Review of: "Myalgic encephalomyelitis/chronic fatigue syndrome as a breakdown of homeostasis"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

Title: Myalgic encephalomyelitis/chronic fatigue syndrome as a breakdown of homeostasis

The purpose of the article is unclear. In the Abstract and Introduction, purpose nor approach have been explained. The manuscript can be seen as an opinion article with elements of a review.
Author presents several considerations and evidences that support a hypothesis that the pathophysiological mechanisms in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are based on imbalance in physiological homeostasis.
In the first chapter, Author describes in general what does the physiological homeostasis mean, and what is its possible relationship with ME/CFS. In the following three chapters, Author handles three hypotheses/explanations for both the presentation of the symptoms and their persistence in patients with ME/CFS. These hypotheses/explanations are: the neuroimmune hypothesis, the microbiome hypothesis and mitochondrial failure hypothesis.
There are some serious shortcomings in this manuscript:

1. There is little novelty. There still exist several publications describing ME/CFS as a disturbance in homeostasis.
2. The choice of the topics seems rather arbitrary. It has been not explained why the microbiome (in the gut) hypothesis takes a prominent place between the neuroimmune hypothesis and the subject of ‘mitochondrial failure’.
3. There are many statements without either explanations or underpinning literature.

Some examples:
a) Pg. 3-4, the first para in ‘The Neuroimmune Hypothesis’ that deals with inflammation; there is no one citation.

1. In the Chapter ‘The Microbiome Hypothesis’, para 1, it is stated: “Microbes influence metabolism, immunity and behavior.” Which metabolism? Which immunity? The behavior of what/who and how? Further: “The microbiota produce and secrete hormones…” Which hormones the Author refers to? Are these “hormones” comparable to human hormones such as corticosteroids or estrogen? “The microbiota… respond to host hormones and regulate expression levels of host hormones”. This is unclear, which hormones? “Hormones and the microbiome are linked to immune responses…” How is

the microbiome linked to immune responses? Is there evidence?

2. Pg. 6, para 1: “When … Escherichia coli (E coli) enter the gut, the HPA can be activated. Stress (psychological stress of the stress of the bacteria?) can induce increased permeability of the gut, allowing bacteria and bacterial antigens to cross the epithelial barrier and activate a mucosal immune response, which in turn alters the composition of the microbiome and leads to an enhanced HPA drive”. This is unclear. A composition of microbiome and enhanced HPA drive are two different things and they should not be placed in one sentence, without explanation. Again there is no supporting reference.
3. Pg. 6, para 2: “Patients with irritable bowel syndrome and major depression show alterations of the HPA which are induced by increased gut permeability. … The gut microbiota play a role in regulating the HPA”. This is inconsistent and irrelevant information: in the following texts, there is nothing about major depression or working mechanisms between HPA axis and microbiota. Instead, an information is given about influences of glucocorticoids, vitamin D and sex-hormones on the immune responses.

1. Author often uses inexact, inconsistent or even incorrect expressions. This is confusing for a reader. Examples:

a) Pg. 1, “The three systems… to control … tissues, organs and *muscles*…”. It seems me not logical to speak about muscles in this place; why not vessels or skin? Furthermore, Author does not deal anything with muscles in the following text.

b) On Pg. 1, there is a control about “…the body, the emotions and the mind”, whereas on Pg. 2 the “bodily functions, experience and behavior” are controlled. If Author uses various but liking expression, please explain the difference and the reason of doing so.

c) in Fig. 1 and in the text, the nervous system and the brain exchange mutually information. This is expressed incorrectly because brain is part of the nervous system. I think it must be ‘the autonomic nervous system’.

1. In the last sentence of the ‘Physiological Homeostasis’ chapter on Pg. 3, Author cites Hatziagelaki et al. (2018) who suggest that the aberrant homeostasis might be a result of inflammation in the hypothalamus. The “inflammation” is merely a hypothesis whereas evidence is only in respect to the disfunctioning HPA axis. It would be correct to mention here that no such inflammation has ever been found in microscopic slices or other technics. The homeostatic disequilibrium can apparently occur through disturbed regulatory systems and without any focal inflammation in the brain.
2. There are in my opinion too many, and copious, quotes from various papers. By this, it is difficult to follow what Author himself want to say. Most of the quotes are accompanied by citations.
3. However, the following large text in the last para on Pg. 6 has been simply copied from the abstract of other publication (Myhill et al, 2009):

“by interventions based on the biochemistry … Centers for Disease Control criteria” and “…correlation is observed … Only 1 of the 71 patients overlaps the normal region”.

1. Abbreviations are not always being clarified. For example, ‘HPA’ is throughout not expressed in words.

And it must be HPA *axis* instead of HPA. In the caption of Fig. 2, there are unclarified abbreviations, such as TNF, CRH, HK-1 and SP.