Reviewer’s report

Title: MRI findings are often missed in the diagnosis of Creutzfeldt-Jakob disease

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Reviewer: Michael Geschwind

Reviewer’s report:

This very interesting paper examines the sensitivity of MRI reads for CJD patients referred to the MRC Prion Unit since 2007. The authors find that the sensitivity of radiological reports from referring centers is quite low. The paper has some important and the findings are of high clinical relevance. Several sentences and sections, however, are poorly written and not clear – something which is very remediable. The paper needs to be read thoroughly by the authors for consistency and editing, as there are several obvious errors and inaccuracies throughout the paper. Another issue is the paper doesn’t report the percent sensitivity of MRI reads for only patients with DWI MRIs, nor does it report how many of the DWI MRIs (either misread or not by referring centers) had accompanying ADC scans and whether those were read as well to confirm the DWI abnormalities. The finding that the cortex was the most misread region is an important teaching point for the reader. Lastly, the conclusions of the paper might be stronger and not back away from faulting radiologists; any radiologist given the authority to read, or bill for reading, a brain MRI should be aware of MRI changes with CJD.

Major Compulsory Revisions (pages were numbered by the reviewer with cover page as #1):

1. Page 3. Line 3. vCJD diagnosed by lymphoreticular tissue is not definite vCJD, but rather probable vCJD, per current criteria to my understanding. For definite vCJD, brain pathology is required.


3. Page 3. Background. The line “reported by clinicians in cases of definite CJD,” doesn’t make sense in the context of this paper. It seems to suggest that the paper will look at clinicians reads of MRIs of definite CJD cases, but this paper looks at radiologist’s reads of many different types of CJD, not limited to definite cases.

4. Page 3. Last line of Background ‘the diagnosis of definite CJD was confirmed in all,” is not the case, as the paper/study includes possible and probable sCJD
cases, probable vCJD, and others that are not “definite.”

5. Page 3. Authors refer to Zerr MRI criteria, but might also wish to cite more recent and detailed criteria Vitali et al 2009 Neurology, which also show even higher sensitivity and specificity with a more appropriate control group of non-prion rapidly progressive dementia subjects initially referred as CJD. Also, Shiga et al 2004 shows high sensitivity and specificity for DWI.

6. Page 4. How many subjects had T2-weighted and no FLAIR or DWI?

7. Page 4. What number scan for each subject was being read? Is this known? Where these the first MRI scan?

8. Page 5. "MRI diagnosis was CJD," is not clear. Most radiological reports will provide a differential of possibilities, but might not state a single most likely diagnosis. The implication in this paper is that only if there was a single diagnosis of CJD was the external MRI formal report review considered as having made the diagnosis. What about the more common situation in which CJD was listed as one of several possible diagnoses? Please clarify how these more common situations were dealt with in this analysis.

9. Page 5. The authors state clearly on Page 4 that they looked at lesions in 3 patterns (1-3) on DWI, FLAIR, and/or T2-weighted images. Then in the exclusion criteria, they state they used the Zerr criteria to assess the MRIs. The Zerr criteria, however, do NOT use T2-weighted sequences, only FLAIR and/or DWI for their MRI criteria (see MRI data section of Zerr et al 2009 Brain, page 2661). Also the Zerr criteria as published are incorrect in that they (accidently per my discussions with the authors) did not require all patients to have dementia and substituted dementia for myoclonus in the 4 symptom categories from WHO 1998 (See Figure 1, Zerr et al 2009). Thus, if referring to the Zerr published criteria, it should be noted whether one is modifying the symptom criteria back to WHO 1998. Also, if T2 is being used in the current study, this would be a modification to the Zerr MRI criteria, and should be stated.

10. Page 6. 3rd paragraph, 3rd -4th lines. The numbers don't add up correctly. If 14 of 91 sCJD cases did not have their MRI changes detected, this would be 77/91=85% sensitivity, not 91%. Please clarify.

11. Page 6. 43/91=47%, not 43% sensitivity for referring centers.

12. Page 7. Discussion. 1st line. Here it mentions the initial scan, but nowhere else in the paper, especially the methods does it mention the scans being read were initial scans. See similar comment above for the Methods. Please clarify.

13. Throughout the paper the authors appear to sometimes refer to the outside readers as “clinicians” and other times as “radiologists.” I assume all outside readers were radiologists? Please correct or clarify.

Minor Compulsory revisions

14. Page 5. Exclusion criteria and classification. The first two lines of this paragraph are not quite clear – some of this might be due to missing punctuation, such as a comma after CJD? Based on the wording, any case in which CJD wasn’t suspected, but later found to have CJD (such as at autopsy) would have
been excluded? Why exclude such cases? They might have MRIs that were more difficult to diagnose.

15. Page 5. How many sCJD or other cases had PRNP analysis for mutations?

16. Page 6. Results. First line. It would be helpful to know how many patients the 133 scans were from.

17. Page 6. 2nd paragraph left out the 3 genetic cases, which should be mentioned as it is confusing to the reader that the numbers stated only add up to 100 (although Table 1 has the full count).

18. Page 6. 3rd paragraph, first line. It would clarify for the reader to state “83 of 91 cases at NPC review,”

19. Page 7 (and Table). What % of the 83 subjects with DWI had MRI changes noted by MRC neuroradiologists and by referring centers? It might be useful to show the sensitivities of the 79% with DWI vs. 21% without DWI. Although not the primary purpose of this paper, it would be helpful for the readers to know if you found a difference as many others have that

20. Page 7. It is not clear whom these 62 patients are. How do they differ from the other 41 cases? One might infer that they are a subgroup that were assessed more thoroughly by the MRC, and hence had certain scales performed. If so, this should be stated clearly that these are a subset of the cohort.

21. Page 7 (and Discussion). Why do the authors think that referring centers were more likely to see the abnormalities in less advanced disease? Could it be because more advanced patients had more atrophy? The atrophy might have made the radiologists notice this and not the FLAIR/DWI changes? Alternatively, in more advanced and prolonged cases in which there is atrophy, the DWI changes often go away (possibly because the tissue with the DWI changes is now gone). Another possibility is that in more advanced cases, the disease has moved from being asymmetric (and easier to notice on MRI), to symmetric (might be confused with artifact or not noted).

22. Page 8. The word unfamiliar follows the wording “unlikely” and thus is a double negative. I think the authors mean that the radiologists will not be familiar with characteristic MRI findings. Please rephrase for clarity.

23. Page 9. Is there a reference for higher field strengths than 1.5T being better at identifying cortical ribboning?

24. Page 9. Perhaps the paper should be more frank about criticizing radiologists for not reading CJD MRIs correctly. These MRI findings have been reported in the literature for more than a decade, and go back to the late 1990s. It seems they should be familiar with these findings, particularly in a country that faced the vCJD epidemic. Clearly there is a lapse in training of radiologists in this area which needs to be rectified.

25. Figure S1 – might be better for readers to have some arrows pointing to abnormalities, as they clearly weren’t obvious to the referring radiologists!

26. Table 1. how many vCJD had the pulvinar sign on FLAIR? On T2? On DWI? Why are there so few vCJD cases. From the methods it doesn’t look they
necessarily excluded suspected vCJD cases; or did they and the six vCJD cases were referred as suspected sCJD?

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

'I declare that I have no competing interests’ I have written a similar paper, based on our experiences in the USA, but it has only been published in abstract form and not yet published as a full paper. I don't feel that this is a competing interest, however.