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

Jan Pieter Konsman[1]

1 University of Bordeaux

Potential competing interests: No potential competing interests to declare.

The review by Chambers “LC, POTS, and ME/CFS: Lifting the Fog” proposes a new pathophysiological framework to better understand some so far medically unexplained syndromes. While I quite like the broad scope of the review establishing links between findings obtained in many different domains of the life and health sciences, I fear that there in the end some approximations and errors that blur the precision of the message. Furthermore, it would be important to clarify how the author uses biomarkers in his reasoning. Finally, there are several other points (regarding, amongst other things, abbreviations and references), detailed below also need to be addressed.

Detailed points of criticism

1. Title: I would propose to write out the syndromes in the title as I fear that starting with three abbreviations that are (likely) not known to everyone will result in many potential readers not going beyond the title.
2. Abstract: MTHFR should be spelled out in the abstract.
3. Abstract: I would suggest to spell out EBV and VZV in the abstract as these abbreviations my not be known to every reader.
4. Introduction: “…resolution of the paradoxes remains frustratingly out of reach”. I would invite the author to either specify more what the paradoxes in question are or to use a different term. Personally, I judge that are clear limits to our current understanding of long Covid, but I do not see any paradoxes in the sense of “a situation or statement that seems impossible or is difficult to understand because it contains two opposite facts or characteristics” (Cambridge Dictionary).
5. Introduction: “Recent research has revealed that the BBB is not all inclusive and that some areas of the CNS are not so protected.” I disagree with the use of recent here as this has been known since the 1960s. Please, rephrase accordingly.
6. Introduction: “Most with this polymorphism are unaware of it.” I think this goes without saying as typically people do not know their genetic make-up, and should, therefore, be dropped.
7. Hypothesis: The abbreviations POTS and CFS should be spelled out here.
8. Hypothesis: “… incriminate low fiber diets that support low bacterial diversity with production of minimal SCFAs, e.g., butyrates, GABA, and B vitamins.” I fail to see how the synthesis of GABA by (presumably) gut bacteria is relevant for nervous system physiology as GABA is typically synthesized in the cytoplasm of the presynaptic neuron from the precursor glutamate by the enzyme glutamate decarboxylase. Please, rephrase to avoid giving the impression that multicellular organisms with nervous systems are dependent on their microbiota for GABA.

9. 1. MTHFR and Homocysteine: The text of the first paragraph needs to be backed up with references.
10. 1. MTHFR and Homocysteine: “So this is an exceedingly common polymorphism with incidence that somewhat reflects the percentage of individuals that develop LC.” I can come up with many phenomena that have comparable prevalence, but that are totally unrelated. As this sentence does not add anything to the argument the author wants to make, it should be dropped.
11. 1. MTHFR and Homocysteine: “Homocysteine is a strong marker for both LC [2], the MTHFR gene [5] , and for ME/CFS [6]. High homocysteine may be a good marker for the MTHFR gene and low folate may be a good negative marker for homocysteine [7]. Homocysteine is a strong marker for thrombosis and may explain the oft encountered thrombosis in Covid-19. Homocysteine via CVOs causes brain fog in LC (see CVO section) [8].” I think that it would be useful to introduce an additional sentence to express what the author concludes from these findings, otherwise the reader may start to wonder. Also, ref [8] does not at all show that homocysteine causes brain fog via CVOs during long Covid. Instead, it shows a correlation between circulating homocysteine concentrations and cognitive impairment. Moreover, CVOs are not even mentioned in this study. To conclude a causal relationship from these findings is, an expression of rather selective citation.
12. 1. MTHFR and Homocysteine: “Methylation status in the body can be determined by measuring whole blood histamine, as histamine and methylation are inversely related.” This statement requires references.
13. 2. Postural Orthostatic Tachycardia Syndrome: “POTS is considered a disorder of the hypothalamus-pituitary-adrenal (HPA) axis …” This statement also requires a reference.
14. 2.A. Low Flow POTS: ARB should be spelled out the first time it is used.
15. 2.A. Low Flow POTS: BKN should be spelled out the first time it is used.
16. 2.A. Low Flow POTS: ACE should be spelled out the first time it is used.
17. 2.A. Low Flow POTS: "Down regulation of ACE (ACE degrades BKN) by estrogen combined with a viral infection can supercharge BKN.” “Supercharged” can be replaced by a more academic term.
18. 2.B. High Flow POTS: MCAS and EDS should be spelled out the first time it is used.
19. 3. Gut Microbiome: As remarked upon above, the speculative links about the role of bacterial GABA production in LC, POTS and ME/CFS, is, in my mind, totally irrelevant. Please, remove.
20. 4. CVOs: “Several recent articles have highlighted CVOs [46],[47].” As mentioned above, CVOs have been known for quite some time. Please refer to the original references rather than to recent reviews to respect the scientific reward system based on citations. BTW, ref [46] is not even primarily about CVOs
21. 4. CVOs: “These areas are the pineal gland, the posterior pituitary a.k.a. neurohypothesis, the paraventricular nucleus (PVN) in the median eminence, the area postrema (AP), the organum vasculosum of the lamina terminalis (OVLT) or supraoptic crest, and the subfornical organ (see figure 2).” The PVN should be removed from this sentence as PVN refers to the concentration of neuronal cell bodies, at the level of which there is a functional BBB, some of which project to the median eminence, which is a CVO. It is, therefore, incorrect to suggest that the PVN would be a CVO itself.
22. 5. Methylation and Shingles: “In a recent review compared to controls, patients that experienced mild to moderate COVID-19 or LC exhibited hypomethylation and hypermethylation [62] respectively. This reflects the methylation

disposition of MTHFR wild type and 677TT respectively, i.e., wild type quickly recovered and 677TT devolved into LC." The second sentence is far too affirmative as the study referred to in the first sentence did not specifically mention the methylation status of MTHFR. Please, tone down.

23. Please, remove all allusions to Justin Bieber, since this does not add much to the argument. Justin Bieber is just one case, and case studies figure at a rather low position in the pyramid of evidence of EBM.
24. 6. Autoimmunity in Females: "In addition estrogen appears to lower cortisol [73] and ACE2, at least in the lungs [74]. Perhaps lower pulmonary ACE2 is Covid 19 protective, but the downregulated ACE2 may be associated with higher levels of des-Arg9-bradykinin (see figure 5). Des-arg-BKN appears to be a prominent kinin in Covid-19 [75]." Please, make it clear to the reader why all this could be relevant for the topic at stake here.
25. 7A. Mitochondria and Oxidative Stress: "The Krebs or TCA cycle with its electron transport chain ETC also requires activated B2 and B3." Contrary to what the authors seems to imply, ETC is not part of the Krebs cycle. Please, rephrase.
26. 7B. Magnesium and Vitamins: "A shortfall in magnesium or B6 compromises monoamine neurotransmitter synthesis and leads to depression …" This statement also requires a reference.
27. 8. Thoughts on Therapy: "Changing one's diet is more difficult than changing one's religion." This is unverifiable and useless statement, unless it one's aim to encourage people to take more medical drugs (which should not be a physician's aim). Please, remove.
28. Conclusion: "In summary LC reveals undiagnosed MTHFR 677TT present in 30-40% of the population." This conclusion is not at all justified. Not anything so affirmative can be concluded. At best, this review allows to suggest some new perspectives.
29. Conclusion: "These latter bacteria produce butyrates (SCFAs), GABA, B vitamins, and can degrade histamine." The production of GABA and the degradation of histamine by gut bacteria is not at all relevant to how these molecules are used in multicellular host tissues. Please, remove these elements from the conclusion.
30. Has the author obtained permission to reproduce the figures from the indicated references?