Reviewer’s report

Title: A Logistic Regression Analysis of Risk Factors in ME/CFS Pathogenesis

Version: 0 Date: 04 Feb 2019

Reviewer: ANTHONY KOMAROFF

Reviewer's report:

The authors report an observational study seeking to find variables that distinguish subjects with ME/CFS from one disease control group (multiple sclerosis) and from healthy control subjects matched for age and sex. Because they find several variables that strikingly distinguish ME/CFS from these two comparison groups, this report could be important in advancing an understanding of ME/CFS.

In addition, the study has considerable strengths. It draws cases from the NHS throughout the UK (the UKMEB database), systematically collected clinical data and biosamples from each subject, and also included a disease comparison group with multiple sclerosis (MS).

However, I have major and minor concerns about the presentation, and possibly about the methodology, that must be addressed.

MAJOR CONCERNS

Given the striking association between certain variables and ME/CFS, two questions are of paramount importance.

DEFINITION OF CASES. The first is how the authors certified cases of ME/CFS. The manuscript states that a previous publication (reference #16) provides the methodologic detail. Yet neither this manuscript nor that publication describes what I would like to know. For example, subjects were entered into the UKMEB database if an accredited physician within the NHS had diagnosed them as having ME/CFS. Yet no information is provided as to HOW the authors certified that the patients met the two case definitions for ME/CFS (references #5 and 6) that they say they used. It appears that the "clinical assessment" referred to in reference #16 involved only a review of questionnaires completed by the participants—not a face-to-face medical history and physical examination conducted by a health professional designed to confirm the subjects' self-report. If so, that is a serious limitation.

What fraction of the cases diagnosed as ME/CFS in the NHS primary care practice rosters agreed to participate? How similar were the participants and the non-participants—e.g., how representative of a larger universe of primary care patients with ME/CFS were the patients in the UKMEB databank?

DEFINITION OF RISK FACTORS. The second important question is how the authors collected data on the variables reported in the analysis. The questionnaires the subjects completed are not presented (even as supplementary material) in this manuscript or in reference #16. So it is not possible to assess how cases were asked about the key variables: the "history of frequent colds/flu", the kind of
immunizations and the time between immunizations and the onset of ME/CFS, the nature and timing of "infections before onset".

Did the questionnaires go into any more detail with regard to key risk factors? For example, if someone said there was a family history of "neurological problems" was further information obtained about which family member was afflicted and the nature of the neurological problem—e.g., a maternal aunt with MS?

Was any attempt made to confirm self-reported risk factors with information in the questionnaires by examining medical records (e.g., history of frequent colds/flu, immunizations in the past 6 months)?

One finding could have serious adverse consequences if it is published, and proves to be wrong, highlighting the importance of defining the risk factors accurately. The authors report a significant association of immunizations with the subsequent development of ME/CFS. People who erroneously attribute various ills to immunizations (such as the development of autism) have reduced community immunization rates—with serious health consequences. In the Discussion, the authors carefully cite prior evidence that immunizations are not triggers of ME/CFS. Still, they report the association.

In my opinion, the manuscript must describe much more precisely how the cases were defined, and how the key variables were obtained.

STATISTICAL QUESTION. The authors state that "For the multivariate models we considered P≤0.05 as statistically significant." What statistical approach was taken to adjust for multiple comparisons?

MINOR ISSUES

For Tables 3-5, the row titles regarding age, sex should be clarified: does "age" refer to younger age or older age? Does "sex" refer to male or female? For example, in Table 4, is it younger age or older age for which the odds ratio is 0.62, and is it the male or the female sex for which the odds ratio is 0.50? In other words, just as you specify what specific marital status you are talking about ("single"), you should make similar clarifications regarding age and sex.

On page 10, the authors should consider one caveat in reporting the female predominance that they (and most of the literature) have found: the cases were not from a random sample of the community but from patients who had sought medical care. Women are more likely than men to seek medical care for nearly all illnesses that can strike both men and women.

On page 10, there is the sentence "There is scant research linking ME/CFS to the common cold or flu-like infections..." The authors might note that the reason there is scant research is that testing for the many agents that cause the common cold, or even testing for influenza virus, rarely are performed in clinical practice. However, many published studies have reported that patients describe a "infectious-like" or "flu-like" illness just before the start of the chronic debilitating fatigue that ultimately is diagnosed as ME/CFS.

On page 11, line 2, there is a typo: it should be "Kaposi's sarcoma".

On page 11, the authors state: "We found a history of anxiety associated with ME/CFS," and then go on to discuss a past literature that finds a higher individual history of anxiety and depression in patients
with ME/CFS. Yet, as I read Table 3, the authors found a FAMILY history, not an INDIVIDUAL history, of anxiety more often in patients with ME/CFS. Nor did they find an individual (or family) history of depression or other psychological disorder more often in patients with ME/CFS. Thus, it seems that the Discussion should state that this study does not concur with those past studies that have found higher rates of past individual histories of anxiety and depression.

On page 14, the authors recognize that recall bias may have created some of the associations that they report, but they don't give this potential limitation of their study adequate weight.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal