СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Review Article / Преглед литературе

Dragan M. Pavlović[1], Jelena Đorđević[2,♣], Aleksandra M. Pavlović[3,4], Mirjana Stjepanović[2], Marko Baralić[5]

Myalgic encephalomyelitis – enigma at the medicine's crossroads

Мијалгични енцефаломијелитис – енигма на раскршћу медицине

[1]University of Belgrade, Faculty for Special Education and Rehabilitation, Serbia;
[2]Dr. Laza Lazarević Clinic for Psychiatric Disorders, Belgrade, Serbia;
[3]Faculty of Medicine, University of Belgrade, Serbia;
[4]Clinical Center of Serbia, Neurology Clinic, Belgrade, Serbia;
[5]Clinical Center of Serbia, Department of Nephrology, Belgrade, Serbia

Received: June 28, 2020
Revised: September 15, 2020
Accepted: October 04, 2020
Online First: October 13, 2020
DOI: https://doi.org/10.2298/SARH200628091P

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

♣**Correspondence to:**
Jelena ĐORĐEVIĆ
Višegradska 26, 11000 Belgrade, Serbia
E-mail: **jelenadjordjevic2000@yahoo.com**

Myalgic encephalomyelitis – enigma at the medicine's crossroads

Мијалгични енцефаломијелитис – енигма на раскршћу медицине

SUMMARY
Myalgic encephalomyelitis is a complex, multisystem disease with chronic course significantly affecting patients' quality of life. Physical and mental exertion intolerability, muscle pain and sleep problems are main features accompanied often with cognitive inefficacy and vegetative symptoms. Prevalence is 7-3,000 per 100,000 adults. It is estimated that 90% of the patients are misdiagnosed. Pathogenesis is still only speculative but current research points to disturbances in immunological system, inflammatory pathways, autonomic and central nervous system, muscle and mitochondria, as well as alterations of gut microbiota and gut permeability. The onset is typically acute, following an infectious disease. Exertional intolerance lasting for more than six months is important diagnostic factor. The core features must be moderate to severe and present at least 50% of the time. Diagnostic criteria should be fulfilled and differential diagnosis should be made to exclude other potential pathological conditions or to diagnose comorbidities. Brain magnetic resonance imaging morphometry showed gray matter atrophy in occipital lobes bilaterally, right angular gyrus, and the posterior division of the left parahippocampal gyrus, consistent with memory problems and potentially with impairment of visual processing. Treatment is still symptomatic and of partial benefit. Symptomatic treatment can include medications for controlling pain and sleep problems, graded exercise and cognitive behavioral therapy. Larger controlled trials are needed to shed more light on this challenging condition.
Keywords: myalgic encephalomyelitis; chronic fatigue syndrome; post-exertional malaise

САЖЕТАК
Мијалгични енцефаломијелитис је сложено, мултисистемско обољење са хроничним током које значајно утиче на квалитет живота пацијената. Слаба толеранција на физички и ментални напор, болови у мишићима и проблеми са спавањем главне су одлике често су праћене когнитивном неефикасношћу и вегетативним симптомима. Преваленција је 7-3.000 на 100.000 одраслих. Процењује се да је 90% ових пацијената погрешно дијагностиковано. Патогенеза је и даље само спекулативна, али тренутна истраживања указују на поремећаје у имунолошком систему, инфламаторном одговору, аутономном и централном нервном систему, мишићима и митохондријама, као и промене микробиоте и пропустљивости црева. Почетак болести је типично акутан и прати инфективну болест. Нетолеранција напора која траје дуже од 6 месеци важан је дијагностички критеријум. Основне карактеристике морају бити умерене до тешке и присутне најмање 50% времена. Искључивање других потенцијалних патолошких стања или коморбидитетних дијагноза захтева задовољавање дијагностичких критеријума и диференцијално дијагностичко сагледавање. Морфометријска снимања мозга магнетном резонанцом показала су атрофију сиве масе у окципиталним режњевима билатерално, десном ангуларном гирусу и постериорном левом парахипокампалном гирусу, што може довести до проблема са памћењем и потенцијално до оштећења визуелне обраде информација. Лечење је и даље симптоматско и само делимично успешно. Симптоматски третман може да укључује лекове за контролу бола и проблема са спавањем, дозирану физичку активност и когнитивно-бихевијоралну терапију. Потребне су веће студије да би се разјаснило ово медицинско стање.
Кључне речи: мијалгични енцефаломијелитис; синдром хроничног умора; слабост после напора

INTRODUCTION

Myalgic encephalomyelitis (ME) with chronic fatigue syndrome (CFS) (myalgic encephalomyelitis/chronic fatigue syndrome / ME/CFS)or systemic exertion intolerance disease (SEID)is a multifaceted condition involving muscular, nervous, hormonal, and immune systems [1, 2]. Patients have difficulties with sleep and attention, experience pain and dizziness, and have extreme fatigue not accountable to any other medical condition

[3].Myalgic encephalomyelitis can be incapacitating and often affects activities of daily living, sometimes making patients immobile (up to 25%). Syndrome is typically chronic, with onset between 40 and 60 years, but it can begin at any age. Women are more prone to ME/CFS than men. This is an overlapping domain of rheumatology, neurology and psychiatry. Prevalence of ME/CFS is 0.1% to 2.2% [4]. It is estimated that 90% of the patients are misdiagnosed. Physicians are often not educated in ME/CFS and there is no confirmatory test.

CLINICAL PICTURE

Symptoms of ME/CFS can develop suddenly or gradually [5]. Sometimes it starts as a flu-like disease or after an infection (viral, bacterial or parasitic) [6]. Involved clinical domains are multiple and can be neurological, cognitive, immune, autonomic, post exertional malaise and pain [7].These patients also face an increased risk for developing diabetes, cardiovascular disease, and thyroid disease.

Patients are fatigued, do not improve with rest and are worse on attempt of physical or mental activity (post-exertional malaise – PEM; systemic exertion intolerance disease - SEID). There is often working incapacity, secondary alcoholism and inability to participate in family and social life. Before the onset of CFS/ME most patients were healthy and active [1].

Typically, there are muscle or joint pains, memory, concentration and information processing speed problems. Perception, speech, motor functions and intelligence are not involved. Patients complain of sorethroat, headaches,unrefreshing sleep, feel dizzy and are generally unwell. Some patients have digestive problems, night sweats or may be intolerant to some foods, chemicals or noise [5].

People can have difficulties to sit or walk, and some might be bedridden (up to 25%). Other group of patients, on the contrary, have preserved functional capacities, but majority have at least some difficulty at work, in family life and/or at school. Approximately 75% of the patients are unable to participate in their professional activities. Symptoms often fluctuate during the day or on various days, last more than six months and cannot be explained by any other disease [1]. Objectively enlarged lymph nodes can be found in the neck or armpits.

Sometimes there are palpitations and irregular heart beat. ME/CFS often lead to depression, social isolation, impairment of activities of everyday living and incapacity for work.

Younger children with ME/CFShave a more equal gender representation compared to adolescents and adults, shorter duration of symptoms, less distinct disability and fatigue, and are less prone to cognitive symptoms, but more oftencomplain of a sore throat [8]. Adolescents have less often have palpitations, dizziness, malaise, pain, anxiety and tender lymph nodes, but more often headaches and comorbid depression than adults [8].

ETIOLOGY

Etiology of ME/CFS is not known but known risk factors are age (40s and 50s), female sex, psychological stress, childhood trauma, lower middle education, low physical fitness, preexisting psychological illness (depression, anxiety), and allergies [1].Epstein–Barr virus (EBV) or human herpesvirus-4 (HHV-4)can cause infectious mononucleosis that causes syndrome that fulfills criteria for ME/CFS in substantial number of affected individuals [9]. Other viral infections that can lead to chronic fatigue are human herpes virus 6 and mouse leukemia viruses. Also there is a possibility of some bacterial infections.

The patients with ME/CFS have slight impairment of immune system: changes in cytokine and immunoglobulin levels, T- and B-cell phenotype and a decrease of natural killer cell cytotoxicity, but also increased certain autoantibodies levels [10, 11]. Some authors hypothesize about possibility of ME/CFS being an autoimmune disease as there are autoantibodies to some neurotransmitter receptors [10]. Autoimmunity can be triggered by infectious agents and/or stress, and immune deficiencies leading to other pathological mechanisms. Increased permeability of intestinal and blood-brain barriers can lead to penetration of antibodies from general circulation into the brain with potential brain tissue autoimmune lesions [9].

So far many autoantibodies have been detected, mainly those targeting nuclear structures (antinuclear antibodies, nuclear envelope, reticulated speckles etc.), membrane structures (phospholipids, cardiolipin,phosphatidylserine, gangliosides), neurotransmitter receptors and neurotransmitters (MAchR,M1 AChR , M3/4 AchR, 5-hydroxytryptamine) and to other antigens [10]. Immunological activation forces change to aerobic glycolysis in order

to keep necessary energy levels, leading to maintenance of chronic inflammation with mitochondrial dysfunction and extreme fatigue.

Some hormonal imbalances can be found in function of hypothalamus, pituitary and adrenal glands but its significance is not known. Many deficiencies of B group vitamins are manifested by malaise and cognitive decline and are of substantial prevalence, but these etiological possibilities need large studies [12, 13].

Genetic factors may play some role in the etiology of ME/CFS. Twin studies show increased predisposition for the condition and there are also studies linking genetic factors and infection [14].

ME/CFS is also characterized by increased measures of oxidative stress while antioxidant potential is decreased. This process leads to impaired lipid-based signaling systems of S-palmitoylation and of omega-3 polyunsaturated fattyacids (PUFAs) [15]. Nitric oxide/superoxide cycle is also involved in cardiac failure and might be the crucial mechanism of increased fatigue [16]. Overproduction of nitric oxide leads to increased levels of superoxide with consequent depletion of adenosine triphosphate (ATP) and activation of excitatory neurotransmitter N-methyl-D-aspartate (NMDA) and then increase of intracellular calcium that continues the vicious cycle with increased activity of nitric oxide.Chronic activation of nuclear factor kappa B (NF-κB)is supposed to be present in ME/CFS and vitamin D3 supplementation could suppress activation of NFκB [16].

PATOGENESIS

Pathogenesis of ME/CFS is still only speculative but current research points to disturbances in immunological system, inflammatory pathways, autonomic and central nervous system, muscles, mitochondria, gut microbiota and permeability [1, 17]. Infectious mechanisms also may play a role in ME/CFS as well as other factors that can initiate similar pathological cascades [17].

Extreme fatigue in ME/CFS, might be the result of energy production disturbances leading to exertion intolerance [2]. Some evidence leads to autonomic nervous system dysfunction such as orthostatic hypotension or tachycardia, at least in some ME/CFS patients

[18]. Metabolic syndrome might not bethe cause but the result of fatigue and lack of physical activity [2].

One study recognized nine biochemical factors common to both male and female ME/CFS patients but not healthy controls with an apparent diagnostic accuracy of more than 90% [19]: decrease in sphingolipid, glycosphingolipid, phospholipid,purine, microbiome aromatic amino acid, branch chainamino acid metabolites, flavine adenine nucleotide and lathosterol. These changes constitutie the hypometabolic profile of ME/CFS.

ME/CFShas been linked with mitochondrial dysfunction, damage of AMP-activated protein kinase, oxidative stress, and skeletal muscle cell acidosis which correlate with core symptoms such as fatigue, exercise intolerance, and myalgia [2]. Contrary to known mitochondrial diseases, in ME/CFS there is no mutation in either nuclear or mitochondrial DNA [20]. Also, there is no ATP reduction. Findings of muscle biopsies from subjects with ME/CFS have shown signs of mitochondrial degeneration and oxidativedamage[2].

There are some indications of impaired function of hypothalamic-hypophyseal-adrenal (HPA) axis [21]. Microglia probably have important role in ME/CFS. It has been proposed that microglia might be activated by various factors such as immune changes, stress etc. via the stimulation of hypothalamic mast cells with consequent focal neuroinflammation and disturbed homeostasis with mitochondrial dysfunction [2].

Some studies advocate for a role for microglia and astrocytes of immunologically induced CFS, that the infection causes sequential signaling such as increased blood brain barrier (BBB) permeability, secretion of IL-1β, upregulation of the serotonin transporter (5-HTT) in astrocytes, reducing extracellular serotonin (5-HT) levels and less activation of 5-HT_{1A} receptor subtype [22]. This etiopathogeneticassumption has found clinical confirmation in achieving positive therapeutic effects using antidepressants from group of theselective serotonin reuptake inhibitors (SSRIs).

Neuroimaging in ME/CFS shows more diffuse activation patterns than controls on attention tests, sometimes structural abnormalitis in the brain stem with signs of inflammation,reduction in the serotonin 1A receptor binding, particularly in the hippocampus bilaterally, and reduced serotonin transporters density in the rostral anterior cingulate [23]. Some studies showed also regional abnormalities but with inconsistent locations and widespread disruption of the autonomic nervous system [24].

Clinical pictures of ME/CFS and d-lactic acidosis (d-la) are overlapping and there is evidence of d-lactate-producing bacteria dysbiosis [25]. Both conditions have neurological disturbances caused by microbiota-gut-brain system dysfunction. d-lactic acidosis is an acute condition causing encephalopathy while ME/CFS is a chronic state with possible subclinical levels od d-lactate making the two entities possibly the parts of the same continuum [25].

DIAGNOSIS

Diagnosis of ME/CFS is made on the clinical grounds and by exclusion of other medical conditions with no specific diagnostic test [1]. Current diagnostic criteria for ME/CFS proposed by the Centers for Disease Control (CDC) are presented in a Table 1 [5]. The onset of ME/CFS is typically acute following an infectious disease. Exercise intolerance lasting more than 6 months is important diagnostic factor. Fatigue is not alleviated with rest. Sleep problems are always present. Optional symptoms are orthostatic intolerance and/or memory and concentration problems. Core clinical features must be moderate to severe and present at least 50% of the time.

Documenting PEM is very important and is defined as a "collapse" after previously tolerated physical and psychic exertion, sometimes during even mild everyday activities [26]. Recommended additional investigations inME/CFS depending of symptoms are: chest x-ray, electrocardiogram, tilt table test for autonomic function, ACTH challenge test or cortisol stimulation test, parathyroid hormone, estradiol, follicle-stimulating hormone, gastroscopy, colonoscopy, gliadin, endomysial antibodies, infectious disease screen including HIV, hepatitis, Lyme disease, Q fever, microbiology of stools, urine, genitals and respiratory tract, antinuclear antibodies, immunoglobulins, functional antibodies and subsets of lymphocytes, MRI of the brain, overnight polysomnography with multiple sleep latency test and cystoscopy [6].

There is still not a unique set of biomarkers that would help in diagnosing ME/CFS. There are many proposed and studied compounds but with yet uncertain significance. Precise measures of potentially elevated d-lactic acid [25]. Human herpesviruses (HHV-1-8), HHV-4 (Epstein-Barr virus; EBV), HHV-6 (including HHV-6A and HHV-6B), and HHV-7 are associated with ME/CFS, but studies did not show significant differences between patients and healthy controls [27].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of ME/CFS is quite wide and consists of [5, 26]:

- **Infectious diseases**: Tick Borne Diseases -Lyme disease (including neuroborreliosis) etc., mononucleosis i.e. Epstein-Barr Virus,Parvovirus, HIV infection and AIDS, influenza, tuberculosis, hepatitis B and C, Giardia, West Nile Virus, Q/fever, Valley Fever, Syphilis

- **Psychiatric disorders**: anxiety, depression and bipolar disorder, alcohol and substance abuse, schizophrenia, delusional disorders, dementia, anorexia/bulimia nervosa; sleep apnea

- **Rheumatological diseases**: fibromyalgia, polymyalgia rheumatica, Sjögren's syndrome, giant-cell arteritis, polymyositis, dermatomyositis, systemic lupus, rheumatoid arthritis

- **Neurological diseases**: Parkinsonism, multiple sclerosis (MS), myasthenia gravis, vitamin B12 deficiency, cerebrospinal fluid leak, Chiari malformation, sleep apnea, narcolepsy, periodic limb movement disorder, malformation, traumatic brain injury, spinal stenosis, craniocervical instability, seizures

- **Endocrine/metabolic diseases**: diabetes mellitus, hypothyroidism, hyperthyroidism, thyroiditis, Addison's disease, adrenal insufficiency, Cushing's disease, hypercalcemia

- **Cardiovascular disorders:** cardiomyopathy, congestive heart failure, coronary artery, disease, pulmonary hypertension,valvular heart disease, arrhythmias

- **Gastrointestinaldisorders:** coeliac disease, food allergy orintolerances, inflammatory bowel diseases, small intestinal bacterialovergrowth, chronic hepatitis

- **Miscellaneous**: anemia, iron overload,various malignancies (primary and secondary), sinusitis, allergic rhinitis,the effect of some drugs, chronic

obstructive pulmonary disease (COPD), asthma, end-stage kidney disease, severe obesity (BMI > 40),overwork/burnt out syndrome, athletic overtraining, heavy metals toxicity (e.g. lead, mercury)etc.

ME/CFS can have remitting course that must be distinguished from MS as they have some overlapping symptoms [28]. These are fatigue, cognitive problems, physical disabilityetc. But MS patients do not have, unlike those with ME/CFS, tender lymph nodes and flu-like symptoms, are younger, more likely to be married, less Caucasian and with less disability [28]. Contrary to depression, ME/CFS does not have anhedonia, low motivation and guilt.

The closely related problem are comorbidities, so diagnostic procedure is nor mere an excluding process. Various diseases can coexist with ME/CFS so they also have to be diagnosed and treated [26].

TREATMENT

There is no causal cure for ME/CFS. Symptomatic treatments can include medications for controlling pain and sleep problems, graded exercise (graded exercise therapy - GET) that is controversial and cognitive behavioral therapy (CBT) [26]. Many medications have been tried but without proved therapeutic effects so they are used off label [29]. Anticonvulsants, mostly gabapentin and pregabalin, are prescribed to alleviate pain and sleep disturbances, but are most effective for neuropathic pain [1]. Antidepressants (nefazodone, mirtazapine, sertraline, amitriptyline and others) can be administered in cases of depression, anxiety and sleep problems but have a plethora of side effects and interact with many other drugs, so one should be very careful in prescribing these medications [30]. Alternative to antidepressants is cognitive behavioral therapy (CBT). In patients with most severe and therapy resistant pain narcotic medicines are prescribed, usually tramarol, codeine etc., for a short period to avoid risk of addiction [31].

In line with the proposed immune and viral etiology, immunomodulatory drugs are given such as rintatolimod andrituximab that suposedly improve exercise capacity, cognition and quality of life, but the studies are of insufficient quality and with equivocal proofs of

drug's efficacy and safety [1]. Steroid treatment is known for its immunosuppressive properties [32] but studies did not show any substantial benefit.

Important aspect of CFS/ME treatment is the use of nutritional supplements in patients with biochemically proven deficiencies [1]. Multivitamin/multimineral tablets containing antioxidant compounds (e.g. alpha-lipoic acid, vitamin C and vitamin E) showed some promise in a study in women with ME/CFS [33]. In prescibing some supplements laboratory follow up in necessary [34, 35]. General fatigue is one of the main symptoms in vitamin B12 deficiency [34, 35, 36]. There is substantial difference in determining "normal" levels of vitamin B12 in the blood among studies, and blood levels are not a good measure of tissue B12 status [34]. Also, different preparations and administration routes further complicate assessment of B12 supplementation in such a controversial entity as CFS/ME. Experience with injections of methylcobalamine in patients with CFS/ME in combination with folic acid is positive [37].

Combination of coenzyme Q10 (CoQ10) and nicotinamide adenine dinucleotide (NADH) is antioxidant treatment that also improves mitochondrial function in CFS/ME due to increased adenosine triphosphate (ATP) production [38]. Essential fatty acids administration in CFS/MEshowed improvement in only one study while others did not find any improvement [39].

Treating gut dysbiosis i.e. antibiotics targeting*Streptococcus* genus is a hypothetical therapy for neurological symptoms in ME/CFS, not much explored so far [40]. Treatment protocol of recent study included 4-week treatment with alternate weeks of erythromycin as ethyl succinate salt 400 mgtwice daily and probiotic (d-lactate free multistrain probiotic, 5 × 1010 cfu) twice daily [40]. Significant improvement was noted in sleep, attention, speed of processing information, cognitive flexibility, verbal memory and fluency, with more impact in males. Level of fatigue, mood, and urine d:l lactate ratio did not change with medication.

PROGNOSIS

A systematic review described improvement and occupational outcomes of people with CFS found that the median full recovery rate was 5% with the range 0–31%, and the median proportion of patients who improved during follow-up was 39.5%, range 8–63% [41]. Return

to work at follow-up ranged from 8 to 30% in relevant studies. In five studies, a worsening of symptoms during the period of follow-up was detected in 5-20% of participants. A good outcome was associated with less fatigue severity at baseline. Other factors occasionally, but not consistently, related to outcome, included age at onset, and attributing illness to a psychological cause and/or having a sense of control over symptoms [41]. Although clinical picture is chronic, most people get better over time with some rest symptoms. Younger age is a favorable prognostic factor.

CONCLUSION

CFS/ME is a complex, multisystem disease of chronic course with serious consequences on patients' quality of life. Physical and mental exertion intolerability, muscle pain and sleep problems are main features accompanies often with cognitive inefficacy and vegetative symptoms. Etiology and pathophysiology are not known but there are many theories based on multiple findings of involvement of immune, endocrine/metabolic, biochemical and other mechanisms. There are numerous comorbidities and differential diagnosis is often complicated. Treatment is still symptomatic and of partial benefit with many drugs of various classes and nonpharmacological measures routinely used. Larger controlled trials are needed to shed more light on this challenging condition.

ACKNOWLEDGEMENT

This article was partially financed by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Project No 175033 and 175022

Conflict of interest: None declared.

REFERENCES

1. Castro-Marrero J, Sáez-Francàs N, Santillo D, Alegre J. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome.Br J Pharmacol. 2017;174(5):345-369. doi: 10.1111/bph.13702.
2. Hatziagelaki E, Adamaki M, Tsilioni I, Dimitriadis G, Theoharides TC. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus? J Pharmacol Exp Ther. 2018;367(1):155-167. doi: 10.1124/jpet.118.250845.
3. Scheibenbogen C, Freitag H, Blanco J, Capelli E, Lacerda E, Authier J, et al. The European ME/CFS biomarker landscape project: an initiative of the European network EUROMENE. J Transl Med. 2017;15:162. doi: 10.1186/s12967-017-1263-z.
4. Estévez-López F, Mudie K, Wang-Steverding X, Johanne Bakken I, Ivanovs A, Castro-Marrero J, et al. Systematic review of the epidemiological burden of myalgic encephalomyelitis/chronic fatigue syndrome across Europe: current evidence and EUROMENE J Clin Med. 2020 May 21;9(5):1557. doi: 10.3390/jcm9051557.
5. CDC. Symptoms Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). www.cdc.gov. 14 July 2017. Retrieved 5 October 2019.
6. Bested AC, Marshall LM. Review of myalgic encephalomyelitis/chronic fatigue syndrome: an evidence-based approach to diagnosis and management by clinicians. Rev Environ Health. 2015;30: 223-249. doi: 10.1515/reveh-2015-0026.
7. Jason LA, Zinn ML, Zinn MA.Myalgic Encephalomyelitis:Symptoms and Biomarkers. CurrNeuropharmacol. 2015;13(5):701-34. doi: 10.2174/1570159X13666150928105725.
8. Collin SM, Nuevo R, van de Putte EM, Nijhof SL, Crawley E.Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts.BMJ Open. 2015;5(10):e008830. doi: 10.1136/bmjopen-2015-008830.
9. Monro JA, Puri BK. A molecular neurobiological approach to understanding the aetiology of chronic fatigue syndrome (myalgic encephalomyelitis or systemic exertion intolerance disease) with treatment implications. Mol Neurobiol. 2018;55(9):7377-7388. doi: 10.1007/s12035-018-0928-9.
10. Sotzny F, Blanco J, Capelli E, Castro-Marrero J, Steiner S, Murovska M, et al. European Network on ME/CFS (EUROMENE).Myalgic Encephalomyelitis/Chronic Fatigue Syndrome - Evidence for an autoimmune disease. Autoimmun Rev. 2018;17(6):601-609. doi: 10.1016/j.autrev.2018.01.009.
11. Vojvodic J, Mihajlovic G, Andonov A, Markovic M, Djordjevic J, Vojvodic P. Immunological Aspects of Depressive Disorder – The Review. Serbian J. of Exp. Clin. Res. Publised online 01.feb 2019. doi: 10.2478/sjecr-2018-0076.
12. Pavlović DM, Pavlović AM. B Vitamins and Dementias. Curr Top. 2013;21(1-2):39-48. UDC 616.892.3-085:577.164.1.
13. Pavlović DM. Orthomolecular neurology and psychiatry. Belgrade: OrionArt; 2019. (in Serbian) ISBN. 978-86-6389-092-3.
14. Sapra A, Bhandari P. Chronic Fatigue Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. PMID: 32491608
15. Morris G, Walder K, Puri BK, Berk M, Maes M. The deleterious effects of oxidative and nitrosative stress on palmitoylation, membrane lipid rafts and lipid-based cellular signalling:new drug targets in neuroimmune disorders. Mol Neurobiol. 2015;53(7):4638-4658.doi: 10.1007/s12035-015-9392-y.
16. Baralic M, Brkovic V, Stojanov V, Stankovic S, Lalic N, Djuric P. et al. Duall Roles of the mineral metabolism disoredes biomarekrs in prevalent hemodialysis patients: in renal bone disease and invascular calcification. J Med Biochem. 2019 Mar 3;38 (2):134-144.doi: 10.2478/jomb-2018-0026.
17. Missailidis D, Annesley SJ, Fisher PR. Pathological mechanisms underlying myalgic encephalomyelitis/chronic fatigue syndrome. diagnostics (Basel). 2019;9(3). pii: E80. doi: 10.3390/diagnostics9030080.
18. Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL. Impaired cardiovascular response to standing in chronic fatigue syndrome. Eur J Clin Invest. 2010;40:608-615.doi: 10.1111/j.1365-2362.2010.02310.x.
19. Naviaux RK, Naviaux JC, Li K, Bright AT, Alaynick WA, Wang L, et al. Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci USA.2016;113:E5472–E5480.doi: 10.1073/pnas.1607571113.

20. Schoeman EM, Van Der Westhuizen FH, Erasmus E, van Dyk E, Knowles CV, Al-Ali S, et al. Clinically proven mtDNA mutations are not common in those with chronic fatigue syndrome. BMC Med Genet. 2017;18:29.doi: 10.1186/s12881-017-0387-6.
21. Morris G, Anderson G, Maes M. Hypothalamic-pituitary-adrenal hypofunction in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) as a consequence of activated immune-inflammatory and oxidative and nitrosative pathways. Mol Neurobiol.2017;54:6806–6819.doi: 10.1007/s12035-016-0170-2.
22. Noda M, IfukuM, HossainS, Katafuchi T. Clial activation and expression of the serotonin transporter in chronic fatigue syndrome. Front Psychiatry. 2018 Nov 16;9:589. doi: 10.3389/fpsyt.2018.00589. eCollection 2018.
23. Shan ZY, Barnden LR, Kwiatek RA, Bhuta S, Hermens DF, Lagopoulos J,et al. Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review. J Transl Med. 2020 Sep 1;18(1):335. doi: 10.1186/s12967-020-02506-6.
24. Maksoud R, Du Preez S, Eaton-Fitch N, Thapaliya K, Barnden L, Cabanas H, et al. A systematic review of neurological impairments in myalgic encephalomyelitis/ chronic fatigue syndrome using neuroimaging techniques. PLoS One. 2020 Apr 30;15(4):e0232475. doi: 10.1371/journal.pone.0232475. eCollection 2020.
25. Wallis A, Ball M, McKechnie S, Butt H, Lewis D, Bruck D. Examining clinical similarities between myalgic encephalomyelitis/chronic fatigue syndrome and D-lactic acidosis: a systematic review. J Transl Med. 2017;15(1):129. doi.org/10.1186/s12967-017-1229-1.
26. U.S.ME/CFS clinician coalition. Diagnosing and treating myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). August 2019.https://forms.gle/kf2RWSR2s1VgFfay7.
27. Blomberg J, Rizwan M, Böhlin-Wiener A, Elfaitouri A, Julin P, Zachrisson O, et al. Antibodies to Human Herpesviruses in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients. Front Immunol. 2019;10:1946. doi: 10.3389/fimmu.2019.01946.
28. Jason LA, Ohanian D, Brown A, Sunnquist M, McManimen S, Klebek L, Fox P, Sorenson M.Differentiating multiple sclerosis from myalgic encephalomyelitis and chronic fatigue syndrome.Insights Biomed.2017;2(2). pii: 11. doi: 10.21767/2572-5610.10027.
29. Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, et al. Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a National institutes of health pathways to prevention workshop. Ann Intern Med. 2015;162(12):841-50. doi: 10.7326/M15-0114. PMID: 26075755.
30. Cleare AJ, Reid S, Chalder T, HotopfM,Wessely S. Chronic fatigue syndrome. BMJ Clin Evid. 2015;28; pii: 1101.PMID: 26415100PMCID: PMC4585442.
31. Degenhardt L, Gisev N, Cama E, Nielsen S, Larance B, Bruno R. The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. Pharmacoepidemiol Drug Saf. 2016;25:521-538.doi: 10.1002/pds.3931.
32. Stjepanović M, MihailovićVucinić V, Jovanović D, MijajlovićM, SkodrićTrifunović V, Stjepanović MM, Treatment of Neurosarcoidosis-Innovations and Challenges. Med Pregl.2014;67(5-6):161-6.doi: 10.2298/MPNS1406161S.
33. Maric D, Brkic S, Tomic S, NovakovMikic A, Cebovic T, Turkulov V. Multivitamin mineral supplementation in patients with chronic fatigue syndrome. Med Sci Monit.2014;20: 47-53.doi: 10.12659/MSM.889333.
34. Pavlović DM. VitaminB12, vitamin D and homocysteine – trio of health and disease. Belgrade: OrionArt; 2018. (in Serbian) ISBN 978-86-6389-068-8.
35. Pavlović DM. Thiamine Deficiency and Benfotiamine Therapy in Brain Diseases. Am J Biomed Sci & Res. 2019;3(1):1-5. doi: 10.34297/AJBSR.2019.03.000621.
36. Pavlović DM, Pavlović AM. Dementias – neuropsychiatric symptoms. Belgrade. Orion Art, 2014 (in Serbian). ISBN 978-86-6389-001-5.
37. Regland B, Forsmark S, Halaouate L, Matousek M, Peilot B, Zachrisson O, et al. Response to vitamin B12 and folic acid in myalgicencephalomyelitis and fibromyalgia. PLoS One 2015;10: e0124648.doi.org/10.1371/journal.pone.0124648.
38. Castro-Marrero J, Saez-Francas N, SegundoMJ, Calvo N, FaroM, Aliste L, et al. Effect of coenzyme Q10 plus nicotinamide adeninedinucleotide supplementation on maximum heart rate after exercisetesting in chronic fatigue syndrome – A randomized, controlled,double-blind trial. Clin Nutr.2016;35: 826–834.doi: 10.1089/ars.2014.6181.

39. Warren G, McKendrick M, Peet M. The role of essential fattyacids in chronic fatigue syndrome. A case-controlled study of red-cellmembrane essential fatty acids (EFA) and a placebo-controlled treatment study with high dose of EFA. Acta Neurol Scand. 1999;99:112-116.doi: 10.1111/j.1600-0404.1999.tb00667.x.
40. Wallis A, Ball M, Butt H, Lewis DP, Mc Kechnie S, Paull P,et al. Open-label pilot for treatment targeting gut dysbiosis in myalgic encephalomyelitis/chronic fatigue syndrome: neuropsychological symptoms and sex comparisons. J Transl Med. 2018;16(1):24. doi: 10.1186/s12967-018-1392-z.
41. Collin S, Crawley E, Specialist Treatment of Chronic Fatigue syndrome/ME: A Cohort Study Among Adult Patients in England. BMC Health Serv Res. 2017 Jul 14;17(1):488. doi: 10.1186/s12913-017-2437-3.

Table 1. Current diagnostic criteria for myalgic encephalomyelitis with chronic fatigue syndrome proposed by the Centers for Disease Control

1	Significantly lowered ability to participate in activities that were routine before the onset of the condition, and persisting more than six months
2	Physical or mental activity causing worsening symptoms that would not have been problematic before the onset of the condition, (post-exertional malaise – PEM)
3	Sleep problems; Additionally, one of the two: · Difficulty with thinking and memory · Worsening of problems with standing or sitting

