Dear Sandra

We thank the reviewers for their careful reviews of this paper. We have dealt with each of the points they raise in our revised manuscript. The alterations are summarised below:

In response to Reviewer 1

* We have made the aims of the study clearer and have expressed them more consistently where they are referred to in Abstract (end of Background section), Introduction (paragraph 5) and Discussion (start of paragraph 2).

* We have provided more information about the study population in paragraph 1 of Materials and Methods. We have also added reference to a website that provides extensive information about the OPTIMA study.

* We have stated the outcome measures at the start of the section on Microscopic Analysis in Materials and Methods (p.8).

* We have re-organised the Results so that they are now described under the main outcome headings of Cortical neuronal CML immunostaining, Basal ganglia neuronal CML immunostaining and Vessel CML immunostaining. Within each section, we have reported (a) the dependence of CML staining on dementia status, (b) the dependence of cognitive function on CML staining and (c) the dependence of age at death on CML staining. We think this improves the clarity of this section and are grateful for the suggestion to reorganise the Results. Figure numbers have been changed to match these alterations.

* We have defined 'survival' in the Clinical Data Gathering section of Materials and Methods. It is simply the age at death.

* Concerns about the statistical analysis have been carefully considered. We agree that we have used many tests to analyse the relations between demographic and neuropathological data. However, our purpose here is to show that the groups with and without dementia were not dissimilar. Therefore, if type 1 error occurred here, it would work against us. Our use of covariates that Dr Beissels considers excessive is only included to give added confidence that our results are meaningful as we state that co-varying did not influence our results. They could be omitted but we think this would lessen the confidence of readers in our findings. We do not agree that our statistical tests are 'unfocussed' as we have taken care to use precisely the tests which best analyse the kind of data and the types of question we addressed (binomial mixed effects models for neuronal CML staining, ordinal generalised estimating equations for vascular CML staining, robust linear models for CAMCOG data and Weibull regression for survival data). We suggest that if you have doubts about this you should consult a statistician and we will be willing to comply with his or her opinion.

* We agree that the post mortem delays are long but we have analysed our results to take this into account and they are not influenced by this.

In response to Reviewer 2

* We have added a statement that the study had Research Ethics approval to the end of the section on
Subjects under Material and Methods.

* We acknowledge that the extensive literature in AGE/CML has necessarily been selectively quoted. We have added two further references to papers by Dr Wautier et al (2003) and Drs Hirata and Kubo (2004). If there are any further references that Dr Wautier considers particularly relevant to this study that we have still omitted we should be glad to be told and are willing to include them.

* Details have been given about the CML monoclonal antibody used in paragraph 2 of the section of Materials and Methods in Immunocytochemistry for CML.