Reviewer's report

Title: Morphometric Variability of Neuroimaging Features in Children with Agenesis of the Corpus Callosum

Version: 5 Date: 6 April 2015

Reviewer: Kirsty Donald

Reviewer's report:

This paper describes a large series of children with agenesis of the corpus callosum (ACC) and associated brain anomalies. ACC is an important developmental brain abnormality as it is common and increasingly reported in clinical context with improved access to MRI scans. The authors are to be commended on this large series.

However, there are some significant concerns with the paper in its current form that will require major revision before publication.

Major essential revisions:

General: The major research question addressed by this study is not clear. In the abstract the aim is stated as "to characterise the diverse presentations of ACC...", but no clinical information on the 201 cases are given beyond their age and sex. In the main body of the the aim is stated as being to "better characterise the spectrum of callosal variants and associated abnormalities in ACC" (This statement seems best aligned to what is presented in the paper) and then in the conclusion the authors state that the results "validate a classification system" which has not really been mentioned as an aim in the rest of the report. This lack of clarity in the main message drawn from this impressive dataset results in a confusing narrative.

Specific:

Cover page: The order of authorship on the manuscript and on the journal reviewer site differ. This should be clarified.

Abstract: The conclusion in the abstract is very thin and not consistent with the message in the conclusion of the main body of the article. There is no real interpretive commentary which would strengthen the abstract considerably.

Background:

In paragraph 1, the authors give a brief definition of ACC and then proceed directly to discussing characterisation strategies previously used. Given that this paper has clinical relevance, it would be important to include a section on the corpus callosum itself (its key position as the major midline structure of the brain connecting the 2 hemispheres and whose role includes the transfer and integration of motor, sensory, and cognitive information between the cerebral hemispheres). Further in the background section the discussion on the
characterisation systems is inadequate. Only one is discussed in detail and then a different system is used without discussing reasons for choosing one over the other. The study would benefit from a broader look at the available literature. The study aim is not clearly defined as above.

Methods:
In general this section would benefit from a more structured approach. Conventional sections including participants (including age ranges, explicit inclusion and exclusion criteria, details regarding the database from which the original 808 clinical records were extracted). There is a discrepancy in the inclusion dates (2002 starting point in the methods, 2003 in the abstract and results. This needs to be clarified). More details also need to be given about the "procedures". Presumably as this is a clinical database, the children had imaging for a specific indication. Some explanation of how this system works (ie can anyone request a scan or in general will it be a paediatrician or neurologist etc). I don't think it is necessary to get this detail on every case, but an understanding of how the clinical system for getting neuroimaging in the NYPH is important context for the reader. In addition some description of the scanner itself (did this change over the 10 years or was it the same scanner. 1.5T or 3T. What standard or minimum sequences do the children get?). Did the neuroradiologist re-review the scans during the study or were these characterisations based on the original clinical report?

It is general convention to discuss the ethical issues at the end of the methods section in a separate paragraph. As this was a retrospective review presumably explicit consent from participants or parents was not sought, but there must have been some checks and balances in place for ensuring confidentiality of data and this is not discussed at all. A more detailed discussion of these issues should be included.

The statistical paragraph provides insufficient detail for adequate assessment.

Under results, no demographic information for the group is given. Although ages and sex is compared between the hypoplasia and complete groups later on, this should be interpreted across the background information of the group as a whole. The flow diagram to illustrate how cases were included or not is helpful. However, more detail for the large group excluded for secondary causes (a further breakdown would be valuable information). Likewise, some explanation for the very large group that were included in the original database as having ACC and were found to have no corpus callosum abnormality should at least be discussed. Was this a problem with coding on the hospital system, discrepancy of opinion between radiologists etc?).

In the description of the different subtypes is detailed, though all the different font types actually more confusing than helpful.

There are two table 1's and two figure 1's. though one is an "e" table and the other presumably in the main document I find this causes confusion and a consecutive numbering system should be used in the text according to when the
The final sentence of the results section does not make sense and should be rephrased.

Discussion:
The second sentence of the discussion really belongs in a limitations paragraph which should be a little further down in the discussion. It also makes no sense as it stands: It is not clear how cases can be "terminated prior to pregnancy".

The significance of the associated abnormalities are well described, but the comment that the classification system by Hanna et al, advances the investigation of the causes without any discussion of the aetiology in the paper detracts from the discussion of the group's own results. It is also not clear how the authors validated the classification system. The term validation implies comparison against another gold standard which hasn't really been done here. The conclusion that the utility of a refined classification system to improve descriptive accuracy for potential diagnostic purposes is an important point, but is not necessarily supported by this data as there is no aetiological or clinical data on the cases described.

Level of interest: An article of importance in its field

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

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

Declaration of competing interests:

I declare that I have no competing interests