Chronic fatigue syndrome after the neuroborreliosis infection

Syndrom chronicznego zmęczenia po przebytej neuroboreliozie

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Wstęp. Syndrom chronicznego zmęczenia charakteryzuje się przewlekłym (trwającym dłużej niż 6 miesięcy) uczuciem wyczerpania i kompleksem innych objawów, takich jak: bóle głowy, bóle mięśni i stawów, zaburzenia pamięci i koncentracji, itp. Przyczyna syndromu chronicznego zmęczenia nie jest znana, nie istnieją obiektywne metody diagnostyczne potwierdzające chorobę i jej leczenie przyczynowe.

Cel pracy. Niniejsza praca ma na celu analizę występowania syndromu chronicznego zmęczenia wśród pacjentów, którzy chorowali na neuroboreliozę.

Materiał i metoda. Biorąc pod uwagę relację między zespołem przewlekłego zmęczenia i zachorowaniem na neuroboreliozę, w 2010 roku przebadano 48 pacjentów przy użyciu kwestionariusza ankiety, ze szczególnym uwzględnieniem kryteriów CDC dla syndromu chronicznego zmęczenia. Wykonano diagnostykę różnicową, która obejmowała: choroby autoimmunologiczne, przewlekłe infekcje, psychozę, pierwotne zaburzenia snu, itp.

Wyniki. W grupie badanych nie mniej niż 71% badanych stanowiło przypadki kliniczne. W 61% przypadków badanych leczonych objawowo, uzyskano poprawę stanu zdrowia.

Wnioski. U pacjentów z przebytą neuroboreliozą często dochodzi do występowania syndromu chronicznego zmęczenia.

Słowa kluczowe: *borelioza, zespół przewlekłego zmęczenia, post-wirusowe zmęczenia*

Introduction. Chronic Fatigue Syndrome is characterized by a chronic (longer than 6 months) feeling of fatigue and a complex of other symptoms such as: headaches, muscle and joint pains, memory and concentration disorders, etc. Its cause is unknown, there are no objective methods of confirming the illness and its causal treatment.

Aim. This paper aims to analyze the prevalence of chronic fatigue syndrome among patients who suffered from neuroborreliosis.

Material & Method. Considering the relations between the chronic fatigue syndrome and the neuroborreliosis infection, 48 patients were examined through a questionnaire with a particular regard of the CDC criteria for the chronic fatigue syndrome in 2010. The patients underwent the differential diagnostic which covered: auto-immunological diseases, chronic infections, psychosis, primary sleep disorders, etc.

Results. In this group no less than 71% represented such clinical picture. Moreover, in 61% cases improvement was achieved after symptomatic treatment advised for chronic fatigue syndrome.

Conclusion. Patients after the neuroborreliosis infection often manifest the chronic fatigue syndrome.

Key words: *borreliosis, chronic fatigue syndrome, post-viral fatigue syndrome*

© **Hygeia Public Health 2013, 48(1): 67-72**

www.h-ph.pl

Nadesłano: 15.01.2013
Zakwalifikowano do druku: 20.02.2013

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Introduction

Chronic Fatigue Syndrome (CSF) is characterized by a chronic feeling of fatigue and a complex of other symptoms. According to the evaluations of Centers for Disease Control and Prevention (CDC) its morbidity in the USA is 75-267/100.000. This syndrome was recognized in patients aged from 5 to 65 years, however, there is a prevalence of patients aged between 25 and 40 years [1]. Younger patients and those without concomitant psychiatric diseases show the best prognosis, although other studies have estimated that the rates for both groups are similar [2].

In children, early dissemination and especially neuroborreliosis usually occurs earlier than in adults. This might be due to a different site of the tick bite. In children the upper trunk and the head are selected more often by the tick than in adults [3].

It has a 2-3 times higher prevalence in women than in men. When analyzing the psychological aspects in adolescents who fulfill the CFS diagnostic

criteria, more than 1/3 have psychiatric diagnoses at the same time, particularly depression, and less often, a generalized anxiety disorder [4].

No evidence exists showing that any socio-economic group is affected most. There were more cases of the syndrome among people of Caucasian race. The illness can affect family members, but isolated cases were found more often.

Most often the chronic fatigue syndrome starts acutely with the flu symptoms (temperature, sore throat, headaches, muscle or stomach pains, general weakness, feeling of fatigue and discomfort), depressive symptoms, cognitive disorders, sleep disorders, or intolerance to physical exertion [5-7]. Oversensitivity to light and cold and sensitivity of lymphatic nodes can also appear. In case of infection these symptoms withdraw in few days, while in case of chronic fatigue syndrome they last continuously with different intensity for months or even years.

In many cases the beginning of the illness is difficult to show, the symptoms increase gradually and after a certain time they achieve an alarming intensity [8].

The first and the most important condition of recognizing the chronic fatigue syndrome is the presence of fatigue, which lasts longer than 6 months and is difficult to explain. There are no objective changes to explain it. There are no specific changes in routine laboratory and X-ray tests [9-12].

The only possible methods of diagnosing the chronic fatigue syndrome are the interview and clinical examination regarding the exact differential diagnostic.

The group of experts from Centers for Disease Control has worked out the criteria of diagnosing and differentiating the chronic fatigue syndrome [13-15]. Patients fulfilling these criteria can be diagnosed as suffering from the chronic fatigue syndrome. As the cause of the chronic fatigue syndrome is unknown, different hypotheses can be taken into consideration [16,17].

The chronic fatigue syndrome (CFS) is known under a variety of names, including allergic encephalomyelitis, immune dysfunction syndrome, neuroendocrine immune dysfunction syndrome, post viral syndrome, Iceland disease, neurasthenia, and Royal Free disease, among others.

The theory of infectious etiology prevails [18-20]. A possible connection between the chronic fatigue syndrome and chronic infection of Epstein-Barr virus was also considered, but so far it remains unproved. The patients with the chronic fatigue syndrome were also examined towards other infections, such as: HSV, human herpes virus-6 (HHV-6), human T cell lymphotropic virus (HTLV-II), Coxsackie B, cytomegalovirus, retroviruses, enteroviruses and also tick encephalitis virus, hepatitis C virus (HCV) [21]. Chronic bacterial infections may also lead to the chronic fatigue syndrome [22]. Patients with chronic fatigue may have intracellular Chlamydia spp. or mycoplasmal infections. Brucellosis and tuberculosis are also important causes of chronic fatigue [23].

It is currently known that the relationships between different parts of the nervous system are mediated by neurotransmitters and that their disorders lead to unbalanced functioning of certain structures and to the development of well known diseases. In patients with fibromyalgia it is known that different clinical manifestations will appear according to the type and the site of action of affected neurotransmitters [24].

Much data from the literature emphasize the connection of the chronic fatigue syndrome with Borrelia burgerdorferi infection [25-27]. In the USA only one species of *B. burgdorferi* sensu lato – namely *B. burgdorferi* sensu strictu – is responsible, whereas in Europe further species – *Borrelia afzelii* and *Borrelia garinii*, and recently *Borrelia spielmanii* [28, 29] – have been identified.

It was proved that patients with positive levels of borreliosis antibodies significantly more often suffer from the chronic fatigue syndrome than those with the seronegative ones [27, 30]. Other researchers state that disorders connected with borreliosis are of a different character that those in the chronic fatigue syndrome [26].

Aim

The aim of this work is an analysis of a group of patients after neuroborreliosis from the point of view of the chronic fatigue syndrome.

Material and Methods

The analysis was applied to a group of 48 persons who had had diseases conveyed by ticks. The average age of the patients was 39 years. All of them suffered from the disease for at least 6 months before the test enrolment.

The study data were collected by means of a questionnaire with focus on the CDC criteria for the chronic fatigue syndrome in 2010.

The patients were submitted for the differential diagnostics which covered:

Auto-immunological diseases, chronic infections, psychosis, primary sleep disorders, etc. The cases of fatigue lasting, according to the patients' report: 'since they remember', were excluded.

As positive was qualified the feeling of fatigue which occurred after borreliosis and was not observed before the disease. In all cases it had a definite or gradual but certain beginning. Patients with significant fatigue were qualified, with symptoms such as:

– being no effect of effort or exercising,
– not disappearing after rest or occurring also in the morning (after waking up),
– causing the lack of normal functioning

Patients were asked about the following symptoms (there had to be 4 from the 8 allowing for the diagnosis of the chronic fatigue syndrome) [15].

1. short-term memory disorders or severe concentration disorders affecting work, school or normal patient's activity;
2. sore throat;
3. sensitive lymphatic nodes (neck or auxiliary);
4. muscle pains;
5. joint pains (without swelling or redness);
6. headaches of changing intensity;
7. sleep giving no rest;
8. fatigue lasting longer than 1 day after any little effort.

Other typical symptoms were also assessed, which consisted of:

- muscle and joint pains,
- disorders of thinking and perception,
- sleep disorders in form of insomnia or hypersomnia,
- headaches,
- emotional changes – touchiness, emotional liability, generalized anxiety, despair, feeling of isolation and loneliness,
- disorders in sensual functioning,
- hypotonia,
- hypertonia of a small degree,
- weight changes (typically – the loss of weight at the beginning, and then gradual gain),
- aches in abdominal cavity,
- heart rhythm disorders (tachycardia, extrasystolia),
- libido reduction, sexual function disorders,

The patients after borreliosis with nervous system seizure or tick encephalitis frequently suffered from anxiety and depressive disorders which might be their reaction to the disease.

It must be emphasized that according to the diagnostic criteria of the chronic fatigue syndrome, patients with anxiety and depressive disorders were not excluded [15].

Results

After diagnoses, the chronic fatigue syndrome was recognized among 43 patients, which makes 50% of the examined group. In the subgroup of patients after borreliosis the chronic fatigue syndrome was diagnosed in 34 persons (up to 71% of this group) (Tab. I).

Table I. Number of patients with chronic fatigue syndrome

	Number of patients	%
Tick	9	24
Encephalitis	0	0
Borreliosis	34	71

In the examined group, frequent pivotal symptoms were memory disorders, joint pains and sleep disorders.

Table II. Pivotal symptoms of the chronic fatigue syndrome. The presence of 4 from the 8 following is demanded.

Chronic fatigue syndrome symptoms – 4 from 8	%	The number of patients
1. short-term memory disorders	81	35
2. sore throat	46	20
3. sensitive lymphatic nodes (neck or auxiliary)	16	7
4. muscle pains	76	33
5. joint pains [without swelling or redness]	86	37
6. headaches of changing intensity	76	33
7. sleep giving no rest	86	37
8. fatigue lasting >1 day after effort	93	40

Hypotonia and undetermined troubles in abdominal cavity were observed.

Table III. Additional symptoms

Symptoms of the chronic fatigue syndrome [other]	%	Number of patients
1. disorders of thinking and perception	44	19
2. hypertermia	28	12
3. other sleep disorders	33	14
4. emotional changes	44	19
5. sensual function disorders	28	12
6. weight changes	40	17
7. aches in abdominal cavity	56	24
8. heart rhythm disorders	17	8
9. hypotonia	60	26
10. libido reduction, sexual function disorders	28	12

The patients were treated symptomatically according to the treatment recommended for the chronic fatigue syndrome. 61% the patients with borreliosis improved.

Discussion and conclusion

Since there is lack of one pathogenic factor, often a possible heterogenic etiology of the chronic fatigue syndrome is taken into consideration – coexistence of infectious, metabolic and immunological factors.

The chronic fatigue syndrome is not a contagious illness and its epidemic occurrence was not found. Despite the fact that the cases of family occurrence of the disease are not rare, the isolated occurrence is far more frequent.

However, immunological disorders are significantly often observed in patients suffering from the chronic fatigue syndrome. The most often observed disorder is diminished cytotoxicity of the natural killer cells. There is a percentage disturbance of equilibrium among T-lymphocytes in favor of those fighting against infection, so it is possible that symptoms of the chronic fatigue syndrome are caused by a chronic, weak stimulation of the immunological system. This stimulation would induce the growth of cytokine level, which (e.g. IL-2) administered to patients, cause the same symptoms, as those found in the chronic fatigue syndrome. But the growth of the IL-2 level was not observed. Instead, higher levels of C-reactive protein, B2- microglobulin and neopterin were found in serum of the patients with the chronic fatigue syndrome in comparison with the healthy control group [31,32]. It was proved that over 65 % the patients with the chronic fatigue syndrome suffered from different forms of allergy. Currently there is no scientific evidence to attribute the cause of this syndrome to a primary disorder of the immune system [33-36].

Progressive inflammatory reactions have been proposed as a model to explain disease progression in depression, psychosis, dementia, epilepsy, autism and other mental illnesses and pathophysiological changes have been associated with oxidative stress, excitotoxicity, changes in homocysteine metabolism and altered tryptophan catabolism [37].

There are different degrees of evidence that infections and the immune reactions to them can cause degenerative neurological disease, mental illness, cognitive decline, developmental disabilities, personality changes and violence and the pathophysiology needs better clarification [38-40]. The disease can result from an interaction of predisposing and precipitating factors [41].

The anamnesis of patients with borreliosis or tick ecephalitis included, among other symptoms for the chronic fatigue sydrome, a persistent hypotonia. It was recorded in 61% of the patients.

However, hypotonia is a pivotal symptom, many authors emphasize its occurrence, what is also confirmed by the results of this work.

Bou-Holaigah et al. [42] demonstrated symptomatical hypotonia during the tilt-test in 96% of the ill. This confirms the presence of central blood pressure regulation disorder.

There is a hypothesis that the primary infection damages the central nervous system. The presence of viral infection symptoms at the beginning of the disease would confirm the theory, as well as further persistent symptoms primarily connected with blood pressure regulation. Other research teams [43] suggest the possibilities of cortisol shortage in patients with the chronic fatigue syndrome.

Subtitutional cortisol treatment brought only a small improvement and a great number of side effects, so this therapy must be rejected.

Further studies [44] did not confirm this hypothesis.

Much literature data emphasize that there occur mood disorders after diseases conveyed by ticks, especially borreliosis. Moreover, they are a dominating symptom in the clinical picture [25].

Attention disorders are often observed after tick encephalitis and borreliosis with the nervous system seizure. They dominate in the clinical picture over fatigue and other pivotal symptoms of the chronic fatigue syndrome.

Depression as a symptom or neurosis unrelated to psychosis does not eliminate the chronic fatigue syndrome. Many researchers think that they are a natural reaction to the disease, which is a severe psychical experience itself.

The knowledge of the following facts may be helpful in the initial differentiation between endogenous depression and chronic fatigue syndrome: in the chronic fatigue syndrome, contrary to depression, many 'bodily' symptoms are present, there is no seasonal intensification of symptoms (spring and autumn), in patient's belief the disease has a rather organic than a psychical cause, the patients doubt in their possibilities rather than blame themselves for all failures, as it happens in case of depression.

Contrary to depression, in the chronic fatigue syndrome sleep disorders refer to non-REM phase. The treatment of sleep disorders is crucial, because many other symptoms seem to be secondary to them.

Currently prevails the opinion that the chronic fatigue syndrome is only one element of the so Post Lyme Syndrome, where mood and cognition disorders can also be found [26, 45-47]. It is very important, because the main co-morbidity is related to psychiatric disorders, such as depression or anxiety, with an approximate incidence of 28% in the Western population [48].

Chronic infections have been recognized to cause chronic stress, sleep disorders, cognitive impairments and chronic fatigue. Sleep disorders are commonly associated with chronic inflammatory diseases and chronic stress-related disorders. The best studied in this regard are rheumatoid arthritis, fibromyalgia, chronic fatigue syndromes and Lyme disease [49].

The cause of the chronic fatigue syndrome is yet unknown [50], so there is no method of the causal treatment. In many clinical tests improvement was achieved. This however was not confirmed in other studies or they turned out to be an open test (without a control group), which significantly impaired its scientific usefulness. No optimum therapy was found, so the treatment of patients with the chronic fatigue syndrome has to be individually fitted.

Diagnosis is the first and very important part of therapy. The reduction of anxiety is especially important for the patient.

The patient should be informed that despite no recognized therapy, some methods can tone down the disorders and improve health status and that there is hope of full recovery. Non-pharmacological methods are effective in the chronic fatigue syndrome treatment, such as: changing the lifestyle, less stress (stress strengthens the symptoms of the chronic fatigue syndrome), physical exercises, physicotherapy, diet. The treatment of sleep disorders seems to be the most important, because sleep improvement may significantly reduce the intensity of other symptoms. Most often typical hypnotics are used, but also tricyclic antidepressant drugs and sedatives. In case of pain non-sterid antiphologistic drugs were administered up to narcotic analgesics in the most severe cases.

Muscle and joint pains were treated mainly by the NLP drugs. Gastric disorders usually passed after the administration of histamine receptor blocker H2 [19, 51].

Depression was a serious problem both in patients after tick encephalitis and borreliosis. Patients with the chronic fatigue syndrome reacted well to small doses of antidepressant drugs. Small doses were used because in case of the chronic fatigue syndrome, therapeutic doses increase the feeling of fatigue [13, 14].

This kind of therapy can also help to differentiate finally between the chronic fatigue syndrome and depression. In the chronic fatigue syndrome the antidepressant drugs improve mood and sleep and do not influence other symptoms, while in endogenous depression all symptoms withdraw together with the mood improvement.

Hypotonia was an important symptom manifested by the examined patients. In chosen cases TILT-test was done. In case of a positive test, an appropriate treatment was included.

The trial of using the NADH (reduced nicotynamidadenine nucleotid) in treating the chronic fatigue syndrome carried on by FDA (Food and Drug Administration) seems to be very hopeful. It is hard to draw final conclusions before it ends, but the initial reports are very enthusiastic, as far as the patients' health improvement is considered. NADH being a coenzyme of oxyreductive reactions fulfils a key part in intracellular energetic transformations, so the possibility of its shortage would soundly explain most of the chronic fatigue syndrome symptoms.

Many authors emphasize that in case of the chronic fatigue syndrome control visits should take place at least once in 6 months. Their aim is to correct the therapy and, what is more important, to check if the diagnosis of the chronic fatigue syndrome does not conceal a serious organic disease, especially in case of new symptoms.

Analyzing the reports on natural process of the disease, we note that total recovery is rare (2-5% during a 2-year observation), but the improvement of health is frequent (40-64%).

In the examined group the improvement of health was achieved.

Patients with borreliosis improved in up to 61% cases after symptomatical treatment recommended in the chronic fatigue syndrome. In the group of patients with tick encephalitis the improvement after treatment was observed in 31% cases.

Piśmiennictwo / References

1. Fernández AA, Martín AM, Martínez MI, et al. Chronic fatigue syndrome: aetiology, diagnosis and treatment. BMC Psychiatry 2009, 9(1): 1.
2. Van der Werf SP, De Vree B, Alberts M, et al. Netherlands Fatigue Research Group Nijmegen. Natural course and predicting self-reported improvement in patients with chronic fatigue syndrome with relatively short disease duration. J Psychosom Res 2002, 53: 749-53.
3. Girschick HJ, Morbach H, Tappe D. Treatment of Lyme borreliosis. Arthritis Res Ther 2009, 11(6): 258.
4. Crawley E, Hunt L, Stallard P. Anxiety in children with CFS/ME. Eur Child Adolesc Psychiatry 2009, 18(11): 683-689.
5. Afari N, Buchwald D. Chronic Fatigue Syndrome: A Review. Am J Psychiatry 2003, 160: 221-236.
6. Wyller VB. The chronic fatigue syndrome-an update. Acta Neurol Scand Suppl 2007, 187: 7-14.
7. Sánchez Rodríguez A, González Maroño C, Sánchez Ledesma M. Chronic fatigue syndrome: a syndrome in search of definition. Rev Clin Esp 2005, 205: 70-74.

8. Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. QJM 1997, 90(3): 223.
9. Bates D, Buchwald D, Lee J, et al. Clinical laboratory test findings in patients with chronic fatigue syndrome. Arch Intern Med 1995, 155(1): 97.
10. Greco A, Tannock C, Brostoff J, Costa D. Brain MR in chronic fatigue syndrome. Am J Neuroradiol 1997, 18(7): 1265.
11. Gupta S, Aggarwal S, See D, Starr A. Cytokine production by adherent and non-adherent mononuclear cells in chronic fatigue syndrome. J Psychiatr Res 1997, 31(1): 149.
12. Plioplys A, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. Neuropsychobiology 1995, 32(3): 132.
13. Fukuda K, Dobbins J, Wilson L, et al. An epidemiologic study of fatigue with relevance for the chronic fatigue syndrome. J Psychiat Res 1997, 31(1): 19.
14. Fukuda K, Gantz N. Management strategies for chronic fatigue syndrome. Fed Pract 1995, 12: 2.
15. Fukuda K, Strauss S, Hickie I, et al. The chronic fatigue syndrome: comprehensive approach to its definition and study. Ann Intern Med 1994, 121: 953.
16. Bennett A, Chao C, Hu S, et al. Elevation of bioactive transforming growth factor-beta in serum from patients with chronic fatigue syndrome. I Clin Immunol 1997, 17(2): 160.
17. Dinan T, Majeed T, Lavelle E, et al. Blunted serotonin – mediated activation of the hypothalamic – pituitary – adrenal axis in chronic fatigue syndrome. Psychoneuroendocrinology 1997, 22(4): 261.
18. Landay A, Jessop C, Lennette E, Levy J. Chronic fatigue syndrome: clinical condition associated with immune activation. Lancet 1991, 338(8769): 707.
19. Levine P. Epidemiologic advances in chronic fatigue syndrome. J Psychiatr Res 1997, 31(1): 7.
20. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. CMAJ 2006, 174(6):765-767.
21. Engleberg N. Chronic Fatigue Syndrome. In: Mandell, Douglas, Bennett, editor. Infectious diseases. Ed Panamericana, Buenos Aires 2002, 1871-1877.
22. Padhan P. Chronic fatigue. CMAJ 2006, 175(4): 386-387.
23. Sabin TD. An approach to chronic fatigue syndrome in adults. Neurologist 2003, 9(1): 28-34.
24. Rivera J. Controversy on the diagnosis of fibromyalgia. Rev Esp Reumatol 2004, 31: 501-506.
25. Elkins LE, Pollina DA, Scheffer SR, Krupp LB. Psychological states and neuropsychological performances in chronic Lyme disease. Appl Neuropsychol 1999, 6(1): 1926.
26. Gaudino EA, Coyle PK, Krupp LB. Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences. Arch Neurol 1997, 54(11): 1372.
27. Sigal LH, Hassett AL. Contributions of societal and geographical environments to „chronic Lyme disease": the psychopathogenesis and aporology of a new „medically unexplained symptoms" syndrome. Environ Health Perspect 2002, 110(4): 607.
28. Maraspin V, Ruzic-Sabljic E, Strle F. Lyme borreliosis and Borrelia spielmanii. Emerg Infect Dis 2006, (12):1177.
29. Herzberger P, Siegel C, Skerka C, et al. Human pathogenic Borrelia spielmanii sp. nov. resists complement-mediated killing by direct binding of immune regulators factor H and factor H-like protein 1. Infect Immun 2007, 75: 4817-4825.
30. Treib J, Grauer MT, Haass A, et al. Chronic fatigue syndrome in patients with Lyme borreliosis. Eur Neurol 2000, 43(2): 107.
31. Buchwald D, Wener M, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. J Rheumat 1997, 24(2): 372.
32. Mawle AC. Chronic fatigue syndrome. Immunol Investigations 1997, 26(1): 269.
33. Lyall M, Peakman M, Wessely S. A systematic review and critical evaluation of the immunology of chronic fatigue syndrome. J Psychosomatic Res 2003, 55: 79-90.
34. Lorusso L, Mikhaylova SV, Capelli E, et al. Immunological aspects of chronic fatigue syndrome. Autoimmun Rev 2009, 8: 287-91.
35. Vernon S, Reeves W. Evaluation of autoantibodies to common and neuronal cell antigens in chronic fatigue syndrome. J Autoimmune Dis 2005, 2: 5.
36. Bassi N, Amital D, Amital H, et al. Chronic fatigue syndrome: characteristics and possible causes for its pathogenesis. Isr Med Assoc J 2008, 10: 79-82.
37. Bransfield RC. The Psychoimmunology of Lyme/Tick-Borne Diseases and its Association with Neuropsychiatric Symptoms. Open Neurol J 2012, 6: 88-93.
38. Miklossy J. Alzheimer's disease – a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation 2011, 8: 90.
39. Brown AS, Patterson PH. Maternal infection and schizophrenia: implications for prevention. Schizophr Bull 2011, 37: 284-290.
40. Ling VJ, Lester D, Mortensen P, et al. Toxoplasma gondii seropositivity and suicide rates in women. J Nerv Ment Dis 2012, 199: 440-444.
41. Bransfield RC. Preventable cases of autism: relationship between chronic infectious diseases and neurological outcome. Pediatr Health 2009, 3: 125-140.
42. Bou-Holaigah I, Rowe P, Kan J, Calkins H. The relationship between neurally mediated hypothension and the chronic fatigue syndrome. JAMA 1995, 274(12): 961.
43. Demitrack M, Dale J, Strauss S, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metabol 1991, 73(6): 1224.
44. Young A, Sharpe R, Clements A, et al. Basal activity of the hypothalamic-adrenal axis in patients with the chronic fatigue syndrome. Biol Psych 1998, 43(3):236.
45. Makhani N, Morris SK, Page A, et al. A Twist on Lyme: the Challenge of Diagnosing European Lyme Neuroborreliosis. J Clin Microbiol 2011, 49(1): 455-457.
46. Broekhuijsen-van Henten DM, Braun KP, Wolfs TF. Clinical presentation of childhood neuroborreliosis, neurological examination may be normal. Arch Dis Child 2010, 95: 910-914.
47. Aucott JN, Seifter A, Rebman AW. Probable late Lyme disease: a variant manifestation of untreated Borrelia burgdorferi infection. BMC Infect Dis 2012, 12: 173.
48. Lee S, Yu H, Wing Y, et al. Psychiatric morbidity and disease experience of primary care patients with chronic fatigue in Hong Kong. Am J Psychiatry 2000, 157: 380-384.
49. Lorton D, Lubahn CL, Estus C, et al. Bidirectional communication between the brain and the immune system: implications for physiological sleep and disorders with disrupted sleep. Neuroimmunomodulation 2006, (13): 357-74.
50. Ljøstad U, Mygland A. Remaining complaints 1 year after treatment for acute Lyme neuroborreliosis, frequency, pattern and risk factors. Eur J Neurol 2010, 17(1): 118-123.
51. Lloyd A, Hickie I, Boughton C, et al. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust 1990, 153(9): 522.