

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Myalgic encephalomyelitis – enigma at the medicine's crossroads

Dragan M. Pavlović¹, Jelena Đorđević², Aleksandra M. Pavlović^{3,4}, Mirjana Stjepanović², Marko Baralić⁵¹University of Belgrade, Faculty for Special Education and Rehabilitation, Belgrade, Serbia;²Dr. Laza Lazarević Clinic for Psychiatric Disorders, Belgrade, Serbia;³University of Belgrade, Faculty of Medicine, Serbia;⁴Clinical Center of Serbia, Neurology Clinic, Belgrade, Serbia;⁵Clinical Center of Serbia, Department of Nephrology, Belgrade, Serbia**SUMMARY**

Myalgic encephalomyelitis is a complex, multisystem disease with chronic course significantly affecting patients' quality of life. Physical and mental exertion intolerance, muscle pain, and sleep problems are the main features accompanied often with cognitive inefficacy and vegetative symptoms. Prevalence is 7–3000 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 the 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 an 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 has shown 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

INTRODUCTION

Myalgic encephalomyelitis (ME) with chronic fatigue syndrome (CFS) (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]. ME can be incapacitating and often affects activities of daily living, sometimes making patients immobile (up to 25%). Syndrome is typically chronic, with the onset between 40 and 60 years, but it can begin at any age. Women are prone to ME/CFS more than men. This is an overlapping domain of rheumatology, neurology, and psychiatry. Prevalence of ME/CFS is 0.1–2.2% [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; 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 are 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 sore throat, headaches, unrefreshing sleep, feeling 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%). The other group of patients, in contrast, have preserved functional capacities, but the 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

Received • Примљено:

June 28, 2020

Revised • Ревизија:

September 15, 2020

Accepted • Прихваћено:

October 04, 2020

Online first: October 13, 2020**Correspondence to:**Jelena ĐORĐEVIĆ
Višegradska 26
11000 Belgrade, Serbia
jelena.jordjevic2000@yahoo.com

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/CFS have a more equal sex representation compared to adolescents and adults, shorter duration of symptoms, less distinct disability and fatigue, and are less prone to cognitive symptoms, but more often complain of a sore throat [8]. Adolescents 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 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 HHV-6 and mouse leukemia viruses. Also, there is a possibility of some bacterial infections.

The patients with ME/CFS have slight impairment of the 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 the 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 the penetration of antibodies from the 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 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 the B complex 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 fatty acids [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, which is followed by an increase of intracellular calcium that continues the vicious cycle with increased activity of nitric oxide. Chronic activation of nuclear factor kappa B (NFκB) is supposed to be present in ME/CFS, and vitamin D₃ supplementation could suppress the 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 be the cause but the result of fatigue and the lack of physical activity [2].

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

ME/CFS has been linked with mitochondrial dysfunction, damage of adenosine monophosphate-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 oxidative damage [2].

There are some indications of impaired function of hypothalamic-hypophyseal-adrenal axis [21]. Microglia

probably have an 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, so that the infection causes sequential signaling such as increased blood–brain barrier permeability, secretion of IL-1 β , 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 etiopathogenetic assumption has found clinical confirmation in achieving positive therapeutic effects using antidepressants from the group of selective serotonin reuptake inhibitors.

Neuroimaging in ME/CFS shows more diffuse activation patterns than controls on attention tests, sometimes structural abnormalities 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 also showed regional abnormalities but with inconsistent locations and widespread disruption of the autonomic nervous system [24].

Clinical pictures of ME/CFS and d-lactic acidosis 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 of 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 United States Centers for Disease Control and Prevention are presented in Table 1 [5]. The onset of ME/CFS is typically acute following an infectious disease. Exercise intolerance lasting more than six months is an important diagnostic factor. Fatigue is not alleviated with rest. Sleep problems are always present. Optional symptoms are orthostatic intolerance and/or memory and concentration

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)
3	Sleep problems; Additionally, one of the two: • Difficulty with thinking and memory • Worsening of problems with standing or sitting

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 in ME/CFS depending on the symptoms are the following: 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, magnetic resonance imaging 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, including HHV-6A and HHV-6B) and Epstein–Barr virus are associated with ME/CFS, but studies have not shown significant differences between patients and healthy controls [27].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of ME/CFS is quite wide and consists of the following [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;

- **Gastrointestinal disorders:** coeliac disease, food allergy or intolerances, inflammatory bowel diseases, small intestinal bacterial overgrowth, chronic hepatitis;
- **Miscellaneous:** anemia, iron overload, various malignancies (primary and secondary), sinusitis, allergic rhinitis, the effect of some drugs, chronic obstructive pulmonary disease, 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 disability, etc. However, 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.

A closely related problem are comorbidities, so diagnostic procedure is not a mere 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 therapy, which 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 CBT. In patients with most severe and therapy-resistant pain, narcotic medicines are prescribed, usually tramadol, 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 and rituximab, which supposedly improve exercise capacity, cognition, and the quality of life, but the studies are of insufficient quality and with equivocal proof of the drug's efficacy and safety [1]. Steroid treatment is known for its immunosuppressive properties but studies did not show any substantial benefit [32].

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 prescribing some supplements, laboratory follow up is 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 methylcobalamin in patients with CFS/ME in combination with folic acid is positive [37].

Combination of coenzyme Q10 and nicotinamide adenine dinucleotide is an antioxidant treatment that also improves mitochondrial function in CFS/ME due to increased ATP production [38]. Essential fatty acids administration in CFS/ME showed 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 a recent study included a four-week treatment with alternate weeks of erythromycin as ethyl succinate salt 400 mg twice 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 8–30% 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 the 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 the main features often accompanied by 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.

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):345–69.
2. Hatzigelaki 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):155–67.
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(1):162.
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 Research Recommendations for Epidemiology. *J Clin Med*. 2020;9(5):1557.
5. CDC. Symptoms Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). www.cdc.gov. 14 July 2017. Accessed October 5, 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(4):223–49.
7. Jason LA, Zinn ML, Zinn MA. Myalgic Encephalomyelitis: Symptoms and Biomarkers. *Curr Neuropharmacol*. 2015;13(5):701–34.
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.
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):7377–88.
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):601–9.
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*. Published online February 1, 2019. doi: 10.2478/sjecr-2018-0076.
12. Pavlović DM, Pavlović AM. B Vitamins and Dementias. *Curr Top Neurol Psychiatr Relat Discip*. 2013;21(1–2):39–48.
13. Pavlović DM. Orthomolecular neurology and psychiatry. *Belgrade: OrionArt*; 2019. p. 492 (in Serbian)
14. Sapra A, Bhandari P. Chronic Fatigue Syndrome. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2020 Jan.
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):4638–58.
16. Baralic M, Brkovic V, Stojanov V, Stankovic S, Lalic N, Djuric P, et al. Dual Roles of the Mineral Metabolism Disorders Biomarkers in Prevalent Hemodialysis Patients: In Renal Bone Disease and in Vascular Calcification. *J Med Biochem*. 2019;38(2):134–44.
17. Missailidis D, Annesley SJ, Fisher PR. Pathological Mechanisms Underlying Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Diagnostics (Basel)*. 2019;9(3):80.
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(7):608–15.
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(37):E5472–80. Erratum in: *Proc Natl Acad Sci USA*. 2017;114(18):E3749.
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(1):29.
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(9):6806–19.
22. Noda M, Ifuku M, Hossain S, Katafuchi T. Clial activation and expression of the serotonin transporter in chronic fatigue syndrome. *Front Psychiatry*. 2018;9:589.
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;18(1):335.
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;15(4):e0232475.
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.
26. U.S.ME/CFS clinician coalition. Diagnosing and treating myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). August 2019. Available from: <https://forms.gle/kf2RWSR2s1VgFfay7>.
27. Blomberg J, Rizwan M, Böhlh-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.
28. Jason LA, Ohanian D, Brown A, Sunnquist M, McManimen S, Klebek L, et al. Differentiating multiple sclerosis from myalgic encephalomyelitis and chronic fatigue syndrome. *Insights Biomed*. 2017;2(2):11.
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.
30. Cleare AJ, Reid S, Chalder T, Hotopf M, Wessely S. Chronic fatigue syndrome. *BMJ Clin Evid*. 2015;2015:1101.
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. *Pharmacoeconomics Drug Saf*. 2016;25(5):521–38.
32. Stjepanović M, Mihailović Vučinić V, Jovanović D, Mijajlović M, Skodrić Trifunović V, Stjepanović MM. Treatment of Neurosarcoidosis – Innovations and Challenges. *Med Pregl*. 2014;67(5–6):161–6.
33. Maric D, Brkic S, Tomic S, Novakov Mikic A, Cebovic T, Turkulov V. Multivitamin mineral supplementation in patients with chronic fatigue syndrome. *Med Sci Monit*. 2014;20:47–53.
34. Pavlović DM. Vitamin B12, vitamin D and homocysteine – trio of health and disease. *Belgrade: OrionArt*; 2018. p. 152 (in Serbian)
35. Pavlović DM. Thiamine Deficiency and Benfotiamine Therapy in Brain Diseases. *Am J Biomed Sci & Res*. 2019;3(1):1–5.

NOTE

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

Conflict of interest: None declared.

36. Pavlović DM, Pavlović AM. Dementias – neuropsychiatric symptoms. Belgrade: OrionArt; 2014. p. 199 (in Serbian)
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(4):e0124648.
38. Castro-Marrero J, Sáez-Francàs N, Segundo MJ, Calvo N, Faro M, Aliste L, et al. Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome – A randomized, controlled, double-blind trial. Clin Nutr. 2016;35(4):826–34.
39. Warren G, McKendrick M, Peet M. The role of essential fatty acids in chronic fatigue syndrome. A case-controlled study of red-cell membrane essential fatty acids (EFA) and a placebo-controlled treatment study with high dose of EFA. Acta Neurol Scand. 1999;99(2):112–6.
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.
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;17(1):488.

Мијалгични енцефаломијелитис – енигма на раскршћу медицине

Драган М. Павловић¹, Јелена Ђорђевић², Александра М. Павловић^{3,4}, Мирјана Стјепановић², Марко Баралић⁵

¹Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;

²Клиника за психијатријске болести „Др Лаза Лазаревић“, Београд, Србија;

³Универзитет у Београду, Медицински факултет, Београд, Србија;

⁴Клинички центар Србије, Клиника за неурологију, Београд, Србија;

⁵Клинички центар Србије, Клиника за нефрологију, Београд, Србија

САЖЕТАК

Мијалгични енцефаломијелитис је сложено, мултисистемско обољење са хроничним током које значајно утиче на квалитет живота болесника. Слаба толеранција на физички и ментални напор, болови у мишићима и проблеми са спавањем главне су одлике и често су праћене когнитивном неефикасношћу и вегетативним симптомима. Преваленција је 7–3000 на 100.000 одраслих. Процењује се да је 90% ових болесника 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 шест месеци важан је дијагностички критеријум. Основне карактеристике морају бити умерене до тешке и

присутне најмање 50% времена. Искључивање других могућих 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 парахипокампаалном гирусу, што може довести до проблема са памћењем и 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-бихевиоралну терапију. Потребне су веће студије да би се разјаснило ово медицинско стање.

Кључне речи: мијалгични енцефаломијелитис; синдром хроничног умора; слабост после напора