

Chronic Fatigue Syndrome - diagnostic challenge in a general practice

1. Katarzyna Banaszczyk, e-mail: kbanaszczyk570@gmail.com, ORCID: 0000-0002-9442-3105
2. Oskar Puk , e-mail: oskar.trebacz@gmail.com ORCID: 0000-0002-6659-2569
3. Adrianna Maliszewska, e-mail: maliszewskaadrianna@gmail.com ORCID: 0000-0001-8517-9027
4. Michał Owsiany, e-mail: michal.o.jr@gmail.com ORCID: 0000-0003-4680-5106

Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń

Abstract:

Introduction: Chronic fatigue syndrome is a heterogeneous disease associated with a vary of symptoms but with severe, prolonged fatigue as the core symptom associated with the disease. This is a condition characterized by an unreasonable sense of tiredness lasting over 6 months that cannot be explained by other conditions. In spite of more and more intensive research, the chronic fatigue syndrome is still insufficiently known and often overlooked in diagnostics.

Aim: The intention of this article is to obtain and summarize current information about the diagnosis of chronic fatigue syndrome and also to increase the awareness of the problem in general medical practice.

Materials and methods: The systematic literature search was performed by the use of Pubmed as a database. An extensive literature study has been carried out covering the period from 2007 until 2018.

Results: This report presents a differential diagnosis of CFS and preliminary tests, that we should do to exclude other diseases associated with fatigue. The article describes presently used questionnaires in CFS – COMPASS and The Chalder Fatigue Scale. The issue of the role of infections in the ethiopathogenesis of CFS has also been raised. The attention was paid to EBV, because of the widespread of its carrier state. The article presents also the potential role of

hipocortisolism and α -melanocorticotropin hormone as the hormonal markers of CFS.

Conclusions: In conclusion, there is an essential need to discover possible markers of CFS and to create standardized diagnostic procedure for this underestimated disease. Analysis of recent studies allow us to create simple scheme which general practicers can use to diagnose CFS and rise quality of life of many patients which is heavily impaired by as common symptom as chronic fatigue is.

Key words: CFS, chronic fatigue syndrome, fatigue

Introduction

Being tired is a plague of our time but it is not always lack of rest or just stress which can easily be treated just by taking some time off and repose. Chronic Fatigue Syndrome (CFS) is a disease which is getting more and more important nowadays, mainly due to its impact on life quality and everyday functioning as a mild but constant negative factor. [1] That is why knowledge and awareness of CFS should increase among both medical society and patients and this is the reason of origin of this article. At the beginning we must define Chronic Fatigue Syndrome to know what to look for and how to do it, however as simple thing as definition is not as easy as it may seems like. There are many definitions and diagnostic criteria, however following ones are most clinically useful. Three most commonly used criteria are gathered in table number 1 but the simplest delineation of CFS seems to be FUKUDA's major criterium: Chronic Fatigue Syndrome is more than six months of severe chronic fatigue not due to exertion or other illness and is interfering with daily life. [2, 3, 4]

Table 1. Diagnostic criteria of CFS

Fukuda criteria of CFS	CANADIAN 2003:	CANADIAN 2011
<p>Major: More than six months of severe chronic fatigue not due to exertion or other illness and interfering with daily life</p>	<p>Major (minimum six months of): Significant new onset, unexplained, persistent fatigue that reduces activity level, and/or Post exertional malaise, and/or Sleep dysfunction and/or Pain in the form of widespread myalgia/arthralgia or headaches</p>	<p>Major: postexertional neuroimmune exhaustion with marked, prolonged postexertional physical or cognitive fatigue with extended recovery period</p>
<p>Minor (minimum four): Post exertional malaise of >24 hours Unrefreshing sleep Impairment to short-term memory or concentration Myalgia Arthralgia without swelling/erythema Headaches of new type Lymphadenopathy Frequent or recurring sore throat</p>	<p>Minor: Minimum neurological/cognitive symptoms: Confusion Poor concentration and short term memory Poor information processing, categorising and word retrieval Perceptual and sensory disturbances Ataxia Muscle weakness Fasciculations and minimum one from two of the following categories: Autonomic: orthostatic intolerance, PoTS, nausea, irritable bowel, urinary frequency, palpitations, exertional dyspnoea Neuroendocrine: loss of thermostatic stability, weight change Immune: lymphadenopathy, recurrent sore throat, general malaise, sensitivities to food/medications</p>	<p>Minor (one symptom from two three of these categories): Neurocognitive impairment Pain Sleep disturbance Neurosensory, perceptual and motor disturbances Flu-like symptoms: Susceptibility to viral infections Gastro-intestinal tract symptoms Genitourinary symptoms Sensitivities Cardiovascular Respiratory Loss of thermostatic stability Intolerance of extremes of temperature</p>

At the first consult physicians should look forward to following symptoms characteristic for CFS: fatigue, sleep disorder, impaired cognition, low-grade fever, myalgia, muscle weakness, headache, visual blurring, nocturia, dizziness, tachycardia, dry eyes, dry mouth, diarrhoea, painful

lymph nodes. Symptoms are segregated from the most to least common ones. [5, 6] As it may be clearly seen, CFS can be easily overlooked by general practitioner, who is the first person that patient worried about his life will come to, thus thinking about fatigue as a disease and right diagnostic path are greatly important and it is the essence of this article.

Role of infections in the etiopathogenesis of Chronic Fatigue Syndrome

Many studies focus on the role of infections in the etiopathogenesis of Chronic Fatigue Syndrome. Epstein-Barr virus has long been discussed as a possible cause of Chronic Fatigue Syndrome. Epstein-Barr virus is widely distributed around the world. It is estimated that about 90-95% of the adult population has been infected with this pathogen, so we should know more about role of this agent in etiopathogenesis of CFS. [7] Straus et al reported on 23 patients with CFS, 83% of whom exhibited persistently elevated antibodies anti-EBV in modest titer to the early antigen, ten of patients had never completely recovered from an episode of acute infectious mononucleosis [8] A more recent study of adolescents with infectious mononucleosis showed that at 6 and 24 weeks of follow-up, 13% and 4%, respectively, had prolonged fatigue that met CDC criteria. [9]

Although there was never any direct virologic evidence favoring chronic, persistent Epstein-Barr virus infection as a cause of CFS, there are also studies refuting this hypothesis. [10] Interesting prospective cohort study made by Hickie I. et al, concerned patients with acute infection with Epstein-Barr virus, *Coxiella burnetii* or Ross River. Disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and also mood disturbance was evident in 29 (12%) of 253 participants at six months, of whom 28 (11%) met the diagnostic criteria for Chronic Fatigue Syndrome. [11] There are studies that also indicate the role of Cytomegalovirus, Human herpesviruses (6,7,8), Enteroviruses, Parvovirus B19, *Mycoplasma* spp., Human spumavirus, *Borellia* and *Brucella* in etiopathogenesis of CFS. [10]

We must remember that there is no reproducible evidence that any single agent is responsible for CFS, but during the diagnosis of CFS, we can pay attention to medical history of viral and bacterial infections, because some of this agent can be confirmed in new researches as a risk factor of Chronic Fatigue Syndrome.

The Chalder Fatigue Scale (CFQ) and COMPASS Scale

One of a several available questionnaires and tools that can help in diagnosing the chronic fatigue syndrome is The Chalder Fatigue Scale (CFQ). The scale is a commonly used instrument to evaluate fatigue in clinical and nonclinical way. The Chalder Fatigue Scale has been used in many configurations including general population, primary/secondary care, randomized controlled trials, cancer, multiple sclerosis and postpolio syndrome.

The questionnaire consists of 11 questions that deal with the problems like: tiredness, the need for a longer rest, drowsiness, inability to start new things, the lack of energy, having less muscle strength, nausea, problems with staying focused, speaking clearly and memory. Each question should be answered by choosing one of the four options on the scale - less than usual/ no more than usual / more than usual / much more than usual. The max. number of points that one can score is 33.

The questionnaire was used in one of British study about chronic fatigue syndrome. The study that consisted of 361 participants who suffer from chronic fatigue syndrome and 1615 participants from community. Patient with CFS included in this study necessary had to meet requirements the Oxford and Fukuda diagnostic criteria for Chronic Fatigue Syndrome and be 18 or more years old. Participants from population were registered from Southeast of England, women and men between the ages 18-45, average around 30. Here are the results of the above study:

- 1) Fatigue levels are not different between women and men, both CFS patients and population group.
- 2) Patient with Chronic Fatigue Syndrome had a median score of 24.4, whereas participants from population had a median score 14.2.
- 3) Questionnaire revealed a correlation between the growing number of points scored on the test and the possibility of having CFS.
- 4) Analysis shows that randomly chosen individual with CFS has a higher value of fatigue, compared to a randomly chosen individual from the general population in more than 90% of the cases.
- 5) A score of 29 differentiated between CSF patient and other participants from community sample in 96% of cases while the score above 30 differentiated 100% of cases. [12]

Another useful tool in diagnosis of Chronic Fatigue Syndrome is COMPASS questionnaire. It consists of 73 questions that assess symptoms, grouped into domains relating to individual aspects of the autonomic nervous system. Each domain is scored on the basis of presence, severity, distribution, frequency and progression of symptoms. [13]

The eight domains relate to:

- I. Orthostatic Intolerance (generalized adrenergic) (maximum score 40 points);
- II. Vasomotor (peripheral adrenergic) (max. 10);
- III. Secretomotor (cholinergic) (max. 20);
- IV. Gastrointestinal (max. 10) (including Autonomic Diarrhoea (max. 20) and Constipation (max. 10) sub-domains);
- V. Bladder (max. 20);
- VI. Pupil Responses (max. 5);
- VII. Sleep disorder (max. 15);
- VIII. Syncope (max. 20).

COMPASS allow to distinguish patients with autonomic system dysfunction what is crucial in diagnostic process since alterations in sympathetic and parasympathetic systems are characteristic for CFS. Research shows that cut-off score in COMPASS questionnaire is 32,5 points. [14,15]

Differential Diagnosis

Table number 2 presents the diseases that we should consider during differential diagnosis of CFS. Unfortunately, we do not have specific markers or laboratory tests for Chronic Fatigue Syndrome. Firstly, we should use basic screening laboratory tests like: complete blood count, erythrocyte sedimentation rate, alkaline phosphatase, creatinine, calcium, phosphorus, ALT, total protein, albumin, globulin, glucose, BUN, electrolytes, TSH and urinalysis. These tests are very helpful in differential diagnosis and what is more they will allow us to exclude most of the diseases presented in the table with differential diagnosis. Serologic tests for Epstein-Barr virus, Candida albicans, human herpesvirus 6, and other studies for immune cellular abnormalities are not useful, moreover these tests are very expensive and generally not recommended in diagnostic process. [16]

Table 2. Differential diagnosis of CFS

Psychosocial	Infection disease	Autoimmune diseases	Endocrine abnormalities	Systemic disorders	Other
depression, dysthymia, anxiety-related disorders	subacute bacterial endocarditis, Lyme disease, fungal diseases	systemic lupus erythematosus myasthenia gravis	hypothyroidism hypopituitarism adrenal insufficiency	chronic renal failure, chronic obstructive pulmonary disease	inadequate rest, sleep apnea, narcolepsy
Sleep apnea	mononucleosis HIV, chronic hepatitis B/C	multiple sclerosis, thyroiditis	Cushing's Syndrome, diabetes mellitus, hyperparathyroidism	cardiovascular disease, anemia	fibromyalgia, sarcoidosis, medications, toxic agent
Substance abuse	tuberculosis chronic infections	rheumatoid arthritis	pregnancy, reactive hypoglycemia	liver disease	Wegener's granulomatosis vitamin deficiency

The importance of selected hormones in chronic fatigue syndrome diagnostics

Salivary cortisol

In recent years a great deal of research on chronic fatigue syndrome (CFS) has been conducted. However, CFS's pathophysiology, and furthermore diagnostic markers were not extensively investigated. The abnormalities in the endocrine system are frequently mentioned factors. In particular, dysfunctions of hypothalamic–pituitary–adrenal axis, which could be diagnosed as a result of decreased cortisol levels in patients with these syndromes, have considerable implications.

Renowned specialists from the Institute of Psychiatry in King's College London have indicated the importance of decreased cortisol levels in results of patients with CFS syndrome.[17] In their paper from Journal of Psychosomatic Research in November 2014, they point out the difference in results of cortisol levels between teenagers with CFS syndrome and their healthy peers. The paper also shows how cortisol levels changed after appropriate therapy. It should be noticed that the control group in the experiment was matched for age, sex, menarche status, menstrual cycle and awakening time. Additionally, cortisol levels were determined from saliva samples taken immediately after waking, several times in fifteen-minute intervals (15, 30, 45 and 60 minutes) and two samples taken during the day (at 4 p.m. and 8 p.m.). The research proved that significantly lower levels of cortisol were observed during the day in the study group, while not finding any relevant differences in the morning cortisol increase between the groups. Based on questionnaires, the relationship between the reduced daily level of cortisol with perfectionism and pro-social behaviour was discovered in the study group. Moreover, saliva samples and questionnaires showed that after therapy the daily level of cortisol (up to the to the correct level)

was raised. The results demonstrate not only the importance of hypocortisolism in CFS's pathogenesis, but also its reversible nature, as well as the large possible impact on the salivary cortisol test in the illness diagnostic process and effectiveness in therapy. In addition, growth of cortisol in patients' saliva after successful treatment was not particularly significant

The correlation between hypocortisolism and CFS as well as significance of cortisol level on patients' saliva are stressed in Dutch scientists' work, which was published in *Psychoneuroendocrinology* in April 2014. [18] To the study group were also included teenagers with diagnosed CFS. Whereas the control group was created by their peers. This time the research proved that significantly lower levels of cortisol were observed in the morning in the study group. Similarly to the research mentioned above, the increase in this hormone levels in patients' saliva after successful treatment was noticed. The above mentioned research indicates not only the relevance of hypocortisolism in CFS's pathophysiology, but also the possible application of a cortisol's level as a marker in the diagnosis and treatment monitoring process.

α -Melanocyte-stimulating hormone (α MSH)

Moreover, it is important to point out that the research on the significance of the endocrine system and disorders in its functioning in the context of pathophysiology as well as the diagnosis of chronic fatigue syndrome, is not limited to hypothalamic-pituitary-adrenal axis and hypocortisolism.

The relevant results in CFS diagnostic were shown in the work of Japanese scientists published in *BMC Neurology* in 2010. [19] The researchers decided to check the levels of α MSH in patients with CFS syndrome. Followed by previously noticed evidence that chronic stress resulted in increasing manifestation of the CFS and that animals under chronic stress had higher levels of α MSH. The study group was created by patients from Osaka City University Hospital with 10 years or shorter history of illness, diagnosed using the clinical criteria proposed by Fukuda. Whereas the control group was created by healthy people. Blood tests, taken on empty stomach, were examined on α MSH, ACTH, cortisol and DHEA-S levels. The results showed that in study group there is relatively higher levels of α MSH levels than in reference one. Moreover, based on statistics the correlation between α MSH levels in the study group with a range of factors were checked. The negative correlation between duration of illness and level of this hormone is confirmed. Furthermore, there is no proved dependency between α MSH levels and other hormones, as well as between α MSH and other features, i.e. gender, age, visual analog scale, performance status score, body mass index (BMI), blood pressure, prescribed medicine, physical and mental symptoms. For this reason the patients were divided to group of those whose illness last no longer than 5 years and group whose illness last 5-10 years. Subsequently, level of α MSH was controlled again. Patients who were ill for no longer than 5 years had significantly higher levels on α MSH than control group. Besides, any difference between patients whose illness is longer than 5 years was noticed. This interesting results prompt authors to propose an application of α MSH as a potentially diagnostic marker of chronic fatigue syndrome, at least during the first five years of the illness. [19]

Conclusions

CFS is a disease that is difficult to diagnose because it is characterized by nonspecific symptoms. Precise exclusion is the main diagnostic path thus we should start with precise anamnesis and exclusion of the diseases given in the differential diagnosis. Basic laboratory tests will allow to exclude basic diseases. It is crucial to exclude depression, as the one of the most

severe diseases considered in differentiation and disease which interfere with diagnostic tests as the source of autonomic disorders. It may be helpful to inquire about infections that have been carried out, as they may be related to the appearance of CFS. We can also use the questionnaires described above (COMPASS and CFQ). We can also measure the level of salivary cortisol and Alfa-MSH. If there is no depression, autoimmune and other diseases and COMPASS is more than 32.5, Chalder Fatigue Scale is more than 28, salivary cortisol is low and alpha-MSH is high, we can be sure that probability of CFS is higher than 95%.

Knowledge and awareness of such a condition as CFS is still insufficient in the medical society. Many doctors underestimate the main symptom of CFS – fatigue. That is why it is so important to make physicians aware of the existence of this disease entity. Today's medicine is not only focused on physical feeling, but also on the quality of life of patients. That's why CFS deserves attention, moreover, more research is needed that will give us more information about the causes and possible treatment of this disorder. What is more there is an essential need to discover possible markers of CFS and to create standardized diagnostic procedure for this underestimated disease.

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