

Chronic fatigue syndrome after neuroborreliosis in farmers from Lublin region (Poland)

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Abstract: Chronic Fatigue Syndrome (CFS) is characterized by a chronic (lasting longer than 6 months) feeling of fatigue and a complex of other symptoms that include headache, muscle and joint aches, memory and concentration disorders, and others. Its etiology is not known. There are no objective methods for confirming the illness nor its causal treatment, which of course, makes the whole matter so. There are suggestions that CFS may be a result of chronic inflammation. In order to consider the potential existence of a causal link between CFS and infection, 48 farmers (everyone in the service region, after exclusions for cause) who suffered from neuroborreliosis were examined 6 months or later after the occurrence of disease. In this group, 37 (77%) presented a clinical picture of CFS. Furthermore, of these 37 people, the condition of 29 (78%) improved after receiving comprehensive symptomatic treatment for CFS. The results are twofold. First, all subjects with borreliosis showed one or more chronic fatigue syndrome attributes after the course of the disease, with 75% meeting all the CDC criteria for CFS. Second, the combined symptomatic treatment, on a patient-by-patient basis, for each manifested clinical CFS symptom, more than 75% demonstrated improvement.

Key words: neuroborreliosis, chronic fatigue syndrome, CFS, myalgic encephalomyelitis

INTRODUCTION

Chronic Fatigue Syndrome is characterized by a chronic (lasting longer than 6 months) feeling of fatigue and a complex of other symptoms that include headache, muscle and joint aches, memory and concentration disorders, and others. According to data from the Centers for Disease Control and Prevention (CDC) its prevalence in the USA is 75-267/100,000. The syndrome has been recognized in subjects aging from 5-65 years, although there is prevalence for ages between 25-40. A slight prevalence of females was also noted (56%). The syndrome is more common in Caucasians. Although the syndrome may affect family members, isolated cases were far more common [1].

CFS starts suddenly with flu-like symptoms, high temperature, sore throat, headache, muscle aches, stomach aches, and includes a general debility together with a feeling of fatigue and discomfort. Oversensitivity to light and cold, and sensitivity of the lymphatic nodes can also appear. In the case of infection, these symptoms usually disappear in a few days, while in the case of CFS, they continue to last with differing intensity over many months, or even years. In many cases, the beginning of the illness is difficult to notice. The symptoms increase gradually and after a certain time achieve an alarming intensity [1].

The first and most important way to recognize chronic fatigue syndrome is fatigue that can last longer than 6 months. There are no objective changes to explain its occurrence. There are no specific changes in routine laboratory and X-ray tests

[2, 3, 4]. The only possible methods of diagnosing chronic fatigue syndrome are to interview and to examine the patient. Experts at the Centers for Disease Control have developed criteria for diagnosing and differentiating the chronic fatigue syndrome [5, 6, 7]. Patients fulfilling these criteria can be diagnosed as suffering from the syndrome. As for the actual cause, different hypothesis may be considered [8, 9].

Infectious etiology prevails [10, 11]. A possible connection between the CFS and chronic infection of Epstein-Barr virus has also been considered, but to date, morbidity has not been well documented. Patients with CFS were also examined for other infections, including HSV, human herpes virus – 6 (HHV-6), human T cell lymphotropic virus (HTLV-II), Cocksackie B, cytomegalovirus, retroviruses, enteroviruses, and tick encephalitis virus. The literature suggests a possible connection between chronic fatigue syndrome and *Borrelia burgdorferi* infection [12, 13, 14]. It has been shown for healthy subjects with positive levels of borreliosis antibodies (in the absence of any clinical manifestation of any form of the disease) may suffer significantly more often from CFS than seronegative groups [14, 15]. Other researchers, however, state that disorders connected with borreliosis are different from those of chronic fatigue syndrome [13].

MATERIALS AND METHODS

Subjects. The study group consisted of 48 individuals who had confirmed diseases conveyed by ticks, and had sought and received treatment for nervous system involvement from borreliosis. Excluded were subjects with co-morbidities, which might have influenced the clinical picture of neuroborreliosis. The ages of the subjects ranged from 5-65 years; the majority were between 25-40, rather more women than men (56%),

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with an average age of 39. All of had suffered from the disease for at least 6 months before enrollment for the test. Self-exclusions were few (less than 3%). 48 people took part in the examination during a period of at least 6 months, to as long as 6 years after borreliosis with CNS involvement. The patients diagnosed because of severe illness episode transmitted by tick (interview) during the years of 1995-2000 were selected. The data was verified on the basis of interviews with patients. Only patients hospitalized because of the disease transmitted by tick were included in the examination. Patients were treated causally and had full medical documentation. Patients who remembered the episode of being bitten were included, and the interview about the disease showed the connection with the occurrence with disease. Patients were included during the period of performance of the study so that they could have at least one check up in at least 6 months after enrolment.

Patients with the following ailments were excluded from the examination:

1. autoimmune diseases such as: lupus (SLE), multiple sclerosis SM, Sjögren syndrome, rheumatoid joint infection (RA), rheumatic disease;
2. viral hepatitis or other chronic infections (AIDS, tropical infections), cancers, sarcoid, and myasthenia gravis;
3. psychosis and other serious psychological disturbances, including those before falling ill;
4. current drug and alcohol addiction or abuse.

Persons who had high levels of positive IgG and IgM and those after KZM were also excluded from the assessment.

Serological method. Borrelia ELISA (Biomedica IgG, IgM, Austria) was used to diagnose the infection. Results were expressed in BBU/ml and considered to be positive according to the levels listed below:

- 9-10 = border line;
- 11-20 = positive;
- 21-30 = highly positive;
- >30 = extremely highly positive.

During the acute period of the disease, all the patients were highly positive and extremely highly positive both in sera and cerebrospinal fluid, both in IgM and IgG classes of immunoglobulines.

In order to avoid dementia, patients over the age of 65 were also not enrolled.

The patients were examined on the day of enrolment, and Neurological, psychological and sera serological examinations were performed.

The protocol was approved by local Bioethical Committee of the Institute of Agricultural Medicine in Lublin.

All participants were voluntary and signed informed consent.

Data for this research were collected by questionnaire with particular attention to the CDC criteria for the chronic fatigue syndrome, physical examination, and serological testing. Each subject underwent a differential diagnostic, covering autoimmune disease, chronic infection, psychosis, primary sleep disorders, multiple sclerosis, other infectious diseases, and severe cognitive impairment. All cases of self-reported, long-lasting fatigue were excluded. However, the feeling of fatigue occurring after neuroborreliosis qualified as positive. In all cases, this fatigue had a sharp or gradual but definite beginning. Subjects with significant fatigue were qualified as follows:

1. no effect on the fatigue of effort or exercise;
2. fatigue not disappearing after rest, or also occurring in the morning (after waking);
3. fatigue causing lack of normal functioning.

Subjects were asked about the following symptoms (the CDC criteria list for CFS; 4 or more positive out of 8 required for positive diagnosis) [5]:

1. short-term memory disorders or severe concentration disorders affecting work, school or normal activity of the patient;
2. sore throat;
3. sensitive lymphatic nodes (neck or axillaries);
4. muscle aches;
5. joint aches (without swelling or redness);
6. intense headaches;
7. sleep giving no feeling of rest;
8. fatigue lasting longer than one day after even the smallest effort.

Other typical symptoms were also assessed, which consisted of the following:

1. disorders of thinking and attention;
2. sleep disorders in the form of insomnia or hypersomnia;
3. emotional changes – irritability, emotional liability, generalized anxiety, despair, feeling of isolation and loneliness;
4. hypotonia;
5. hypertonia to a small degree;
6. weight changes (typically initial loss of weight, then weight gain);
7. ache in abdominal cavity;
8. heart rhythm disorders (tachycardia, extrasystolia);
9. libido reduction, sexual function disorders.

After contracting neuroborreliosis, subjects frequently suffer from anxiety and depressive disorders, a possible reaction to the disease. According to the diagnostic criteria for CFS, subjects with anxiety and depressive disorders were not excluded [5].

RESULTS

For subjects after neuroborreliosis, CFS was diagnosed in 36 persons (75 % of the group). The most frequent pivotal symptoms were short-term memory disorders, muscle and joint aches, and sleep disorders (Table 1). Hypotonia and other symptoms of undetermined cause in abdominal cavity were observed (Table 2). The key findings are as follows:

1. 77% of all patients who contracted neuroborreliosis and were treated for the initial infection, showed positive for CFS;

Table 1 Pivotal symptoms of chronic fatigue syndrome in the group with neuroborreliosis (presence of 4 of the 8 following is essential).

Chronic fatigue syndrome 4 from 8	%	Number of patients
1. Short-term memory disorders	71	34
2. Sore throat	42	20
3. Sensitive lymphatic nodes (neck or axillaries)	15	7
4. Muscle aches	77	37
5. Joint aches (without swelling or redness)	77	37
6. Intensive or changing headaches	69	33
7. Sleep giving no rest	77	37
8. Fatigue lasting >1 day after effort	77	37

Table 2 Additional symptoms of CFS in patients with neuroborreliosis

Symptoms of chronic fatigue syndrome (other)	%	Number of patients
1. disorders of thinking and perception	44	19
2. hyperthermia	25	12
3. other sleep disorders	29	14
4. emotional changes	36	19
5. sensual function disorders	25	12
6. weight changes	35	17
7. aches in abdominal cavity	50	24
8. heart rhythm disorders	17	8
9. hypotonia	54	26
10. libido reduction, sexual function disorders	25	12

2. of the CFS positive subjects, a preponderance (78%) responded positively to a (CDC recommended) comprehensive regimen of symptomatic treatment;
3. of all patients who contracted neuroborreliosis and were treated for the initial infection, none demonstrated a clinical presence of disease at the time of study; they were therefore not suggested for an antibiotic course of treatment for CFS;
4. all patients who contracted neuroborreliosis and were treated for the initial infection exhibited 2 or more of the criteria (but less than the 4 required) for CFS diagnosis, resulting in all of them experiencing chronic discomfort.

DISCUSSION

Chronic fatigue syndrome is not a contagious illness, and no epidemic occurrence has been found. Many papers suggest the coexistence of infectious, metabolic, or immunological factors in the pathogenesis of CFS. Since we know of no single pathogenic factor, a possible heterogenic etiology of CFS is often taken into consideration. Despite the fact that cases of family occurrence of the disease exist, isolated occurrences are far more frequent. Significant immunological disorders are observed in subjects suffering from CFS. The most common pathologic affect is diminished cytotoxicity of the natural killer cells. There is also a disturbance of equilibrium among T-lymphocytes in favour of those acting against infection; it is therefore suggested that the symptoms of chronic fatigue syndrome may be caused by a chronic, weak stimulation of the immunological system. A likely candidate for this would be IL-2 a stimulation of which or when administered to subjects caused the same symptoms as those for chronic fatigue syndrome. Growth of the IL-2 level, however, was not observed; instead higher levels of C-reactive protein, B₂-microglobulin and neopterin were found in sera of the subjects with chronic fatigue syndrome, compared with the healthy control group [16, 17]. Interestingly, it has been shown that over 65 % of subjects with chronic fatigue syndrome suffer from different forms of allergy [18].

The cause of chronic fatigue syndrome is unknown, and there is no known course of causal treatment. In many clinical tests, however, improvement was achieved, although this remains to be confirmed by other research. This leaves the treatment of patients with chronic fatigue syndrome as an individually planned regimen. First and most important is a confirmed diagnosis, following which a reduction of anxiety is especially beneficial. Patients are then informed that

despite the fact that no recognized therapy exists, appropriate treatment can diminish symptoms and improve the quality of life. Non-pharmacological methods for the treatment of CFS may also be effective. These methods include change of lifestyle, physical exercises, physiotherapy, and attention to diet. Follow-up visits should take place at 6-month intervals to assess the patient's condition, correct the therapy, and most important, to ensure that the diagnoses of chronic fatigue syndrome does not conceal a serious organic disease. This is especially important in cases with additional new symptoms. What follows are comments on the most frequent symptoms of CFS in study subjects and their treatment. There is a currently prevailing opinion that chronic fatigue syndrome is only one element of the so-called Post-Lyme Syndrome, in which mood and cognition disorders may be found [13].

Much literature data emphasize the occurrence of mood disorders connected with diseases conveyed by ticks, especially borreliosis. Furthermore, mood disorders are the dominant symptom in the clinical picture [14]. The literature suggests that depression was a serious problem in patients who suffered from borreliosis [19]. Study subjects with CFS reacted well to small doses of antidepressant drugs. The literature also reports that small doses are used in the case of chronic fatigue syndrome, since therapeutic doses increase the feeling of fatigue [5, 6]. This therapy may also help identify the difference between chronic fatigue syndrome and depression in the following way: in CFS, antidepressant drugs improve mood and sleep, but do not affect other symptoms, whereas in endogenous depression, all symptoms should decrease together with improvement in mood. This effect was observed in our patients.

Besides depression, attention disorders and emotional disorders are often observed as a result of borreliosis, and these tend to dominate the clinical picture over fatigue and other pivotal symptoms of CFS. Emotional changes – irritability, emotional lability, generalized anxiety, despair, feeling of isolation and loneliness were reported in 36% of our patient with CFS.

Almost one third of patients with CFS had sleep disorders. Contrary to depression, sleep disorders in chronic fatigue syndrome refer to the non-REM phase. In our patients, we observed difficulty in falling asleep rather than awakening. The treatment of sleep disorders is crucial, since many other symptoms seem to be secondary to them. This is important, since the improvement of sleep significantly reduces the intensity of other symptoms. Typical hypnotics are often used, as are tricyclic antidepressant drugs and sedatives. Unexplained abdominal pain is reported in course of CFS. This symptom was also common in our patients (50%). It was reported that gastric disorders usually disappeared after administration of the histamine receptor blocker H₂ [11, 20]. This treatment was used in our patients and was generally effective.

The anamnesis of subjects after neuroborreliosis was augmented by enquiry into the possible presence of persistent hypotonia. Persistent hypotonia was recorded in 61% of the subjects. Many authors emphasize that hypotonia is a pivotal symptom observed during patient examination. This has also been confirmed by the results of the presented study. Bou-Holaigah *et al.* [21] demonstrated hypotonia during the tilt-test in 96% of their subjects. This confirms the presence of central blood pressure regulation disorder. Literature postulates that the primary infection damages the central nervous system, and such damage appears as vaso-vagal

syndrome. The presence of viral infection symptoms at the beginning of the disease confirms the theory, as do persistent symptoms primarily connected with blood pressure regulation. Other research teams [22] suggest the possibility of cortisol shortage in subjects with chronic fatigue syndrome. In a different study, treatment with steroids (cortisol) produced only a small improvement, but resulted in a large number of side effects. Hypotonia was an important symptom exhibited by the examined subjects. Our study subjects who were positive for tilt-test were treated with an appropriate diet. In cases where diet control alone was insufficient, steroids were included. Analyzing the published reports on the natural process of the disease, it was noted that total recovery is rare (2-5% of patients during a 2-years observation period), but the improvement of health is frequent (40-64% of patients). In our study group, a substantial number showed such an improvement in their health. Subjects with borreliosis improved in up to 78% cases after the comprehensive symptomatic treatment recommended in chronic fatigue syndrome.

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