Author’s response to reviews

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

Authors:

Gerwyn Morris (activatedmicroglia@gmail.com)
Michael Maes (dr.michaelmaes@hotmail.com)

Version: 2 Date: 10 August 2013

Author’s response to reviews: see over
To the Editor
BMC Medicine
Claire Barnard

Re: 1181306890101913
Myalgic encephalomyelitis / chronic fatigue syndrome and Encephalomyelitis disseminata / multiple sclerosis show remarkable levels of similarity in phenomenology and neuro-immune characteristics.
Gerwyn Morris and Michael Maes

Dear Claire Barnard,

In attach the revised version of our paper. We have revised it according to all points made by the referees (except one). We have also made all editorial revision as requested.

**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: 22 July 2013
Reviewer: Ian Clark
Reviewer's report:
On reading this text in detail I found it well-written, with a few glitches arising from symbol recognition (see below) and, considering its length, few typos. Myalgic encephalomyelitis and multiple sclerosis are conditions that to date have yielded little to investigations into their pathogenesis, and thus rational treatment. This detailed comparison of their clinical, biochemical and immunological characteristics is novel. It seems a very plausible narrative to me, although I have of course not read most of the numerous references. The remarkable similarities of dysregulation that these authors have been brought to our attention warrant being on record in order to alert others in the field to experimental possibilities that they otherwise might have not appreciated.

1. Section 5 on pages 12-13 has several symbol errors (beta, gamma, and kappa), perhaps a technical font-reading problem. A similar error is on page 27.
2. 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.

We have changed the text according to this remark:
End of section 2 we now state:
It appears however that ME/cfs patients may be more sensitive to physical or cognitive activities than patients with MS.
End of section 5 we now state: While Coenzyme Q10 is clearly related to fatigue in ME/cfs, the findings in MS are less evident.

End of section 6 it was and is stated that: While MS is characterized by increased in vivo expression of CD69, a decreased ex vivo CD69 expression is found in ME/cfs. Both MS and ME/cfs are accompanied by reduced NKCA.

Section 7: here (autoimmunity) there are similarities only.

Section 8: it was and is stated that: 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.

In our conclusions, we have summarized the differences between both MS and ME as: There are however also differences in symptomatic and immune profiles between both diagnoses. Thus, patients with ME/cfs seem more sensitive to increases in physical or cognitive activity than patients with MS. ME/cfs patients may suffer more from infections, while the number of infections is associated with increasing symptom severity. While MS is characterized by increased expression of CD69, a decreased CD69 expression is seen in ME/cfs. Accelerated glycolysis is reported in ME/cfs but not in MS. Neuronal damage to the respiratory chain has been found in MS but not in ME/cfs. T cell exhaustion seems to be more of an issue in ME/cfs than in MS. When taken together the range of surrogate markers for O&NS and the range of autoantibodies is wider in ME/cfs than in MS and this may be due to an increased severity of O&NS in ME/cfs. While coenzyme Q10 is related to fatigue in ME/cfs, the findings in MS are less evident. Finally, while both ME/cfs and MS are chronic immune-inflammatory diseases, inflammation of the central nervous system is clearly more prominent in MS than in ME/cfs.

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.

A new figure (now Figure 1) has been added to the text, see section 10. Figure 1 shows a diagram which integrates the numerous pathways into a mechanistic model emphasizing the shared and interactive immune signaling and metabolic pathways that explain the symptomatic similarities in both diseases.

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
When discussing the comorbidity issues (Figure 3) we now also discuss these possibilities as: Other possibilities are that ME/cfs could increase the odds to develop MS or when comorbid with MS could aggravate the severity of MS. It is also possible that there is a junction in immune-inflammatory progression that could explain bifurcation to ME/cfs rather than MS. For example, the initial lesions in ME/cfs could be smaller than in MS but at the expense at greater bioenergetic impairments.

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?


We now state:
CD26 expression is associated with Th-17 cells and IL-17 production is related to the CD26+CD4+ T cell subset [182].

Minor Essential Revisions.

We have decided not to describe Ampligen because Ampligen is not used to treat MS and this paper focuses on a comparison between ME and MS. We don’t think that it is needed to add another section on the working mechanism of ampligen because this is not relevant to the MS-ME comparison. In addition, there are many more treatments for ME (more important than ampligen) that we did not discuss simply because it is not the aim of this review. Finally, I do not think that Ampligen is an asset in ME/cfs.
6. On page 12 and in other places throughout the text, incorrect symbols appear when referring to IL-1α, TNFα and TGFβ. NF-kappa B also shows as NF-6B in the text. These are corrected in the revision.

Discretionary Revisions.

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

Editorial comments.

1. Please format the article to adhere to our guidelines for Opinion articles (http://www.biomedcentral.com/bmcmed/authors/instructions/opinion). The instructions for Opinion article abstracts are not correct on the website at present, but it should be structured into separate sections headed Background, Discussion and Summary.

   We have followed all guidelines.

2. Please provide the following sections at the end of your manuscript:
   a) Abbreviations list
   b) Competing interests
   c) Authors’ contributions
   d) Authors’ information
   e) Acknowledgements (if appropriate)
   More information can be found at http://www.biomedcentral.com/bmcmed/authors/instructions/opinion#formatting-abbreviations

   The sections are now conform the guidelines.

3. Figures: Please confirm whether the figures were made exclusively for this manuscript, or whether permission was obtained from the copyright holder to reproduce them from elsewhere if they are not original.
The figures were made exclusively for this journal.

We hope that the paper is now in acceptable format,

Kind regards,

Michael Maes