Reviewer's report

Title: IgG-index predicts neurological morbidity in patients with infectious central nervous system diseases

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Reviewer: Justin Green

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Major Compulsory Revisions

1. Would this be allowed by an ethics panel in other EU countries? This is not presented as an audit, therefore as research it ought to have ethical scrutiny. Perhaps mentioning data was anonymised etc. might clarify this.

2. In LR were data log transformed to ensure normality before entering in model? How did they decide which variables were entered initially, did they use non-parametric test results to decide what to enter or was all entered initially? Did the use forward or backward methodology?

3. Diagnosis – LM was by cytology only – any immunohistochemistry? Why such a low yield in diagnosis for VM, e.g. tests not done?

4. Heavy bias with poor outcome by LM – what diagnosis did these patients have? e.g. B-cell lymphoma might influence IgG index or T-cell lymphoma would not produce increase in IgG index. Table 2 could include this data.

5. Are all CSFs lumped together for analysis? Day 0 CSF might be better predictor or change between paired samples. It is not clear to me that this was done.

6. Figure 1 A-G has no clear statistical test results on graphs, with only a comment in legend. The authors note that the K-W test gives a statistical result, but it cannot differentiate between the groups. In addition when data are log transformed the appropriate test to use is an ANOVA with a post test correction (e.g. Bonferroni) assuming the log transformation normalises the data. In addition they ought to give y-axis a log scale. Otherwise it might be better to present data non-log transformed and do simple MWU tests between groups. I suspect between many of the groups results are not statistically different.

7. IgG index will not help clinicians determine who has viral and who has bacterial disease. In those patients with LM they will be older and possibly have disease elsewhere (we are not told this) so I cannot see this being as useful a laboratory test as the authors conclude.

8. The authors conclude that there is a wide consensus that steroids should be used as an adjunct for treatment, but a recent Lancet Neurology meta-analysis has challenged this. In addition they do not state how many of their patients have been treated with steroids, which may (or may not) influence CSF parameters and so ought to be a co-variate in the analysis.
Minor Essential Revisions

1. Retrospective data - 592/835 patients excluded due to insufficient data/inconclusive diagnosis – does this skew their results? When was clinical outcome measured (e.g. death at d28?).

2. Why have the authors included TBM and Lyme disease as “bacterial meningitis” when the pathogenesis of these conditions is very different to pyogenic organisms.

3. Only 243/1675 analysed (14.5%).

4. Glasgow Outcome score reference. Maximum/minimum and how calculated could be a little better explained in the text (it is done well in one figure).

5. Why were age and sex included as mandatory in LR – is gender associated with outcome? If so then needs a ref.

6. Did they perform LR with just death as an outcome rather than GOS 5/6? If so this is not clear from the text.

Discretionary Revisions

1. Figure 2 might be better presented as a table with univariate and then multivariate OR (95% CI) and P-value.

Level of interest: An article of limited interest

Quality of written English: Acceptable

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

Declaration of competing interests:

Conflict of interest declared that I am employed by GSK, a pharmaceutical company. However, as far as I am aware the company does not hold interests related to this paper. The comments in the review are purely my own personal opinion, uninfluenced by GSK policy.