Author's response to reviews

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

Authors:

Maria Landqvist Waldö (Maria.Landqvist@med.lu.se)
Alexander Fritzell Santillo (Alexander.Santillo@med.lu.se)
Ulla Passant (upas49@hotmail.com)
Henrik Zetterberg (Henrik.Zetterberg@clinchem.gu.se)
Lars Rosengren (Lars.rosengren@vgregion.se)
Christer Nilsson (Christer.Nilsson@med.lu.se)
Elisabet Englund (Elisabet.Englund@med.lu.se)

Version: 2 Date: 28 December 2012

Author's response to reviews: see over
Author's response to reviews:

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

Authors:
Maria Landqvist Waldö (maria.landqvist@med.lu.se)
Alexander Frizell Santillo (Alexander.santillo@med.lu.se)
Ulla Passant (upas49@hotmail.com)
Henrik Zetterberg (henrik.zetterberg@clinchem.gu.se)
Lars Rosengren (lars.rosegren@vgregion.se)
Christer Nilsson (christer.nilsson@med.lu.se)
Elisabet Englund (elisabet.englund@med.lu.se)

Version: 2 Date: 28 December 2012
Reviewer's report

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

Version: 1 Date: 4 November 2012

Reviewer: John Ringman

Reviewer's report:

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.

We completely agree with the reviewer. We actually made it more complicated than necessary. We inserted a sentence stating that CSF values of NFL had no pivotal effect on the diagnosis. Methods section, page 8, paragraph 1.

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

No, only cases with a clinical diagnosis of bvFTD, SD or PNFA were included, see Methods section, page 8, paragraph 1.

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

After consulting our statistician we chose to use the 250 values in the statistical analyses. As we used the non-parametric Mann-Whitney test it made no difference to the results if we used the detection limit (250) as the lowest possible value or if we would have assumed that some of the 250 values were actually lower and thus used 250/2 =125. As we use non-parametric tests we present median values instead of mean values.
These are not influenced by the lowest values, except in the control group where the median value is at the detection limit (250). This value might actually be even lower. The 250 values were found almost exclusively in the control group and AD group. Only 2 out of 34 FTD cases (1 PNFA, 1 bvFTD) showed a value at the lower detection level. We have inserted the individual NFL values in the boxplot as suggested (Figure 1). We have also added a couple of sentences about the lowest values in the Results section (page 12, paragraph 2) and in the Discussion (page 14, paragraph 3).

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

Thank you for pointing this out for us. It is true that there are very few presentations of severity grading, and these are not particularly comprehensive. One grading, however, has been used in this department for 30 years, and it is described in detail on page 10, paragraph 2. We also inserted new references to the two earlier grading publications.

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.”

We inserted the reference (Neary et al 1998), page 8, paragraph 2.

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.

The pathologically proven cases were a separate group. This has been made more clear in the Abstract (page 3, paragraph 2) and Methods section (page 7, paragraph 3).

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.

This has been done.

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).

The sentence was removed from the abstract and inserted in the discussion (page 14, paragraph 2) as suggested.

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).
We agree and we have added the individual data.

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

This has been changed accordingly.

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

This has been added as suggested. We also moved the text from below the figures to the legends and supplemented the text of the legends slightly.


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).

The clinical diagnoses were made before the publication of the Gorno-Tempini classification and thus not all aspects of the new diagnostic criteria of PPA were possible to answer in retrospect. We therefore decided to keep the former consensus criteria (Neary 1998). In future prospective studies we agree that it would be appropriate to use the new consensus criteria.

For the same reason we used the 1998 criteria for bvFTD, even though we also referred to the new consensus criteria in our manuscript (ref 21). As the sensitivity, but not the specificity, of the new criteria is thought to be higher, the use of the 1998 criteria instead of the new criteria should avoid false positive bvFTD cases.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being Published

The manuscript was copy edited by Edanz as suggested by the editor. We have changed the manuscript accordingly (language corrections NOT highlighted in yellow). On request the tracked Edanz copy could be sent separately.

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.
Author’s revision:

The following minor changes were done in the manuscript:

Alexander Fritzell Santillo was corrected into Alexander Frizell Santillo.

The numericals of the references were changed as the following references were added in version 2 of the manuscript:


Also, we noticed a mistake in one of the references. This was corrected as follows:
