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Opinion Article

The Role of Immunity and Inflammation in ME/CFS and Post-COVID Syndrome: Implications for Treatment

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Abstract

Probably one in seven patients who have experienced acute COVID-19 continue having long-lasting complaints, called post-COVID syndrome or long-COVID, that are similar to those observed in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). There are good reasons to believe that common immunological, epigenetic and inflammatory mechanisms are involved in the pathogenesis both diseases. To date, various therapeutic approaches have been recommended, but with moderate success.

In the present opinion paper, the author weights his clinical experience against data from the literature, and suggests novel approaches.

In addition to general measures and paramedical approaches, food supplementation with a specific nutraceutical can be completed by oral administration of sodium dichloroacetate and Meldonium to optimize glucose metabolism and mitochondrial energy generation. Alternatively, intravenous infusions with magnesium salt and multivitamins can be completed with glutathione, m-tranexamic acid, and cultured stem cells. Preliminary results of an open-label, prospective, two-centre trial suggest more than four in five patients benefit from combined oral and infusion therapy with significantly diminished fatigue and improved well-being.

Monoclonal antibodies in "biologicals", blocking the effects of cytokines, and "small molecules" with Janus kinase inhibiting activity may offer novel opportunities by focusing on both immunologic and inflammation targets. A pilot trial with, in particular, one of the Janus kinase inhibitors could be considered.

Keywords: Post-COVID syndrome; long COVID-19; Myalgic encephalomyelitis; Chronic fatigue syndrome; ME/CFS; Biologicals; Janus kinase

Introduction

So far, the search for a single causal factor of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) has been fruitless, thus no causal treatment is available [1]. However, the recent pandemic of so-called Long-COVID or Post (acute) COVID syndrome has provided new insights into the pathogenesis of ME/CFS as patients suffering from either disease present remarkably similar signs and symptoms [2-4].

Louis Pasteur (1822-1895) stated that every disease results from the interaction of "le grain et le terrain", the grain and the soil. This means that a disease can only arise when a triggering factor (the grain) can act on a soil of predetermined personality structure or in a specific environment. Factors like genetics, nutrition and toxic environment, but also education and acquired stress tolerance make up the "soil" on which factors such as infection or trauma can trigger a disease. The mechanisms by which this process acts interfere with systemic regulators, mainly neuro-endocrine and immunological, resulting in epi-genetic, inflammatory and metabolic disorders [5].

Stress may constitute a trigger and can be purely emotional like in life trauma [6], or be related to disruption of physical integrity by injury or surgery, or result from exhaustion. Important stress may temporarily suppress immune responsiveness [7,8]. In optimal conditions the immune regulation will return to equilibrium within a short period of time. However, the system may present a "rebound" generating an excessive and long-lasting cellular and humoral response with an elevated production of immunoglobulins [9]. Epigenetic changes may occur to genes involved with inflammation [10]. On the other hand, any infection caused by bacteria or viruses evokes an immune response, which may be exaggerated in terms of intensity and duration.

Disordered immunity may target the body's own tissues or organs, manifesting itself as auto-antibodies against e.g., cell nuclei (anti-nuclear antibodies), the thyroid gland (e.g., anti-thyroglobulin antibodies), joints and entheses, and rarely against the pancreas or the adrenal glands. Cellular substructures, such as the mitochondria or the Golgi apparatus, can also be targeted [11]. Auto-immune diseases may result like connective tissue disease, systemic lupus erythematosus, Hashimoto's disease, or Sjogren's syndrome.

Immunoglobulin-activated complement is cytotoxic provoking inflammatory reaction with the production of cytokines (interleukins) and the activation of several kinases [12,13]. The intracytoplasmic Janus-Kinase (JAK) transfers phosphate molecules from Adenosine Triphosphate (ATP) to the Interleukin receptor, activating the nuclear genetic initiators of e.g., articular and tendinous inflammation. The phosphorylating activity of pyruvate-dehydrogenase-kinase reduces the conversion of pyruvate to acetyl-coenzyme A, with decreased generation of ATP by the citrate (Krebs) cycle. The accumulated pyruvate can be recycled in the cell cytoplasm to glucose (Cori cycle), however with excessive production of lactate [14]. The high

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concentration of lactate and lactic acid, together with the reduced ATP production explains muscle soreness and poor performance during exercise, difficult recovery, and the general lack of energy which are typical of the chronic fatigue syndrome.

Lactate accumulation also occurs in the cerebrospinal fluid and causes brain disfunction with poor memory and capacity to concentrate [15], as well as impaired cognitive function and brain fog [16]. Cognitive disturbances may also be associated with enhanced glutamate accumulation [17] because of decreased clearance of this metabolite by the astrocytes the function of which cells is reduced by proinflammatory cytokines [18]. An elevated concentration of inflammatory biomarkers has indeed been detected in cerebrospinal fluid [19]. Some specific changes of the genome induced by COVID appear to be similar to those predisposing to dementia [20]. Overall, 40% of Post-COVID patients were reported to present neurologic outcomes [16].

Due to inflammation, the oxidant-antioxidant balance is disturbed, causing oxidative stress. This leads to oxidative changes in the fatty acid composition with reduced fluidity of the cell membrane, decreasing receptor sensitivity and impairing biosynthetic processes in the cytoplasm.

Neuro-SPECT investigations have typically revealed decreased isotope captation in the supra-orbital and prefrontal regions, as well as in the hypothalamus and the brain stem [21]. This reflects impaired blood perfusion to these regions, and may possibly relate to the deregulation of autonomous nervous functions, with orthostatic hypotension, tachycardia, and functional intestinal disorders. Impaired intestinal peristalsis may favor bacterial dysbiosis with increased mucosal permeability in the so-called "leaky gut" syndrome [22].

In addition, COVID-19 may inflict complementary damage to the lungs and the heart being the sequelae of the direct invasion by the SARS-Corona virus.

Therapeutic Options

General approach and patient intake

Considering the complexity of ME/CFS and the Post-COVID syndrome, and since there is no proven treatment eradicating possible causal factors, therapy can only aim at correcting the pathogenetic mechanisms and/or mitigating the severity of clinical signs and symptoms [23]. However, since this is a chronic, non-lethal disease, the ethical principle "first do not harm" (primum non nocere, original Hippocratic Oath) should rule.

The first step in treatment consists of patiently and empathically listening to the patient's history and complaints. After that, a comprehensive blood and urine analysis must be performed, including testing of cellular and humoral immunity and of endocrine markers and metabolism, as well as the measurement of trace elements such as zinc and selenium, and of markers of infection and inflammation.

Next, psychological guidance and teaching a meditation technique (e.g., transcendent meditation), instruction on sleep hygiene and healthy nutrition, with the avoidance of ultra-processed food, moderate sporting activity such as aqua gym and walking, as well as pulmonary rehabilitation and coaching of professional activity are recommended [24].

Alternative and complementary medicine

Before allopathic medication is prescribed, so-called alternative and complementary treatments may be tested by patients who prefer so-called natural remedies. Osteopathy, acupuncture and homeopathy are among the approaches most commonly used.

Nutritionist will recommend adhering to a high-quality dietary pattern, plant-based diet in particular, which has been associated with a lowered risk of clinical COVID-19 disease and hospitalization [25]. Diet therapy together with probiotics has been recommended for the treatment of post-COVD sarcopenia [26]. Administering separate substances such as zinc or high-dose of Ubiquinol Q10 would be beneficial according to some trials [27].

The multi-ingredient nutraceutical QALY® (JonaPharma, Elversele, Belgium) focusses on several aspects of the pathological process, including inflammation and oxidative stress and adds ingredients with adaptogen and general support capacity [28,29].

There is contradicting experience concerning treating ME/CFS patients with transcranial electromagnetic wave stimulation. Hyperbaric oxygen chamber (caisson) treatment has been advocated as efficient in ME/CFS patients by one group of researchers, but the application of this technique is limited by the scanty availability and high cost of the appropriate equipment. To our knowledge these treatments have not been explored in post-COVID patients.

Unregistered medications

The "orphan drug" Sodium dichloroacetate (DCA lab, Vilnius, Lithuania) has been proven to inhibit the adverse effect of pyruvate dehydrogenase kinase on glucose metabolism [30,31]. When given in a dose not exceeding 12.5 mg/kg body weight this substance is not toxic, and its effectiveness can be enhanced by adding Vit B1, Alpha lipoic acid, and Ubiquinol Q10.

Sodium dichloroacetate can successfully be combined with Meldonium (Mildronate®, Grindex, Riga, Latvia) that activates glycolysis [32], and increases the transfer of pyruvate into the mitochondria by lowering l-Carnitine biosynthesis [33]. Meldonium enhances blood supply to the brain, particularly to the prefrontal and the supraorbital regions, as well as to the hypothalamus and the brain stem [11,34].

An option that is recommended consists of infusion therapy by slow intravenous administration of physiological salt solution with multivitamins (Meyer's solution) [35], and magnesium sulphate. Glutathione may be added, perhaps together with stem cells of human and plant origin cultured *in vitro* [36,37]. Considering the observation that fibrin micro clots blocking capillaries can be involved in post-COVID sequelae [38], infusion of m-tranexamic acid may be beneficial. This acid increases the fibrinolytic activity of plasmin, and activates the immune defense capacity of the microglia [39].

The combined oral and infusion therapy has been applied in a prospective open-label study with 113 patients suffering from either long-lasting ME/CFS or from post-COVID syndrome. Over four in five patients reported significant and lasting improvement of fatigue and well-being, allowing many of them to resume their work after a few months' treatment, albeit commonly on a part-time basis [29].

Medication interfering with inflammation and with immunity

Approximately two thirds of ME/CFS presents biological markers of immune disorder. Aside from common abnormalities of the relative proportion of T-lymphocyte clusters, the prevalence of positive anti-

nuclear antibodies was significantly higher than in non-ME-patients [11]. Also, many patients presented positive antibodies against thyroid, mitochondria, Golgi apparatus, parietal, and other cells.

Therefore, it seems logical to use immune suppressive or Disease-Modifying Antirheumatic Drugs (DMARS). However, neither treatment with Rituximab nor with Methotrexate [40] did cure ME/CFS patients. Hydroxychloroquine may be given as a complementary medication in some cases, but its effect on general complaints is limited. This suggests that the systemic immune disorder, though being an important element in the pathogenesis, is not the primary cause of the disease.

Anti-inflammatory medication may offer an interesting option for treatment, particularly among patients with articular and muscular pain (fibromyalgia), or with enthesopathy. Intermittent intravenous administration of 40 mg to 80 mg methylprednisolone, preferentially given together with the infusion therapy, is well tolerated and causes no feedback inhibition of the hypothalamic-pituitary-adrenal axis. Most patients experience immediate benefits on fatigue and pain, and may sometimes feel slightly euphoric. The combination with Non-Steroidal Anti-Inflammatory (NSAID) medication enhances and prolongs the favorable effects of the IV corticoid treatment.

Future options

Newer injectable "biologicals" focus on the inflammation process beyond inhibiting the Cyclo-Oxygenase (COX) conversion to prostaglandins. These drugs antagonizing particular inflammatory cytokines [41]. They are, however, expensive and must be given by injection.

The next generation of anti-inflammatory medicines, called small molecules, are administered orally, and inhibit the activity of the Janus-kinase. They are highly effective against joint inflammation and enthesitis but have not yet been tested in patients with ME/CFS or post-COVID syndrome. It should be warranted to perform clinical trials with these drugs, in particular in patients with biological markers of immune disorder or inflammation.

Conclusion

To date, no causal treatment is available for patients suffering from ME/CFS or post-COVID syndrome. While the pathogenetic mechanisms have been reasonably well elucidated, treatment remains limited to alleviating signs and symptoms and supporting physical and mental well-being. The pivotal role of disordered immunity and chronic inflammation has been established, and treatment of these factors may still offer the best treatment options. Newer drugs such as biologicals and Janus kinase inhibitors certainly merit clinical trials. In addition, the oral administration of a specific nutraceutical and of substances optimizing cellular metabolism deserve attention, as does intravenous infusion therapy.

However, the main message should be that the prevalence of post-COVID disease should be reduced as much as possible, which appears to be achievable through timely treatment with Nirmatrelvir and through generalized vaccination [42,43].

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Conflict of Interest

The author owns the patent for the formulation of the QALY nutraceutical.

References

1. Deumer US, Yaresi A, Floris V, Savioli G, Mantovani E, Carrasco PL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): An overview. J Clin Med. 2021;10(20):4786.
2. de-Las-Peñas CF, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. Eur J Intern Med. 2021;92:55-70.
3. Wong TL, Weitzer D. Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)- A systematic review and comparison of clinical presentation and symptomatology. Medicina (Kaunas). 2021;57(5):418.
4. Kedor C, Freitag H, Meyer-Arndt L, Wittke K, Hanitsch LG, Zoller T, et al. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat Commun. 2022;13(1):6009.
5. Comhaire F. Treating patients suffering from myalgic encephalomyelopathy/chronic fatigue syndrome (ME/VFS) with sodium dichloroacetate: An open-label, proof-of-principle pilot trial. Med Hypotheses. 2018;118:45-8.
6. Klopack ET, Crimmins EM, Cole SW, Seeman TE, Caroll JE. Social stressor associated with age-related lymphocyte percentages in older US adults: Evidence from the US health and retirement study. Proc Natl Acad Sci U S A. 2022;119(25):e2202780119.
7. Dantzer R, Kelley KW. Stress and immunity: An integrated view of relationship between, brain and the immune system. Life Sci. 1989;44(26):1995-2008.
8. Dhabhar FS. Effects of stress on immune function: The good, the bad, and the beautiful. Immunol Res. 2014;58(2-3):193-210.
9. Dau PC. Immunological rebound. J Clin Apher. 1995;10(4):210-7.
10. Chlamydas S, Papavavissilou AG, Piperi C. Epigenetic mechanisms regulating COVID-infection. Epigenetics 2021;16(3):263-70.
11. Comhaire F, Deslypere JP. News and views in myalgic encephalomyelopathy/chronic fatigue syndrome (ME/CFS): The role of co-morbidity and novel treatments. Med Hypotheses. 2020;134:109444.
12. Goldberg BS, Ackerman ME. Antibody-mediated complement activation in pathology and protection. Immunol Cell Biol. 2020;98(4):305-17.
13. Karsten CM, Köhl J. The immunoglobulin, IgG Fc receptor and complement triangle in autoimmune diseases. Immunobiology. 2012;217(11):1067-79.
14. Katz J, Tayek JA. Recycling of glucose and determination of the cori cycle and gluconeogenesis. Am J Physiol. 1999;277(3): e401-7.
15. Roessler M, Tesch F, Batram, M, Jacob J, Loser F, Weidinger O, et al. Post-COVID-19-associated morbidity in children, adolescents, and in adults: A marched cohort study including more than 157000 individuals with COVID-19 in Germany. PLoS Med. 2022;19(11):e1004122.
16. Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. Nat Med. 2022;28(11):2406-15.
17. Wiehler A, Branzoli F, Adanyeguh I, Mochel F, Pessiglione M. A neuro-metabolic account of why daylong cognitive work alters the control of economic decisions. Curr Biol. 2022;32(16):3564-75.
18. Rönnbäck L, Hansson E. On the potential role of glutamate transport in mental fatigue. J Neuroinflammation. 2004;1(1):22.
19. Eden A, Grahn A, Bemell D, Aghvanyan A, Bathala P, Fuchs D, et al. Viral antigen and inflammatory biomarkers in cerebrospinal fluid in patients with COVID-19 infection and neurologic symptoms compared with control participants without infection or neurologic symptoms. JAMA Netw Open 2022;5(5):e2213253.

20. Reiken S, Sittenfeld L, Dridi H, Liu Y, Liu X, Marks AR. Alzheimer's-like signalling in brains of COVID-19 patients. Alzheimers Dement. 2022;18(5):955-65.

21. Dougherty P. Central control of autonomic nervous system and thermoregulation. Neuroscience Online. Section 4: Homeostasis and higher brain functions. 2020.

22. Farré R, Vicario M. Abnormal barrier function in gastrointestinal disorders. Handb Exp Pharmacol. 2017;239:193-217.

23. Ledford H. Long-COVID treatments: why the world is still waiting. Nature. 2022;608(7922):258-60.

24. Al-Mhanna SB, Mohammed M, Noor NM, Afolabi HA, Irekeola AA, Bello KE, et al. Effectiveness of pulmonary rehabilitation among COVID-19 patients: A systematic review and meta-analysis. Healthcare (Basel). 2022;10(11):2130.

25. Ramati M, Fatemi R, Yon DK, Lee SW, Koyanagi A, Shin JI, et al. The effect of adherence to high-quality dietary pattern on COVID-19 outcomes: A systematic review and meta-analysis. J Med Virol. 2022;e28298.

26. Cseppento CD, Moga TD, Bungau AL, Tit DL, Negrut N, Pasca B, et al. The contribution of diet therapy and probiotics in the treatment of sarcopenia induced by prolonged immobilization caused by the COVID-19 Pandemic. Nutrients. 2022;14(21):4701.

27. Ben Abdalla S, Mhala Y, Trabelsi I,Sekma A, Youssef R, Ali KBH, et al. Twice-daily oral zinc in the treatment of patients with coronavirus disease 2019: A randomized double-blind trial. Clin Invest Dis. 2022;ciac807.

28. Wood E, Hall KH, Tate W. Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/chronic fatigue syndrome: A possible approach to SARS-CoV-2 'long-haulers'? Chronic Dis Transl Med. 2021;7(1):14-26.

29. Comhaire F, Pen J. Boosting health recovery by food supplements: The case of ME/CFS versus post-COVID-19 syndrome. J Clin Pharmacol Ther. 2021;2(3):1022.

30. Milic NS, Dolinar K, Mis K, Metkovic U, Bizjak M, Pavlin M, et al. Suppression of pyruvate dehydrogenasekinase by dichloroacetate in cancer and skeletal muscle cells is isoform specific and partially independent of HIF-1α. Int J Mol Sci. 2021;22(16):8610.

31. Katayama Y, Kawata Y, Moritoh Y, Watanabe M. Dichloroacetate, a pyruvate dehydrogenase inhibitor, ameliorates type 2 diabetes via reduced gluconeogenesis. Heliyon. 2022;8(2):e08889.

32. Strobersberger W, Dünwald T, Gmeiner G, Blank C. Story behind meldonium-from pharmacology to performance enhancement: A narrative review. Br J Sprots Med. 2017;51(1):22-5.

33. Dambrova M, Makrechka-Kulka M, Viskersts R, Kuka MEJ, Liepinsh E. Pharmacological effects of meldonium: Biochemical mechanisms and biomarkers of cardiometabolic activity. Pharmacol Res. 2016;113(Pt B):771-80.

34. Eser MH, Bektasoglu PK, Gurer B, Bozekurt H, Sorar M, Ozturk OC, et al. The vasorelaxant and neuroprotective effects of mildronate in a rabbit subarachnoid hemorrhage model. Turk Neurosurg. 2020;30(2):163-170.

35. Ali A, Njike VY, Northrup V, Sabina AB, Anna-Leila W, Liberti LS, et al. Intravenous micronutrient therapy (meyer's cocktail) for fibromyalgia: A placebo-controlled pilot study. J Altern Complement Med. 2009;15(3):247-57.

36. Krikham AM, Bailey ALM, Monaghan M, Shorr R, Lalu MM, Fergusson DA, et al. Updated living systematic review and meta-analysis of controlled trials of mesenchymal stromal cells to treat COVID-19: A framework for accelerated synthesis of trial evidence for rapid approval-faster approval. Stem Cells Transl Med. 2022;11(7):675-87.

37. Comhaire F, Pen J, Deslypere JP. Nutraceutical therapy for patients suffering from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), post-COVID syndrome (PCoS), or alzheimer disease (AD). Ann Neurodegener Disord. 2022;6(1):1032.

38. Pretorius E, Venter C, Laubscher GJ, Kotze MJ, Oladejo SO, Watson LR, et al. Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/post-acute sequelae of COVID-19 (PASC). Cardiovasc Diabetol. 2022;21(1):148.

39. Atsev S, Tomov N. Using antifibrinolytics to tackle neuroinflammation. Neural Regen Res. 2020;15(12):2203-6.

40. Fluge O, Rekeland IG, Lien K, Thürmer H, Borchgrevink PC, Schäfer C, et al. B-lymphocyte depletion in patients with myalgic encephalomyelitis/chronic fatigue syndrome: A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2019;170(9):585-93.

41. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: A prospective observational study. Lancet Respir Med. 2022;10(8):761-75.

42. Xie Y, Choi T, Al-Aly Z. Nirmatrelvir and the risk of post-acute sequelae of COVID-19. MedRxiv. 2022.

43. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-Cov-2 infection in UK users of the COVID symptom study app: A prospective, community-based, nested, case-control study. Lancet Infect Dis. 2022;22(1):43-55.