Reviewer's report

Title: Myalgic encephalomyelitis / chronic fatigue syndrome and Encephalomyelitis disseminata / multiple sclerosis show remarkable levels of similarity in phenomenology and neuro-immune characteristics.

Version: 1 Date: 23 July 2013

Reviewer: Gordon Broderick

Reviewer's report:

This is a very timely submission, one that addresses an important topic in a very articulate manner, with a clearly stated goal. This also presents as an extensively researched and comprehensive review with the material being very well organized. I encourage the publication of this manuscript and have only relatively minor suggestions for improvement:

Major Compulsory Revisions:

1. The discussion of similarities in clinical presentation between ME/CFS and MS are very convincing. However, it might be equally interesting to discuss what might be some of the most striking differences. I would encourage the authors to perhaps broaden their discussion of these many similarities and cast these in the context of variants that are specific to each illness. This is done very nicely when discussing the results of Table 5. For example:

“…Impaired oxidative phosphorylation is an issue in both disorders but accelerated glycolysis in muscles has been reported in people with ME/cfs but not in people with MS. Conversely, damage to the mitochondrial respiratory chain in neurons has been reported in MS but not in ME/cfs.”

It would be interesting to the reader if similar comments were made regarding the other tables. Of course this suggestion only applies to situations where such a change in context exists between illnesses.

2. Many dimensions of illness are discussed in this very comprehensive review. It would be helpful to the reader if a diagram were constructed that would integrate these numerous observations into a model of the proposed mechanisms of illness, possibly emphasizing the shared core mechanisms and the disparities. This is different from the Venn diagram of Figure 1. Immune signaling and metabolism are interactive and it would be interesting to summarize the many facts presented by integrating them into a cause-and-effect diagram that would show some of the feedforward and feedback relationships.

3. The authors mention ME/CFS as a co-morbid condition in MS patients; could ME/CFS also lead to MS? Is there a junction in immune progression that would explain bifurcation to ME/CFS rather than MS or is this simply a question of severity of the initial insult?
4. At the top of pg. 16, the authors mention the following:

“… The majority of CD26 expressing T cells (approximately 98%) in the immune system are Th17 cells [182].”

According to Fletcher, et al., author’s reference [186], it is unlikely that this statement is correct. Fletcher, et al. reported 52% of CD2+ cells (a subset that includes all T cells and CD56+ (NK) cells) are CD26+ in healthy controls. If Fletcher, et al. is correct, and the current submission is also correct then 50% of T cells are Th17 cells. We believe this to be very unlikely. Perhaps this was stated out of context or was meant to describe a specific compartment or lesion?


Minor Essential Revisions.

5. When discussing B cell dysfunction the authors refer to Rituximab trials and justly so. They may also want to mention Ampligen trials when discussing NK cell dysfunction. The author’s may want to consider and comment on the following:


6. On page 12 and in other places throughout the text, incorrect symbols appear when referring to IL-1a, TNFa and TGFb. NF-kappa B also shows as NF-6B in the text.

Discretionary Revisions.

7. The author’s may want to specify that Table 1-5 may be found in the supplementary file.

8. Have there been any studies of sex-specific differences in immune signature in MS?

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.