Author’s response to reviews

Title: Follow-up study of neurodevelopment in 2-year-old infants who had suffered from neonatal hypoglycemia

Authors:

Lin-Xia Qiao (mumeer@126.com)
Jian Wang (574694795@qq.com)
Ju-Hua Yan (86088500@qq.com)
Su-Xiang Xu (93950308@qq.com)
Hua Wang (493855164@qq.com)
Wen-Ying Zhu (Yaner_suda@sina.com)
Hai-Yan Zhang (4727977@qq.com)
Jie Li (42247170@qq.com)
Xing Feng (feng_xing12@126.com)

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Author’s response to reviews:

Dear Dr. Cassady-Cain:

Thank you very much for your decision letter and advice on our manuscript (Manuscript: BPED-D-18-00683), entitled “Follow-up study of neurodevelopment in 2-year-old infants who had suffered from neonatal hypoglycemia.” We also thank the reviewers for their constructive and valuable comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by Medjaden Bioscience Limited.
We hope that the revision is acceptable for publication in your journal, and we look forward to hearing from you soon.

Yours sincerely,

Xing Feng, M.D.

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1

Specific Comments

Abstract

1. Is A1 and A2 <2.6 instead of >2.6?

Response: The concentrations should be < 2.6 mM. Several mistakes have been corrected in the Abstract of the revised manuscript (Page 3, Lines 36–38) to address this issue.

2. Describe the controls - were they also babies of diabetic mothers?

Response: A total of 144 infants whose mothers had no high risk for gestational diabetes mellitus were followed up as the control group during the same period. This information has been added to the Abstract (Page 3, Lines 41–43).

Background

1. Clarification between hypoglycaemia in infants of diabetic mothers and non-diabetic mothers should be made

Response: The babies enrolled in this study were born from diabetic mothers. (Page 7, Lines 102–104).
2. What is the individualised perinatal network model for gestation diabetes mellitus (line 85)? Is there a reference?

Response: It consists of a cell phone-based app as a means to connect doctors with the parents of newborns. Thus, the parents can provide fresh data of blood glucose levels to the doctor. This explanation has been added to the revised manuscript (Page 6, Lines 91–93).

Methods

1. The cohort is quite confusing. I am not sure what fig 1 refers to. Where did weight loss enter into the study? Does Fig 1 even relate to this study? The initial cohort is 1865 children - I can't find this in the text?

Response: The number of 1865 in the old figure was a mistake. The correct figure is included in the revised manuscript. We did not enroll 1865 children in this study. The numbers that we enrolled are shown in Fig. 1.

2. Why was the Gessell method used? This is not a widely acceptable test due to questions about its validity and reliability

Response: This is a good question. Indeed, our hospital (a local hospital) only uses the grasp Gessell method, but not the Bayley method.

3. Were the examiners blinded?

Response: The treatment groups of the neonates with hypoglycemia were not blinded; however, the follow-up was single-blinded and is described on Page 9, Lines 157–159.

Results

1. Again, the numbers are confusing and without clarification will make interpretation difficult

Response: I’m sorry for including the wrong figure; a corrected Fig. 1 has been attached.
Discussion

1. Please comment on the clinical significance of adaptability

Response: It includes the ability of fine-motor coordination for objects and scenes, hand-eye coordination, problem solving, and application tools. This information has been added to the revised manuscript (Page 12, Lines 230–231).

2. The implication that long-term observation for babies with hypoglycaemia is necessary needs a bit more justification (line 267) when the major finding is an adaptability difference

Response: Long-term observation should be performed because fine motor development of children occurs until they reach 8 years old. (Ref.: Fine Motor Development Chart. https://childdevelopment.com.au/resources/child-development-charts/fine-motor-developmental-chart/). This explanation has been added on Page 15, Line 287.

Replies to Reviewer 2

the following concerns:

1. It seems blood glucose was measured by a micro glucose meter and not confirmed in the laboratory.

Response:


Neurodevelopment was tested by the Gesell method but it is not stated which version was used.

Response: The second edition (1992) of the Chinese version of the standardized Gesell Developmental Scales (GDS) was used in this study.
The reference to the assessment given in the manuscript (reference 24) is not a valid reference for the test.


The Gesell Developmental Observation- Revised is the validated version and is only applicable from 2 years 9 months of age but followup in this study was at 2 years corrected age.

Response: The Chinese version of the standardized Gesell Developmental Scales (GDS) is used for 0- to 3-year-old children, which was modified by the Chinese Pediatric Association to adapt to the Chinese population. This method has been widely applied to evaluate infant development in China (see the references below).


2. Influences of rearing style on the intellectual development of infants.

3. Air pollution effects on fetal and child development: a cohort comparison in China.
Tang D, Li TY, Chow JC, Kulkarni SU, Watson JG, Ho SS, Quan ZY, Qu LR, Perera F
Environ Pollut. 2014 Feb; 185():90-6.

There is no description of the clinical course of the infants admitted to the neonatal unit, such as the need for assisted ventilation or oxygen therapy, or feeding difficulties, which might influence neurodevelopment.

Response: Thank you very much for your insightful suggestions. The description has been added to the revised manuscript (Page 11, Line 204) to address this issue. Table 1 has been revised as well.
There are a number of errors such as the less than (<) and more than (>) signs are not always
given correctly, eg in the definitions of hypoglycaemia and subgroups;

Response: Several mistakes have been corrected in the Abstract of the revised manuscript (Page 3, Lines 37–38) to address this issue.

The statement at lines 82-84 that neurodevelopment of infants suffering neonatal hypoglycaemia
has not been performed is incorrect;

Response: We changed the description to: Regrettably, the effect on the neurodevelopment of the infants who had suffered from neonatal hypoglycemia still has not been clearly elucidated (Page 6, Lines 87–89).

The formula for scoring assessment items in lines157-161 is not clear and needs to be checked.

Response: “The lowest level and the highest level of each energy zone were measured. For final scoring, the following formula was applied: DQ = DA/CA × 100, where DA = (sigma (M × N) (N) / Sigma), DQ is the developmental quotient, DA is the childbearing age, CA is the actual age, M is the age in months divided by the score, and N is the number of the signal “+” in monthly items.” has been changed to “Independent doctors were employed to perform the Gesell Infant Development Scale (GESELL) (Chinese revised edition) to measure five parameters: gross motor skills, fine motor skills, adaptability, language, and personal social activity. The observed behavior pattern was compared to the corresponding normal behavior. The infant development score was calculated according to the following formula: DQ = DA/CA × 100, where DA = (sigma (M × N) (N) / sigma), DQ is the developmental quotient, DA is the childbearing age, CA is the actual age, M is the infant age in months divided by the score, and N is the number of the positive signals in the monthly items. Infant development was defined as follows: DQ <70 is abnormal, DQ = 70–84 is suspected abnormal, and DQ > 85 is normal. During treatment, DQ served as an indicator for the degree of development disorder (DD).” (Pages 9–10; Lines 166–176).

The primary outcome of the study needs to be clearly stated and the conclusion needs to relate to the primary outcome and objective of the study. In the manuscript the conclusion in the abstract and main manuscript differ.

Response: Corrections to the Conclusion (Page 15, Lines 291–292) as well as the Results (Page 11, Lines 205–207) have been made to address this issue.
The manuscript requires revision and language corrections.

Response: Thank you for your advice. This manuscript has been revised by Medjaden, an English language editing company.