Review of: "LC, POTS, and ME/CFS: Lifting the Fog"

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Potential competing interests: No potential competing interests to declare.

Dear Author,

I read with great interest your article about Long-COVID, POTS and ME/CFS. The unifying hypothesis including autonomic dysfunction, MTHFR polymorphisms, gut microbiome, autoimmunity and mitochondrial oxidative stress provides important insights in the main alterations and possible mechanisms underlying these conditions.

I have few comments for the author:

1. In the NIH Consensus Meeting on POTS (doi: 10.1016/j.autneu.2021.102828) the main pathophysiological classification reports hyperadrenergic, neuropathic and/or hypovolemic subtype, often one patient displaying overlapping alterations and a predominant phenotype. Cardiovascular deconditioning, autoimmune and genetic mechanisms also contribute. It is not clear to me the definition used in the article of “low flow” vs “high flow” POTS. I would suggest the author to better clarify the distinction, stressing the relevance of this classification in terms of pathophysiology/treatment strategies.
2. ME/CFS (doi: 10.1016/j.mayocp.2021.07.004) is a condition bearing alterations in energy utilization and production, cognitive and neurological abnormalities and orthostatic intolerance. My suggestion for the author is to elaborate more on the role of mitochondrial dysfunction and reduced energy utilization in the setting of ME/CFS, which seems a strong molecular-clinical link (doi: 10.1111/j.1365-2362.2011.02567.x).
3. The model of Varicella-Zoster Virus infection and Long-COVID is not clear to me. Assuming the Area Postrema is a vulnerability site for pathogenic viruses, it seems resonable to hypothesize that Sars-CoV2 virus may take advantage of that in Long-COVID rather than re-activation of latent infections. During viremia Sars-CoV2 can take advantage of its neurotropic behaviour (doi: 10.1007/s12028-020-01049-4) and infect important neural structures. My suggestion for the author is to better clarify why VZV may be especially important in Long-COVID patients, providing supporting evidence.

In summary, the body of evidence here presented supports an association between body methylation level and inappropriate viral response and post-viral syndrome susceptibility. However, interpretation should be cautious as association is supported and not demonstrated and stronger data are needed to assess causation.