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ПРЕГЛЕД ЛИТЕРАТУРЕ / REVIEW ARTICLE

Chronic Fatigue Syndrome

Snežana Brkić, Slavica Tomić, Maja Ružić, Daniela Marić
Hospital for Infectious Diseases, Clinical Centre of Vojvodina, Novi Sad, Serbia

SUMMARY
Chronic fatigue syndrome (CFS) is defined by a profound, debilitating fatigue, lasting for at least 6 months and resulting in a substantial reduction of occupational, personal, social and educational status. CFS is a relatively poorly recognized clinical entity, although everyday experience shows that there are many patients with CFS symptoms. The incidence and prevalence of CFS remain unknown in most countries; however, the working population is most affected with predominantly female patients in generative period. Although, CFS was first mentioned four centuries ago, mysterious aethiopathogensis of CFS still intrigues scientists as hundreds of studies are still published every year on the subject. About 80 different aetiological CFS factors are mentioned, which can be classified into five basic groups: genetics, immunology, infectious diseases, endocrinology and neuropsychiatry-psychology. Even today the condition is passed established based on the diagnosis by exclusion of organic and psychiatric disorders, which demands u multidisciplinary approach. As the syndrome is often misdiagnosed and mistreated, self-medication is not uncommon in CFS patients'. In addition, such patients usually suffer for years tolerating severe fatigue. Thus, at the moment there are three priorities regarding CFS; understanding pathogenesis, development of diagnostic tests and creating efficient treatment program.
Keywords: chronic fatigue syndrome; aetiology; diagnosis

INTRODUCTION

Chronic fatigue syndrome (CFS) is a relatively poorly recognized clinical entity in medical practice, although everyday experience teaches us that there are many patients who have CFS symptoms. The unwritten rule is that the syndrome is associated with viral infections as triggers or with a protracted subfebrile condition, so that they are mostly managed by infectious disease specialists, despite requiring most serious multidisciplinary approach.

The first records of CFS date from the 17th century when the syndrome was described as "muscle rheumatism". Later, in the 20th century, it was termed military fever, exhaustion disease, chronic mononucleosis, chronic candidiasis, endemic neurasthenia, Island fever, Royal Free disease, Yuppie flu, etc [1, 2]. Finally, in 1988 the Centers for Disease Control and Prevention (CDC) put an end to the long list of terms by defining precise clinical criteria for the diagnosis of CFS [3]. However, in different worldwide regions there are still other terms for the same condition, such as myogenic encephalomyelitis and low natural killer (NK) cell syndrome [4, 5, 6].

Mysterious aetiopathogenesis of CFS still intrigues a large portion of the public which is best illustrated by the hundreds of studies on the subject published every year [6, 7]. CFS is now a well recognized and important health, as well as a socioeconomic, issue. In the USA alone there is an annual 9 billion dollar loss due to reduced productivity in people with CFS [7].

EPIDEMIOLOGY

The incidence and prevalence of CFS remains unknown in most countries. The largest and most numerous epidemiological studies come from the USA. The first widely publicized study of CFS epidemiology was initiated by the CDC in the late 1980's. The prevalence rates of CFS were found to range from 4.0 to 8.7 individuals per 100,000 cases [8]. The majority of CFS cases were Caucasian females with medium and high income. Similar to other studies, a sample for this study was composed of patients who visited physicians [8, 9]. In a study conducted from 1995 to 1998, Jason and colleagues [8] screened a random sample of 18,675 subjects for CFS symptoms. CFS was confirmed in about 42% (420 per 100,000) examinees. The results of this study indicated that in the USA over 800,000 people could be affected by the syndrome. Middle-aged females also predominated in this study, but this time they were of middle to lower socioeconomic status. Besides, about 90% of identified patients had not been previously diagnosed prior to the participation in the study nor did most of the patients ever visit a physician due to their problems [8, 9].

Up-to-now published studies have report ed very different prevalence rate of CFS. The variations are above all caused by different subject samples, but also by the difference in socioeconomic factors in countries where the studies have been conducted [9].

Correspondence to:
Snežana BRKIĆ
Hospital for Infectious Diseases
Clinical Centre of Vojvodina
Hajduk Veljkova 1-9
21000 Novi Sad
Serbia
tomkis@eunet.rs

ETHIOPATHOGENESIS

Facing the diseased disarms the superego of the conventional medicine, stimulating us to return to the primeval conception of the man; a unique unrepeatable union of spirit and body. The approach to CFS cannot be exclusively either psychological or physiological; on the contrary, it requires a wide biological and psychological consideration [6].

Several hundreds of studies mention about 80 different aetiological CFS factors which can be classified into five basic groups, i.e. medical fields; genetics, immunology, infectious diseases, endocrinology and neuropsychiatry-psychology.

Genetic aetiology

CFS is occasionally seen in several family members and therefore there may be a familial predisposition or a genetic link to the disease. Hickie et al. [10] studied a population of twins to evaluate genetic and environmental factors of prolonged fatigue. A genetic variance for fatigue were found even in 44%, however a considerable lower rate for other forms of psychological stress, as well as a negligible difference of environmental factors influence on chronic fatigue. On the other hand, Cho et al. [11] have detected that although genetic predisposition is a factor in the development pf chronic fatigue, the environmental factors still play a predominant role. Clearly, further research is needed to determine precisely the relationship between these factors.

Immunologic aetiology

It can be said that most scientists consider CSF to be the result of immune system response to different known or unknown triggers, such as infective causes, various vasoactive peptides, etc. [12]. In numerous studies the loss of immunological control or tolerance has been attributed to the increased activity of proinflammatory cytokines, NK cells dysfunction and the subsequent loss of coordination between innate and acquired immunity, and the reactivation of various latent infections, such as Epstein Barr virus (EBV) infection [13, 14].

Several mechanisms that decrease NK function have been evaluated; decreased potency of NK cells subpopulation, decreased levels of NK cells modulating cytokines or the presence of various inhibition factors [15, 16].

So far, the most precise mechanism of NK cell damage was described in a study by Maher who registered a decrease in perforin concentration, a lytic protein of NK cells suggesting that in future this protein could be also used as a diagnostic marker [17].

The third group of authors advocating the immunological model has studied disorders of T lymphocyte subpopulation activity disorders and the decrease of antibody-dependent cell-mediated cytotoxicity [17]. In addition, the studies involved the evaluation of other cytokine deregulation models with a still undefined role of proinflammatory cytokine concentration increase or decrease [18].

Recent studies have shown disorders of B lymphocytes function with decreased levels of IgG 1 and IgG 3 and increased levels of CD20+CD5+ lymphocytes in CFS [17]. A study by Maes and al. [19] disclosed a presence of IgM induced immune response to membrane lipid components released under the influence of lipid peroxidation and NO-modified amino acids implying the role of oxidative stress. These findings could explain the decrease of antiviral potential in CNF patients. Another potential cause of impaired antiviral defence mechanisms in CFS is explained by the alteration of 2-5 oligoadenilate synthesis due to interferon by the production of L-cell RNA [20, 21, 22].

Infective aetiology

Infections have long been considered to be the most important participating factor in the development of CFS. There are two reasons for this. First, CFS is often diagnosed during a follow- up exam after an acute EBV infection, influenza virus, Parvovirus B19, enteroviruses, Coxsackie B, Herpes simplex virus 4,6 or 7, Brucella spp. or Chlamydia pneumoniae. Secondly CFS is often seen in endemic regions which can be associated with Lyme disease, Q fever, Ross River fever, Nypah encephalitis etc. [23].

Of all infective causes, EBV has been most frequently studied, so that in the 1990s "chronic EBV infection" was in fact a synonym for CFS which was later completely abandoned [24-29]. Recent studies on the roles of viral infection in CFS aetiology speak in favour of a possible VP1, RNA and non-cytopathogenic enteroviral infections detected in patients' gastric mucosa biopsy specimens. The authors suggest that a significant number of CFS patients may have a chronic disseminated non-cytopathogenic for of enteroviral infection which could be diagnosed by biopsy [29]. Also, there is a most recent study on a possible influence of XMRV retroviral infection, as this virus was detected in blood cells of CFS patients [30].

Endocrinological and metabolic disorders

One of the modern theories on the pathogenesis of CFS deals with disorders in the hypothalamic–pituitary–adrenal axis (HPA). A decreased activity of HPA due to increased antiadrenocortical antibodies has been found in some CFS patients [31]. Other metabolic disorders found in CFS include low levels of magnesium, arachidonic acid, L carnitine, dehydroepiandrosterone sulfate etc. [10].

Neuropsychiatry – psychology

It is very difficult to distinguish psychopathologic phenomena in CFS patients from organic disorders, especially when

they could be coexisting conditions. In two studies done by Rangel et al. [10] and Endicott [32] there is convincing evidence that persons who were under increased stress (prenatally, in childhood or during adolescence) are at an increased risk of CFS. There is also a clear relationship between sleep disorders and CFS, regardless of psychiatric co-morbidities [33].

DEFINITION OF CFS AND CRITERIA FOR ITS DIAGNOSIS

CFS is characterized by profound and long-lasting fatigue. Although fatigue is present in many diseases, in CFS it is a specific symptom without visible organic causes [34].

CFS was defined by the CDC in 1988 and revised in 2001 and again in 2003 [35]. According to this definition, CFS is characterized by profound, debilitating fatigue which is persistent or recurrent, lasts for at least 6 months, not caused by physical strain and does not subside after rest, which finally results in the decrease of life activities; occupational, personal and social [36-40].

CDC criteria of CFS diagnosis are:

1. Unexplained, persistent and debilitating fatigue that does not withdraw after rest, which lowers the level of average daily activity by 50% continually over a 6-month period, with a healthy patient before onset.

2. Beside fatigue, the patients present four or more of the following symptoms which are persistent or occasional over a minimal period of 6 months, and can occur prior to fatigue: impaired memory or concentration, post-exertion malaise (extreme, prolonged exhaustion and exacerbation of symptoms following physical or mental exertion), non-refreshing sleep, muscle pain, multi-joint pain without swelling or redness, headaches of a new type and severity, localization or severity, frequent or recurring sore throat, tender cervical or auxiliary lymph nodes.

Less often other symptoms could be present, such as increased thirst, recurrent infection of oropharyngeal or urogenital regions, allergic reactions, night sweats, malaise, paresis and premenstrual syndrome [41].

Although CFS criteria were revised in 2003, the American version insists more on physical symptoms, which partially prejudices the hypothesis that CNF is basically an immunological disorder. On the other hand, the Oxford's criteria are more focused on the presence of myalgia, mood and sleep disorders [36].

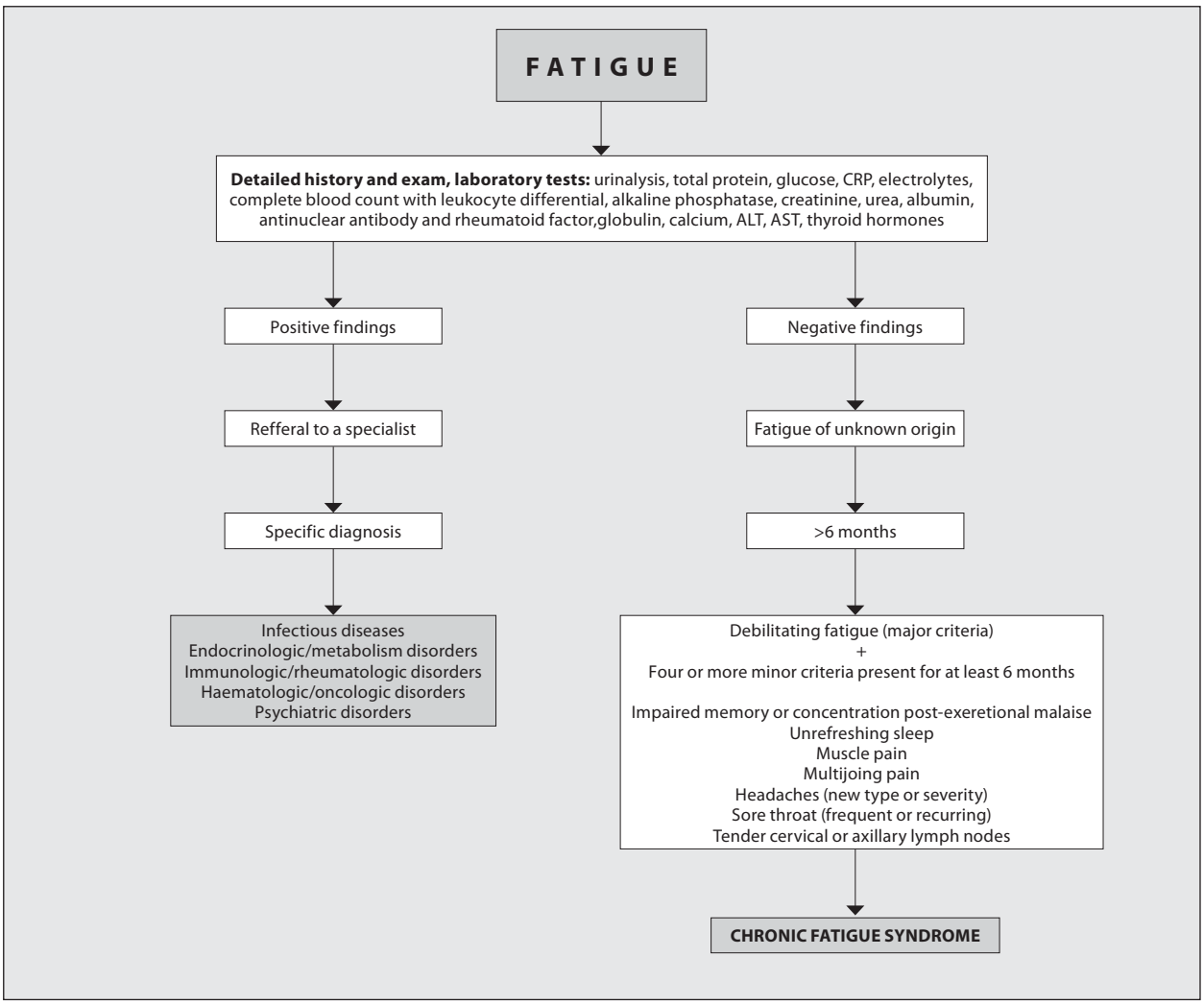

Figure 1. Algorithm for Evaluating Chronic Fatigue Syndrome (CFS)

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Physical examination of a CFS patient can be positive for tender cervical lymph nodes, sore throat, hypotension, orthostatic hypotension, mild or slightly increased fever, tachycardia and occasionally a positive Romberg test [3].

Defined criteria for exclusion of CFS criteria that are the following: current unresolved condition or disease that can cause fatigue, psychotic, melancholic or bipolar depression (excluding uncomplicated minor depression), psychotic disorders, schizophrenia, dementia, anorexia or bulimia nervosa, alcohol or drug abuse, obesity.

CFS diagnosis is very complex, particularly because the symptoms can be very similar to other conditions like fibromyalgia, Sjörgen syndrome, Gulf war syndrome etc. [42]. At the moment, the diagnosis is based on clinical criteria by excluding organic and psychiatric disorders [43]. That is why establishing a diagnosis requires a multidisciplinary approach and collaboration between different specialists including a psychiatrist and a psychologist.

Because fatigue is the leading symptom in CFS, there have been many attempts to measure its levels. One of the most widely used methods is the Fibro Fatigue Scale. The scale was primarily designed for comparison of different treatment options. It involves a six grade scale containing 12 variables: pain of entire body, muscle tension, joint pain, fatigue, concentration and concentration and memory disorders, increased sensitivity, sadness (depressive mood), sleep disorders, autonomic disorders, headaches and intestinal disorders [44, 45]. A detailed illness history is the most important part of the diagnosis and demystification of this up-to-now unclarified disease. The saying that a meticulous illness history taken from the patient makes 50% of diagnosis is completely true in regard to CFS. An appropriate algorithm for evaluating CFS is s hown in Figure 1.

LABORATORY TESTS FOR CFS

There is no specific diagnostic laboratory test for CFS [43]. Many routine laboratory tests are a part of CFS diagnostic protocol, because it is necessary to exclude organic disorders characterized by fatigue (cardiovascular diseases, tumours, immunological, endocrine and haematological disorders, infectious diseases). After these preliminary tests, only a working diagnosis of CFS can be established. In order to give a definite diagnosis other, more precise tests should be done, such as serological tests for viruses (ELISA IgM and IgG Cytomegalovirus, EBV, Herpes simplex virus 6 Coxsackie, HIV), tests for chemicals and toxins, etc. [46]. In order to assess HPA levels of cortisone, DHEA, somatomedin C, estrogen, melatonin, arginine, vasopressin, serotonin and ACTH should be determined [47, 48].

THERAPY

Even 31 different therapies for CFS can involve about 350 available meta-analyses [34, 49].

Because there is no consensus on aetiology, therapeutic options are focused on symptoms relief, regain the patient's strength and functioning.

It is not uncommon for CFS patients to self-medicate, as the condition is often misdiagnosed and mistreated. On the other hand, some patients are desperate to find the right physician and are willing to try any kind of therapy, often with little success. Both groups of CFS patients suffer of fatigue for years, while suffering becomes an integrated part of their everyday working, social and personal activities.

There is no specific aetiological treatment for CFS. If a current infection is definitively confirmed the diagnosis of CFS is discarded and a specific antiviral or antibacterial therapy can be administered [50, 51].

Nonsteroidal antiinflammatory drugs and other analgesics can be used to treat pain and suppress inflammatory response. Hydrocortisone therapy may be used in some patients when there is evidence of HPA disorder in order to decrease DHEA levels. Still, because of serious side effects, as for example, suprarenal suppression, hydrocortisone is not used routinely [50].

The use of antidepressants and antianxiety agents has shown as efficient in relieving psychopathologic symptomes in almost all studies [51-54].

Cognitive behavioural therapy and, to a lesser degree, some other psychotherapeutic modalities have shown most promising results in relieving symptoms of CFS [34, 52]. Dietary supplementation with antioxidants is also supported by advanced medicine due to its potentially positive effects on the neutralization of free radicals, and maintaining oxy-redox homeostasis in CFS patients [46, 55, 56]. Also, supplementation with omega 3 fatty acids has been shown to reduce the concentration of omega-6 unsaturated fatty acids in erythrocyte membranes [57].

In several meta-analyses long-lasting complex physical rehabilitation and kinesitherapy combined with cognitive behavioural therapy have shown to be the best therapeutic option for CFS patients. Physical activity has shown to improve oxygen delivery, which in turn relieves some of the symptoms [58, 59, 60].

CONCLUSION

The up-to-date problem of CFS symptomatology research presents variations in the methods of data collection and analysis in different countries and regions. It is certain that CFS patients should be diagnosed more efficiently. In this a contribution would be certainly made once the term "chronic fatigue" is replaced by another, better term for this profoundly devastating condition [41]. According to Edward Conley, the author of America Exhausted, at least 50% of CFS patients do not fit the CDC criteria, which certainly does not mean that these patients are healthy [36].

There are three priorities regarding CFS: understanding pathogenesis, development of a diagnostic test (protocol) and achieving efficient treatment. Although an in depth analysis of CFS patients' mortality has not yet been carried

out, there is increasing evidence of increased suicidal tendencies in these patients.

At the moment, there are three existing priorities in the field of CFS research; understanding of pathogenesis, development of a diagnostic test and achievement of efficient treatment [50]. The detailed studies of mortality among patients with fatigue and persons with CFS have not been conducted yet, but several resources report that CFS is associated with increased risk of suicide [25].

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Синдром хроничног умора

Снежана Бркић, Славица Томић, Маја Ружић, Даниела Марић
Клиника за инфективне болести, Клинички центар Војводине, Нови Сад, Србија

КРАТАК САДРЖАЈ
Синдром хроничног умора (СХУ) је тежак, онеспособљавајући умор који траје бар шест месеци и доводи до значајног поремећаја пословног, личног, друштвеног и образовног стања. СХУ се у нашој средини ретко дијагностикује, иако нас свакодневни рад са пацијентима уверава да особа са симптомима СХУ има много. И поред чињенице да су инциденција и преваленција СХУ непознате, зна се да се ово стање углавном јавља код радно активне популације са предоминацијом жена у генеративној доби. Први подаци о СХУ датирају од пре 400 година, али његова још неразјашњена етиопатогенеза и даље заокупља пажњу научне јавности. У доступној литератури помиње се око 80 различитих етиолошких фактора који се могу разврстати у пет група: генетски, имунолошки, инфективни, ендокринолошки и неуропсихијатријско-психолошки етиолошки фактори. Дијагноза СХУ се искључиво поставља *per exclusionem* органских и психијатријских поремећаја, што захтева мултидисциплинарни приступ овом проблему. С обзиром на то да се синдром често погрешно дијагностикује, а болесници лоше или неадекватно лече, неретко се дешава да особе са СХУ узимају терапију на своју руку. Такође, ови болесници годинама живе с тешким умором, који постаје део њих и њихове свакодневице. Зато се у овом тренутку могу издвојити три приоритета у погледу лечења од СХУ: разумевање патогенезе, развој дијагностичких тестова и постизање ефикасног програма лечења.
Кључне речи: синдром хроничног умора; етиологија; дијагноза

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