Reviewer's report

Title: "Early identification of brain injury in infants with hypoxic ischemic encephalopathy at high risk for severe impairments: accuracy of MRI performed in the first days of life"

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Reviewer: Floris Groenendaal

Reviewer's report:

In their manuscript Agut et al describe MRI findings in neonates with HIE who were treated using hypothermia. The authors conclude that MRI during the first days of life may be a useful tool for prognosis.

The manuscript contains important data, but some questions are not addressed sufficiently.

Background

The remaining adverse outcome of a significant part of neonates treated with hypothermia are not only seen in major trials, but also in out-of –trial situations (PLoS One. 2013 Dec 31;8(12):e83742; and Neonatology. 2013;104(1):15-21). This could be added to the manuscript.

Very early MRI/proton MRS has also been performed in a small study almost a decade ago (Biol Neonate. 2005;88(4):306-12).

The validity of MRI after perinatal asphyxia has been published in detail by Rutherford et al.

The importance of the present study is the repeated MRI in 15 cases.

The authors should focus on this novel and important aspect.

Methods

Reference 13 deals with a method of classifying encephalopathy which has not been used by many authors. How does this method relate to more commonly used systems as the Sarnat or Thompson scores?

MR imaging

In general, optimal use of diffusion weighted imaging is beyond the first 48 hours of life, but before 8 days of life. Could the authors make a graph or table of the exact scanning times during the first week of life. This time could be added easily to table 3, e.g.

How many patients were examined during hypothermia, and how was the temperature maintained and monitored?
Page 6: In the online version of reference 14 the page numbers and classification system cannot be found. Please provide an alternative reference, or give the classification as an (on-line) appendix.

Results
Of 40 infants 33 had an MRI. Six died without an MRI. What happened to the seventh without MRI?

The p-values of Inborn, and Emergency CS do not seem to be correct!

One neonate with severe HIE did not show (any) abnormalities. How did this patient do, and at what time was this scan with unexpected findings performed?

“Early versus late MR imaging” –this is the most important aspect of the present study, and the authors should focus more on this part. Correlation is not the most informative aspect.

In table 3 findings between 1st and 2nd scan are similar in 9 cases (mainly without abnormalities), increased in 4 cases and decreased in 2 cases. It would be very interesting to hear in detail about these changes. Were serious abnormalities missed on the 1st scan?

Did serious abnormalities of the 1st scan normalize in the second week? This is of utmost clinical importance.

Discussion:
Some relevant and/or recent references are missing (Biol Neonate. 2005;88(4):306-12 on very early MRI; Radiology. 2011 Oct;261(1):235-42 on Diffusion Weighted MRI and proton MRS).

Page 10, top paragraph: this statement is only important, when redirection of care is considered. In all other cases MRI can be postponed until the full injury has developed.

Figures 1 and 2 can be omitted (information in table 3), and be replaced by an example of an MRI with diffusion weighted changes on 1st MRI and abnormalities in T1/T2 on the 2nd MRI.

To summarize: the main findings of the present manuscript are the similarities and differences between the 1st and 2nd MRI in patients who had 2 MRIs. The authors should focus on this aspect.

Details:
Punctata (table 2 and throughout the manuscript) -> punctate. I assume punctate white matter lesions?

Page 8: 64±51: mean± s.d.?

Wilkinson - please provide reference number

Page 9: Thorensen -> Thoresen
Page 9 and Throughout the manuscript: MRS -> proton MRS or 1H-MRS
Page 9 more over -> moreover
Table 1: pH values – umbilical cord? Capillary? Arterial? Venous?
Table 1: advance resuscitation? What does this mean?
Table 2: please group according to the severity of HIE, and then to the pattern of injury.
Table 2: what does “A” mean?

**Level of interest:** An article of importance in its field

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

The reviewer is inventor of 2-iminobiotin in "Use of 2-iminobiotin for the prevention or treatment of perinatal asphyxia in neonates".
The reviewer has no competing financial interests.
The reviewer has been expert witness in several court cases of presumed perinatal asphyxia.