Reviewer's report

Title: Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia

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Reviewer: John Ringman

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Differentiating among the neuropathological subtypes of atypical dementias during life is a very important goal as future treatments and the studies to prove their efficacy will be optimized by studying pathologically homogenous groups. This paper contributes to our knowledge regarding the utility of NFL in differentiating among different FTLD pathological subtypes and therefore is a relevant contribution to the literature. There are several limitations, however, as addressed below.

Major Compulsory Revisions

If I understand this sentence correctly: “The initial case selection, however, was made from the existing medical records, based on clinical diagnoses at the time of investigation and thus observers were not formally blinded to CSF examination results” it means that the NFL levels were used in the process to come up with clinical diagnoses in the first place. I’m not sure how NFL level might have been taken into account to come up with the diagnosis – was it presupposed that FTD-spectrum patients have higher levels before this study? This is an important issue with regard to circularity of the results and therefore recognition and discussion of this should be made in the Discussion section.

Was the patient thought clinically to have AD but then shown to have FTLD pathology included in the clinical series?

Also, how were levels that were below the level of detection of the assay dealt with statistically? This should be described.

On page 10 it states, “The overall severity of degeneration was noted as mild, moderate or severe.” What was this rating based on?

Minor Essential Revisions

In the following sentence on page 8, the exact criteria used should be stated:

“Seven cases were diagnosed as SD and four cases as PNFA based on existing clinical criteria.”

Were any (all?) of the 10 pathologically proven cases among the 34 in the main study? Whether or not this is the case needs to be made more clear in the Abstract and Method section.
Also in the Methods section of the abstract, the number of tau-negative (7) and tau-positive (3) cases among the autopsied cases should be stated.

I would remove the sentence, “Within the FTD group, the NFL levels were highest in SD; however, the difference was not statistically significant” from the abstract as findings that are not statistically significant findings should not be highlighted in the abstract (though can and should be discussed in the body of the article).

I would prefer to see the individual data points in Figure 1 (not just the boxplots) in the manner they are shown in Figure 2. This would help the reader get a better feel for the degree to which results are different, to what degree they overlap in the diagnostic groups, and in how many and which subjects the NFL levels were below the limit of detection (250).

In the second paragraph on page 13, I would change “The main strength of this study…” to “A strength of this study…”

It would be helpful to have the “n”s in the legends of the figures.


Discretionary Revisions

Though I suppose it is acceptable to use the 1998 FTD criteria, it would have been preferable to use the new criteria for bvFTD (*) and PPA (**) throughout as these more clearly define the clinical syndromes and are more sensitive for the diagnosis (at least for bvFTD).

**Level of interest:** An article of importance 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.