Reviewer’s report

Title: Natural killer cell function is depressed in Gulf War Illness.

Version: 1 Date: 21 January 2009

Reviewer: Donald Staines

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Whistler et al; ‘Natural killer cell function is depressed in Gulf War Illness’

Minor Essential Revisions

This is a good in-depth study of immune responses following exercise in Gulf War Syndrome patients, albeit in a small sample. Using various methods the authors have performed a thorough analysis of this condition. The authors have provided a reasonable documentation of the research literature and it is presented in a balanced way. The title and abstract are a reasonable summary of findings. The authors have outlined the aim of the study but perhaps the aims could be more explicit or expanded on hypotheses being tested. Data appear appropriately set out and Figures and Tables are informative. Limitations of the study size are noted.

The method is a case-control study with a very small sample size. A large array of genes has been analysed. The study arguably may have benefited from a larger sample size as this may have provided data on more subtle changes in the genes observed. The small sizes of the study cases and controls make interpretation of the data difficult. However findings are broadly consistent with those of other researchers, for example in natural killer (NK) cell findings in CFS. There are other interesting data findings (below). Nonetheless the results from immune function and gene expression studies provide insight into the condition.

However, a few changes are required and are listed below;

1. Page 6: Exercise challenge
Line 15 & 16- “diurnal variation” needs greater clarification in terms of “assessment” as there is an uncertainty as to whether the “assessments” refer to immune function.
Line 17-“uniform breakfast” needs to be referenced from perhaps exercise journals and detail information on the major food groups that constitute the uniform breakfast.
Line 19 (page 6) to line 2 (page 7)-A reference for the exercise protocol was not provided.

2. Page 7:
“urging” is not specified whether authors used vocal urgings

Authors did not provide information on whether this was a uniform standard of 30mins post exercise. Authors need to consider immune function analysis post exercise is sampled immediately after exercise testing. However, questions are raised whether this paradigm is fully understood in terms of possible adverse consequences for participants. Many CFS/ME patients describe profound fatigue or post-exertional malaise and whether this occurred in the study participants is not stated. The subsequent recommendation suggesting extending the exercise challenge paradigm to other complex syndromes may be premature without patient acceptability validation and explicit ethical approval. However the findings of this study appear significant only after exercise testing and therefore the study suggest a legitimate application of the exercise paradigm.

An expansion of the various cytokine abbreviations is necessary

“high sensitivity ELISA”- is this in terms of pg and could authors clarify the sensitivity

Line 8: before/ prior

3. Page 8

Line 1: Again “high sensitivity”

Line 15-16: Need to increase font size

4. Page 9:

Line 1-2: Can the sentence be rephrased

Line 14: “Two”

5. Page 14

Line 8: “have” tense structure

Line 12-13: Authors need to outline if this was significant

IL-5 needs clarification and interpretation as it is referred to both as Th1 and Th2 cytokine

6. Page 15:

Line 12-13: Authors need to outline if this was significant

7. Page 16

Line 8-9: has been presented in the discussion

8. Page 17

Line 5: “CFS” and reference is a bit confusing as no mention of CFS was made in the reference [6]

Line 18-19: Arguably, this is not a sports science paper. However, literature in exercise immunology clearly outlines post immune depression where these immune cells return to pre exercise.
9. Page 19
Line 4: “enhanced” font is different.

10. The findings attributing changes in NK appear sound. There is a brief discussion regarding the findings of Th1 vs Th2 responses found in various studies and the significance of the findings to the present study are not explored in detail against other studies with contradictory findings. For example Table 3 appears to indicate more of a Th1 response in IL-6, plasma and PHA SN, TNFa and some impaired Th2 response with IL10 plasma in cases vs controls. There appears to be no comment on the findings regarding IL-5 and its context (see below). Hypofunction of the Hypothalamo-Pituitary-Adrenal (HPA) axis is suggested from the data.

11. Figures may benefit from better interpretation within the text of the article, although comments on Figures are reasonable.

Accept after minor essential revisions (which the authors can be trusted to make)

Level of interest
The paper is a useful addition to the literature, although limited by the small sample size.

Statistical review
Expert comment on research methodology may be useful to ensure appropriateness of application of tests and validity of findings.
No, the manuscript does not need to be seen by a statistician

Quality of written English
The writing style is acceptable and the standard of English is acceptable.

Declaration of competing interests
We declare that we have no competing interests in submitting this review.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:
We declare we have no competing interests.