Chronic Fatigue Syndrome: Characteristics and Possible Causes for its Pathogenesis

Nicola Bassi MD[1], Daniela Amital MD[2], Howard Amital MD[3], Andrea Doria MD[1] and Yehuda Shoenfeld MD[4*]

[1]Department of Rheumatology, University of Padova, Padova, Italy
[2]Department of Psychiatry B, Ness Ziona Mental Health Center, Ness Ziona, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[3]Department of Psychiatry A, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University
[4]Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel

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Abstract

Chronic fatigue syndrome is a heterogeneous disorder with unknown pathogenesis and etiology, characterized by disabling fatigue, difficulty in concentration and memory, and concomitant skeletal and muscular pain. Several mechanisms have been suggested to play a role in CFS, such as excessive oxidative stress following exertion, immune imbalance characterized by decreased natural killer cell and macrophage activity, immunoglobulin G subclass deficiencies (IgG1, IgG3) and decreased serum concentrations of complement component. Autoantibodies were also suggested as a possible factor in the pathogenesis of CFS. Recent studies indicate that anti-serotonin, anti-microtubule-associated protein 2 and anti-muscarinic cholinergic receptor 1 may play a role in the pathogenesis of CFS. It has been demonstrated that impairment in vasoactive neuropeptide metabolism may explain the symptoms of CFS.

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Chronic fatigue syndrome is a heterogeneous disorder affecting more than 267 per 100,000 people [1]. It has been estimated that in the United States approximately 1 million people suffer from CFS symptoms [2]. The reported prevalence of CFS is 0.2–2.6%, with women being affected almost twice as often as men [3]. A similar prevalence was found in different geographic locations and in diverse ethnic groups [4].

The pathophysiology and etiology of CFS are unknown, because there are no characteristic physical signs or diagnostic laboratory abnormalities [5]. It is defined by self-reported symptoms and disability, but only about 1% of the patients who are given the diagnosis in primary care settings meet the criteria for CFS [6]. CFS patients suffer from disabling fatigue, headaches and concentration difficulties and memory deficits (90%). Additional symptoms are often observed, such as sore throat (85%), tender lymph nodes (80%), skeletal muscle pain and feverishness (75%), sleep disruption (70%), psychiatric problems (65%), and rapid pulse (10%) [3]. Due to these complaints patients often face social problems, the loss of jobs and the break-up of marriages [7].

The diagnosis of CFS is complex due to its similarity with other ill-defined disorders, such as fibromyalgia, Gulf War syndrome and Sjögren's syndrome [8]. In 1994 Fukuda et al. [9] reported the significant overlap between CFS and fibromyalgia, and considered CFS as a subclass of prolonged fatigue. They proposed a method for obtaining the correct diagnosis: a patient must present four or more symptoms concurrently for at least 6 months. These criteria are: a) a coexisting medical or neuropsychiatric condition that does not explain the chronic fatigue; b) the level of fatigue, including subjective and performance aspects; c) the total duration of fatigue; and d) the level of overall functional performance [9]. Characteristics excluding patients from CFS include active medications, past or current major depressive disorders, alcohol abuse, and severe obesity [9]. However, some of the criteria are difficult to interpret [10], and opinions differ regarding the classification of chronic fatigue cases with a history of psychiatric illnesses [11]. All these evaluations can be performed with available instruments [12], as well as the Medical Outcomes Study Short Form 36 [13] and the Sickness Impact Profile [14].

Effect of exercise in CFS patients

CFS patients suffer from exacerbated fatigue after physical exertion, and can do exercise less often and to a lesser intensity than healthy controls [15]. It has been hypothesized that cytokines may mediate some of the symptoms and immunological disturbances [16]. But other studies failed to demonstrate abnormal cytokine concentrations in CFS patients compared to healthy subjects, at rest [16,17], and the only elevation was in transforming growth factor-beta levels [16]. Higher levels of TGFβ were found in CFS patients immediately and within 40 minutes at rest after mild exercise (walking 1 mph for 30 min) [18]

* Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel Aviv University.

CFS = chronic fatigue syndrome
IgG = immunoglobulin G
TGFβ = transforming growth factor

Also, cerebral perfusion defects were often recorded, but no relationship was found between the detected perfusion defects and TGFβ levels [18]. Patarka [19] demonstrated higher serum levels of interleukin-4 and interferon-gamma and lower levels of TGFβ. Fulle and co-authors [20] showed a dysregulation of the Na^+/K^+ and Ca^{2+}-ATPase pumps and alterations in ryanodine channels in sarcoplasmic reticulum membranes in CFS patients. Extracellular K^+ accumulation can induce a negative feedback signal for sarcolemma excitability [21], and dysregulation of the pump activities can cause increased sarcoplasmic reticulum membrane fluidity [20], leading to the formation of lipid hydroperoxides [22]. All these alterations in muscle excitability can cause post-exercise oxidative stress, explaining muscle pain and post-exertional malaise reported by the patients [23]. The oxidative stress can be generated by a lower maximal aerobic capacity and by a reduced baseline oxygen uptake by tissues that occurs in CFS patients [23].

Infections and CFS

CFS was first described in the 1980s and was thought to be the consequence of a viral or bacterial infection, because of the patients' immunological findings. One of the first suspected pathogens was Epstein-Barr virus, because patients often have higher titers of IgM to the EBV viral capsid antigen [3]. Also, antibodies against cytomegalovirus [3] and human herpes virus-6 [3] were detected more often in CFS patients, although other reports failed to repeat these results [3]. Another virus family studied as a possible cause of CFS is the enterovirus, since RNA copies were detected in muscle biopsies of CFS patients but not in a healthy control group [3]. In other studies no association between enteroviruses and serological tests was recorded [3]. Parvovirus B19 is considered one of the most probable causes of CFS, based on several case reports of patients with a chronic course of fatigue after infection, fulfilling the criteria for CFS diagnosis [3]. In addition, a higher prevalence of Mycoplasma infections has been reported in CFS patients than in healthy subjects [3].

Gene expression in CFS patients

It has been proposed that the integration of gene expression with clinical and epidemiological data in CFS patients can be used to identify CFS subgroups. But results are inconsistent and controversial. Vernon and team [24] showed that peripheral blood mononuclear cell gene expression can distinguish the majority of CFS cases from non-fatigue controls. A year later, the same group investigated levels of gene expression in 23 individuals with CFS, concluding that the heterogeneity of CFS, which is often associated with various metabolic perturbations, results in a differential gene expression [25].

Kaushik et al. [26] showed that CFS patients have reproducible alterations in gene regulations. They revealed differential expression of 35 genes, confirming with real-time polymerase chain reaction the same results in 16 of these genes. Their suggested gene profile is associated with T cell activation and perturbation of neuronal and mitochondrial functions [26].

Nevertheless, no clear association between gene expression and individual symptom domains was found by other researchers, suggesting that CFS symptomatology probably cannot be elucidated by individual laboratory tests or gene expression [27].

Role of the immune system in CFS

CFS patients present an immune imbalance, characterized by a decreased function in NK cells and macrophages, reduced mitogenic response of lymphocytes, IgG subclass deficiencies (IgG1, IgG3) and decreased complement levels [28]. But no evidence of a clear link between abnormal immunity and CFS was established [29].

It was previously found that 52% of CFS patients have autoantibodies to components of the nuclear envelope, in particular to nuclear envelope laminin B1 molecule [1]. This same group suggested that autoantibodies to insoluble cellular antigens are a unique feature that might help to distinguish CFS from other rheumatic autoimmune diseases [6]. Plioplys [30] did not find a pathogenic role for antinuclear antibodies or antimuscle autoantibodies in this disorder. Recently, Nishikai [31] demonstrated that there are several antinuclear antibodies, and in CFS the antinuclear antibody is specific against the anti-68/48 kD protein antibody. No antibodies to dsDNA were found [1,32]. Young patients (age 18–29 years) with CFS present antibodies to ssDNA, but these results were not confirmed by other groups [32]. Moreover, these authors demonstrated that CFS patients are significantly positive for microtubulin-associated protein 2 antibodies, when compared with healthy controls, particularly subjects who are affected for more than 5 years ($P = 0.025$) [32]. No association was found between CFS and Sm, U1-RNP, SS-A/Ro, SS-B/La, Scl-70 and centromere antibodies [32]. Sirois and Natelson [8] detected anti-SSA and anti-SSB, implying that a subset of patients with CFS may have primary Sjögren's syndrome. Hypothalamic-pituitary-adrenal axis abnormalities have also been linked to CFS [9,33], raising the possibility that this dysfunction is associated with depression [33].

Several years ago it was postulated that antiphospholipid antibodies that were previously detected in CFS patients may have a pathogenetic role. Antiphospholipid antibodies were found in CFS patients only in 1995, by Klein and Berq [34], and then confirmed in 1998 by Heller and team [35]. Moreover, there is evidence that antibodies to neurotransmitters – such as serotonin [34,35], adrenals [36], adrenocorticotropin hormone [37], and receptors like muscarinic cholinergic receptor 1 and mu-opioid receptor 1 – play an important role in the pathogenesis of CFS [38]. The most prominent of these autoantibodies are anti-serotonin [34,35], anti-CHRM1 [38] and MAP2 [32]. Indeed, levels

EBV = Epstein-Barr virus

NK = natural killer
CHRMI = muscarinic cholinergic receptor 1
MAP2 = anti-microtubule-associated protein 2

of anti-MAP2 were significantly higher in CFS patients than in controls ($P = 0.003$) [32], and anti-CHRM1 ($P < 0.0001$) [38] and anti-serotonin antibodies were found in 62% of CFS patients [34,35].

Role of vasoactive neuropeptides in CFS

Vasoactive neuropeptides of the adenylate cyclase-activating type are small peptides formed by about 38 amino acids that exert effects on modulating and regulating biological systems. It has been proposed that they might have a role in the pathogenesis of CFS [7]. In fact, they are strongly preserved in evolutionary terms [7,39], resembling ancestral viral genes that have become incorporated into the human genome. Dysfunction of the immunological and anti-inflammatory role of vasoactive neuropeptides [7] may therefore contribute to the skeletal muscular pain. Moreover, vasoactive neuropeptides regulate the effect of nociception and the neuronal answer to external stimuli, modulating the receptors to neurotransmitters. One could therefore speculate that dysfunction to the CNS and abnormal hormonal regulation might cause depression and sleep disturbance [7].

Conclusions

CFS is a heterogeneous disorder with an unknown etiology that impairs concentration and sleep and causes muscular pain, leading to difficulties in patients' social life [7]. It is difficult to reach an accurate diagnosis due to the disorder's common characteristics with other diseases like fibromyalgia, Gulf War syndrome and Sjögren's syndrome [8]. Moreover, the criteria proposed for the diagnosis of CFS [9] are difficult to interpret [10], and opinions differ regarding the classification of chronic fatigue cases with a history of psychiatric illnesses [11].

Several factors have been related to the pathology of CFS, like anti-virus and autoantibodies, but the results from different studies are controversial and conflicting. It is therefore important to stratify the study groups in terms of symptoms, age, gender, duration of disease, and treatments for other disorders [9], and to investigate gene expression. Only some autoantibodies to neurotransmitters and their receptors were found to be significant in the pathogenesis of CFS [6,35,36]. It has been proposed that vasoactive neuropeptides may be related to all neurological and immunological dysfunctions, but the cause for the impaired functions of these neuropeptides has not been discovered [7].

Several reports suggest that symptoms of the Gulf War syndrome may be attributed to the vaccines that were administered to soldiers, for example, vaccination against anthrax [3,7]. It has been demonstrated that viral infections and some vaccinations induce a Th2 dominant response [3] and, when the response fails to be switched off, a chronic immune activation occurs and is clinically expressed as the symptomatology of CFS.

Further research is needed to understand the exact pathology of CFS and to clarify whether this disorder is truly a distinct one.

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Correspondence: Dr. Y. Shoenfeld, Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621. Israel.
Phone: (972-3) 530-2652
Fax: (972-3) 535-2855
email: shoenfel@post.tau.ac.il