Reviewer’s report

Title: Diagnostic accuracy of cerebrospinal fluid protein markers for sporadic Creutzfeldt-Jakob disease in Canada: a 6-year prospective study

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Reviewer: P. Gambetti

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This is a well performed study aimed at characterizing the performance of three CSF markers, 14-3-3, tau, and S100B. The narrative suffers somewhat by deviating from the central theme, some repetition, and by omitting important simple detail. The paper relies heavily on stasticial modeling and shows a preference for likelihood ratios. This satisfies a more statistically inclined reader. However, likelihood ratios have failed to gain wide acceptance in general clinical practice despite frequent recommendations. Nevertheless, with appropriate modification, the manuscript provides valid and useful information.

Suggested changes follow:

1. P9 ln17 # P10 ln 4. Standard associated procedure with too much detail needs to be shortened.

2. P10 ln20. Were tau and S100B assayed with the same frequency as 14-3-3? Were controls included in these quantitative assays? If yes, what were the precision statistics, mean, CV%, number of values.

3. P11 ln9 #19 and P13 ln3 #12. These narratives and Figure 1 provide repetitious information.

4. P12 ln2 #8. One short sentence should suffice.

5. P13 ln3 #21. This section as well as Fig.1 are confusing, raising a number of questions to which the authors should answer:
   a. Why the 29 cases with the diagnosis of “probable” sCJD were excluded in view of the high probability that many of these cases were actually sCJD.
   b. Is it fair to exclude “probable” sCJD and to keep probable nCJD?
   c. If the PRNP was determined in only 72 cases how could it be “definitely” confirmed that 127 cases were sCJD and 5 fCJD? Alternatively, were they definitely prion disease and “probably” sCJD?
   d. Is there an explanation as of why no “possible” cases of sCJD were observed.

6. P14 ln2. ROC curves are an important determinant for comparing assays with both shape and AUC being helpful. These curves should be shown in a single figure.

7. P15 ln20. This equation has been derived from the data used for the manuscript, and cannot be applied with confidence to other data sets. That being the situation, the authors need to provide alternative models for other potential
users wishing to use the joint markers. Possibilities include: if either tau or S100B is positive, then the case is deemed positive, or both tau and S100B have to be positive for the case to be deemed positive, etc. Each model will have to be tested to find the most appropriate.

8. P16 ln10 #18. This appears to be considering selective data where both tau and S100B are either both above or below the chosen thresholds. How many cases are there where the values are discordant?

9. It is generally accepted that as more of the clinical symptoms of ataxia, dementia, and myoclonus occur there is an increased probability of CJD being present in a patient. Figure 4, if kept, should be placed in the supplement. More useful, and more helpful than figure 2, would be a pair of Venn diagrams showing the three assays as positives and negative cases, with optimal decision points being used.

10. P19 ln9 # 23, P20 ln 1 #5, and Figure 5. As these 29 cases are excluded, and the definitive statuses of these cases are not known, the analysis of these data separately adds nothing to the main body of data. Consequently, this section and Figure 5 should be eliminated, or placed in the Supplement.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

PrioNet Canada has reimbursed my travel expenses to attend meetings.