MAIN NEUROENDOCRINE FEATURES, DIAGNOSIS AND THERAPEUTIC POSSIBILITIES IN THE CHRONIC FATIGUE SYNDROME, AN UNDERDIAGNOSED ENTITY

Ioana Cristina Amihăesei, Elena Cojocaru
University of Medicine and Pharmacy “Grigore T. Popa”- Iași
Faculty of Medicine
Discipline of Histology

MAIN NEUROENDOCRINE FEATURES, DIAGNOSIS AND THERAPEUTIC POSSIBILITIES IN THE CHRONIC FATIGUE SYNDROME, AN UNDERDIAGNOSED ENTITY (Abstract): Chronic fatigue syndrome is characterized by severe, persistent fatigue which is not relieved by rest and is not associated to other medical conditions. Other common symptoms are including concentration and memory impairment, muscle and multiple joints pain, extreme exhaustion after physical or mental exertions, irritable bowel syndrome-like symptoms and depression, anxiety, mood swings and panic attacks. Etiology of the syndrome is not yet clear, post-viral and stress hypotheses were not verified. Diagnosis is confirmed in case of new onset of severe fatigue, for six consecutive months or more; fatigue is leading to significant reduction of the activity levels and is accompanied by other four or more of the specific associated symptoms, which are also lasting for six months or longer. The management of the disease is based on cognitive behavioral therapy, graded exercise therapy and pacing; medication plays a minor role in therapy. The occupational status is severely affected, more than half of the cases being unable to work. Full recovery rate is in average of about 5 %. Keywords: CHRONIC FATIGUE SYNDROME (CFS), HYPOTHALAMIC-PITUITARY-ADRENAL AXIS (HPA axis), HYPOCORTISOLISM

Chronic fatigue syndrome (CFS) is the term used to define a significantly disabling medical condition, characterized by persistent fatigue and other troubling symptoms which are lasting at least six months in adults and three months in children or adolescents. The fatigue is not due to exertion, is not relieved by rest and is not tributary to other medical conditions (1). Other terms used to designate the syndrome are myalgic encephalomyelitis or post-viral fatigue syndrome. Although genetic, infectious and psychological hypotheses were proposed, the etiology of CFS is not known and data are supporting the idea that the syndrome should have multiple causes (2).

In 1934, an out-break of a then so-called atypical poliomyelitis took place at the Los Angeles County Hospital; numerous doctors and nurses were affected and the disease resembled a lot with what is now described as chronic fatigue syndrome. In 1955, another out-break at the Royal Free Hospital in London was called benign myalgic encephalomyelitis. The term of chronic fatigue syndrome was first introduced in 1987 (3).
**NEUROENDOCRINE FEATURES, POSSIBLE ETIOLOGY**

Main endocrinological research findings in chronic fatigue syndrome are mild hypocortisolism, a blunted adrenocorticotropin (ACTH) response to stressors and enhanced negative feed-back sensitivity to glucocorticoids. Yet, there is no specific or uniform dysfunction of the HPA axis in CFS and approximately half of the relevant studies did not show evidence of hypocortisolism, or of an abnormal response to various types of challenge tests.

Prospective studies suggest that HPA axis is not a factor involved in the pathogenesis of the early stages of CFS, but it is believed that it might play a role in perpetuation and enhance of the symptoms later on, in the course of the disease (4).

A 2011 meta-analysis evidenced a mild but statistically significant hypocortisolism in chronic fatigue syndrome; hypocortisolism being associated with a weaker response to cognitive behavioral therapy (5).

At the level of the central nervous system, a hyperserotonergic state and hypoactivity of the HPA axis are characteristic, but still there is no answer if these abnormalities are a cause or a consequence of the syndrome. Alterations in serotonin signaling can develop physiologic and behavioral changes in these subjects (3).

Polymorphism in genes encoding serotonin pathways may show genetic predisposition in the pathophysiology of CFS. Gene-related dysfunction of HPA axis which regulates the stress response might be involved in CFS (6).

A prospective study found that after viral and non-viral infections, some of the cases met the criteria for CFS, concluding that post-infective fatigue syndrome is a valid model for the investigation of one possible pathway to CFS. Nevertheless, prevalence and roles of both infection and stress in the etiology of the syndrome are not known (7).

All racial and ethnic groups are affected by the disease; lower income groups of population show a slightly higher risk to develop chronic fatigue syndrome. Between 60 and 85 % of cases of CFS are women but it seems that the prevalence among men is underreported. The disease is occurring more frequently between the ages of 40 and 59; CFS is developing more rarely among children and adolescents than among adults. Blood relatives of people with chronic fatigue syndrome seem to be more predisposed to develop the disease than the rest of the population (7, 8). National health organizations estimated that more than one million Americans and a quarter of a million people in the UK have chronic fatigue syndrome; even more, it is estimated that approximately 80 % of the existing cases are undiagnosed (8).

**DIAGNOSIS**

The onset of CFS is abrupt, frequently accompanied by a flu-like illness, while a large number of cases begin with several months of severe adverse stress (9).

The three most important diagnosis criteria are: a new onset of severe fatigue for six consecutive months or more, not related to effort, not substantially relieved by rest and which is not determined by other medical conditions; the fatigue is the cause of significant reduction of the previous activity levels. These criteria are associated with four or more of the following symptoms, lasting six months or longer: post-exertion malaise, physical or mental effort bringing on extreme, prolonged exhaustion and sickness; impaired memory or concentra-
tion, unrefreshing sleep; muscular pain, multiple joints pain, headaches of a new type or more severe, recurrent sore throat, cervical or axillary tender lymph nodes.

Other common symptoms are: brain fog, difficulty in maintaining orthostatic condition (dizziness, balance problems or fainting); irritable bowel syndrome-like symptoms, such as bloating, stomach pain, constipation, diarrhea and nausea; chills and night sweats; visual disturbances (sensitivity to light, blurring, eye pain); allergies or sensitivities to foods, odors, chemicals, medications or noise; depression, anxiety, panic attacks, mood swings. Cognitive symptoms are especially deficits of attention, memory and reaction time. Processing speed of complex and simple information is impaired (10, 11).

A common diagnosis of CFS is characterizing a disease in which functional capacity of the affected subjects is varying a lot. While there are cases which had relatively normal lives, there are others who are totally bed-ridden and are unable to take care for themselves. The majority of the persons with CFS diagnosis are drastically reducing work, school and family activities, for long time periods. Severity and disability of the syndrome are the same in both genders (11, 12).

Many cases are suffering from disabling chronic pain. Important reduction in the level of physical activity and in the complexity of the conducted activities, were noticed. The impairment is comparable to that found in late-stage AIDS, lupus, rheumatoid arthritis, chronic obstructive pulmonary disease and end-stage renal disease (13). CFS affects the functional capacity and the well-being of an individual, more than major medical conditions such as multiple sclerosis, congestive heart failure and type II diabetes mellitus (14).

Since there are no characteristic laboratory abnormalities to diagnose chronic fatigue syndrome, the recommended tests are used to exclude other causes for typical symptoms. Conditions which must be excluded are hypothyroidism, anemia, diabetes, psychiatric disorders – major depression, anorexia nervosa, bulimia, bipolar disorder, alcohol and other substances abuse. Multiple chemical sensitivity, Gulf War syndrome and post-polio syndrome have symptoms similar to those of CFS (14).

**THERAPEUTIC POSSIBILITIES**

Most often, even under therapy, a full recovery from chronic fatigue syndrome is rare. Cognitive behavioral therapy, graded exercise therapy, as well as pacing have been moderately effective for many cases. These therapeutic methods are useful in monitoring and self-consciousness, in managing the symptoms and adapting the level of activity to the possibilities of the subject (15). Since the syndrome is polymorphous and shows different manifestations in different subjects, the therapy should be adapted to the needs of each individual.

Medication plays a minor role in management of the syndrome. Antidepressants and immune-modulators are used; the role of antidepressants remains controversial (16, 17).

**PROGNOSIS**

Evolutions with remission and relapse, which make more difficult the management of the syndrome, are frequent. In remission, the extending of the activities may easily worsen the symptoms, with relapse.

Occupational disability is important, since more than half of the cases are unable to work, while almost two-thirds of the cas-
Main neuroendocrine features, diagnosis and therapeutic possibilities in the chronic fatigue syndrome, an under diagnosed entity

es are limiting their work; less than a fifth of the cases are working full-time (11).

The average full recovery rate in people with chronic fatigue syndrome is of 5 % (range 0-31 %). In the conducted studies, an improvement with consequently in-
crease of the quality of life, is reported in 39.5 % (18).

Yet, the etiology, pathophysiology, no-
mencature and diagnostic criteria of the chronic fatigue syndrome are a matter of controversy among specialists (18).

REFERENCES