may be treated appropriately with magnesium supplementation (68).

6.2. Non-pharmacological Treatment

An analysis of many studies involving the treatment of CFS showed that cognitive behavioral therapy and graded exercise were effective palliative treatments of CFS (40). Referrals to specialists should take place within six months for those with mild symptoms, within three to four months for more moderate symptoms, and immediately for those who present with severe cases. The guidelines emphasize a holistic, patient-centered approach that takes into account physical, mental, and social well-being (69).

6.3. Minimally Invasive Treatment

Although noninvasive therapy has shown to be effective, minimally invasive management of CFS has been limited (70-72). A randomized controlled study concluded that transcutaneous electrical acupoint stimulation of target points produced a significant improvement of fatigue and associated symptoms (73). Dexmedetomidine has been used as an adjuvant in many regional and neuraxial pain management techniques, and it may have a beneficial role in treatment of CFS associated with chronic pain (74). Tully et al. describes the benefits of using lidocaine infusion for treatment of chronic pain, and given that chronic pain may be present in CFS, this too can be a promising multimodal approach to managing CFS (75). Studies have shown that neuromodulation (Dorsal Root Stimalation and Pulsed Radiofrequenscy) has been effective in various chronic pain syndromes, some of which may be associated (72, 76).

6.4. Difficulties of Treatment

Due to the varied presentation of symptoms, CFS is difficult to diagnosis and manage for both patients and physicians (43). Patients' commonly reported difficulties in diagnosis and treatment of CFS include getting a correct diagnosis, accessing medical professionals, receiving emotional support, disapproving of the medical care received, being skeptical of behavioral and physical therapy, and developing psychological problems (43). The biopsychosocial approach to treating patients has been labeled narrow and inadequate due to it not taking the patient's narrative into account (19). The biomedical approach is preferred by most patients and focuses on each patient's experience of their illness (19). The best management of CFS stems from a healthy physician-patient relationship to find effective treatment plans to maximize quality of life (19). As described by Khan and Imani, management of such chronic syndromes often requires a balance between the provider and the patient that must consider the biopsychosocial aspect of the illness (77).

7. Conclusions

CFS is a debilitating syndrome that significantly affects the daily lives of those afflicted. Its clinical presentation can vary from patient to patient, making a prompt diagnosis and its management a difficult task. Groups of men and women affected by CFS have shown two peaks of its incidence based on the age group, though women have shown to have a more distinct second peak than men. Many potential etiologies for the syndrome are being considered, ranging from autoimmune, neuroendocrine, and autonomic system dysfunction. Aside from the different clinical presentations of the syndrome, the fact that fatigue is a very subjective symptom makes the diagnosis even more difficult. And thus far, much of the medical management has focused on alleviated the symptoms rather than tackling the syndrome itself. This is partly due to the currently limited understanding of the cause of the syndrome. Given its association to psychiatric comorbidities, such as depression and anxiety, patients have been treated with antidepressants and CBT. The potential infectious trigger of EBV has also led to treatment with antivirals, such as valacyclovir. Many other forms of treatment, including approaching the syndrome with alternative medicine has been utilized and shown in some studies to be efficacious. Further reliable clinical trials are essential to furthering our understanding of this syndrome. This will provide opportunities in its timely diagnosis and effective management.

Footnotes

Authors' Contribution: Study concept and design: NN, IU, AD, LR, VK; Analysis and interpretation of data: EMC, ADK, FI, MN, GV, OV, FI; Drafting of the manuscript: NN, IU, AD, LR, VK, EMC; Critical revision of the manuscript for important intellectual content: NN, IU, AD, LR, VK, EMC, ADK, FI, MN, GV, OV; Statistical analysis: NN, IU, AD, LR, VK, EMC.

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