Reviewer's report

Title: 3-D reconstruction of a human foetus with combined holoprosencephaly and synophthalmia

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Reviewer: Inger Kjaer

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Dear editor

Please find below my review of manuscript: 3-D reconstruction of a human foetus with combined holoprosencephaly and synophthalmia

Major compulsory revisions

Holoprosencephaly occurs in different degrees of severity such as cyclopia, etmocephaly, cebocephaly, midline cleft and short philtrum. The actual foetus in the study has a cyclopia type malformation. This designation should appear in the title.

Background

The authors state that embryological documentation of the severe forms is scarce and refer to references 2-7. The authors have not been aware of the following article: Kjær I, Keeling JW, Græm N. The midline craniofacial skeleton in holoprosencephalic fetuses. J Med Gen 1991;28:846-55. In this study 8 human holoprosencephalic foetuses representing all degrees of severity, including cyclopia, were described. This study showed, by radiographic and histological examination, that the cranial deviation is limited to the region anterior of the sella turcica and that no ethmoid cartilage is seen in cyclopia. The histological examination also included the proboscis and indicated that small islands of cartilage were present in the proboscis of the cyclopia foetus.

The following sentence needs an explanation: 'The multifactorial etiology of holoprosencephaly is considered to be the course of the heterogeneity of the clinical severity of the malformation'.

Methods

The authors must be given credit for the extensive work with the valuable 3-D reconstruction of horizontal sections from the foetus.

Results

How can the authors conclude that the midaxial incisor is a central incisor? It must be a midaxial single lateral. This is also in congruence with the tooth anlage observed and described in the two maxillas.

The pathological findings should be related to published normal findings and relevant references should be given.
There are some unclear statements, such as ‘No bony roof of the orbita was present as the ethmoid bone was missing’ (page 7). The ethmoid bone is not a part of the orbita roof!

Discussion
The authors practically confirm previous findings regarding cartilage tissue and osseous tissue. Discussion of findings such as the respiration epithelium in the proboscis is missing. The news in this paper is the elucidation of arteries and peripheral nerves and the fine illustrations hereof. This aspect should be included in the title of the paper. Particularly Figure 4a showing optic nerve and 8b showing the relation to the diencephalon are excellent.

Figures
There are too many figures and in some of the figures it is difficult to orientate (e.g. 4b and 6a).
Figure 1b is unnecessary. It is the same image as seen in 1a (only slightly enlarged).

The following figures are important: 2, 4, 4a, 5, 6, 7 and 8b (is the arrow on the optic nerve correct?). If Figure 9a should be included, the text to the figure must be extended and relevant structures marked by arrows on the image.

Minor compulsory revisions
Examples are:
Minor spelling errors:
Fig 8 nerv = nerve
Fig 9a an = and
Page 10: Genetic or environmentally – not correct endings.

Discretionary revisions
Focus on nerve and artery courses in cyclopia. Reduce the number of figures.
Consider remarks and questions.

Sincerely yours
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Denmark
**Level of interest:** An article whose findings are important to those with closely related research interests

**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.