Association between Exposure to Histological Chorioamnionitis and Neurodevelopmental disorders of Very Preterm Infants at 6 Years of Age: The Neonatal Research Network Japan

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Abstract

Background: The study aimed to evaluate the association between exposure to histological chorioamnionitis (HCA) and neurodevelopmental disorders of very preterm infants. **Method:** This multi-center retrospective observational study enrolled singleton infants without congenital anomaly born <29 weeks of gestation who were registered in the Neonatal Research Network Japan between 1 January 2011 and 31 December 2016 and underwent medical checkups at age 6 years. The study subjects were categorized pathologically according to presence or absence of HCA, and neurodevelopment was compared between the two groups. The primary outcome was composite including cognitive impairment, motor impairment, behavioral disorder, sensorineural impairment, and demand of home health care. **Results:** During the study period, 859 patients underwent medical checkups at 6 years of age, of whom 479 (55.8%) were exposed to HCA in utero. The incidence of neurodevelopmental disorders in the exposed to HCA and control groups was 47.8% and 44.7%, respectively. In the multivariate regression analysis, exposure to HCA in utero was not associated with neurodevelopmental disorders (odds ratio 1.14, 95% confidence interval 0.83-1.57). **Conclusion:** Exposure to HCA is not associated with neurodevelopmental disorders of patients who were born <29 weeks of gestation at 6 years of age.

Introduction

Intrauterine inflammation including chorioamnionitis and funisitis is one of a major cause of preterm birth, [1, 2] and several studies have documented that it is associated with increased risk of prematurity-associated neonatal adverse outcome, such as perinatal death, [3] sepsis, [4-6] bronchopulmonary dysplasia (BPD), [7] and perinatal brain injury including periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH), [5] which can cause future cerebral palsy. [8, 9] It has been also known that the incidence of intrauterine inflammation increases with decreasing gestational age at birth, [1, 10] and the impact of intrauterine inflammation, independent of gestational age, on neonatal outcome is difficult to evaluate. [11, 12] Moreover, impact of HCA on log-term neurological sequelae of infants who were born preterm has not been well investigated.

The Neonatal Research Network of Japan (NRNJ) is a nation-wide cohort, which includes 202 facilities, and covers more than 70% of infants who were born less than 32 weeks of gestation in Japan. Although some reports have documented the impact of intrauterine inflammation on outcome of preterm infants using the NRNJ database, long-term outcome has not been assessed in the studies. [13, 14]

Our research hypothesis is that histological and clinical chorioamnionitis additively affect adverse developmental outcomes in preterm infants.

Methods

Study designs and subjects: We conducted a multi-center retrospective observational cohort study of singleton inborn infants born <29weeks (22 + 0 - 28 + 6) registered in the NRNJ during 1 January 2011 and 31 December 2016 and underwent medical checkups at around 6 years of age. We excluded infants with congenital major organ abnormalities or infants with inadequate medical record. We classified the study subjects based on the presence or absence of HCA. We compared the outcome between groups. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tokyo Women's Medical University.

Clinicodemographic data collection: Neurodevelopment was assessed at around 6 years of age. Cognitive function was mainly assessed with Wechsler Intelligence Scale for Children version 4 (WISC-Ⅳ). [15] Cognitive impairment was defined as full scale Intellectual quotient below 70 or judged by physician in a case whose developmental delay was obvious. Motor impairment was diagnosed with Gross Motor Function Classification System level 2 or higher. [16] Behavioral disorder including autism spectrum disorder and attention deficit hyperactivity disorder was diagnosed by physician. Sensorineural impairment was defined as any of the following: blindness or light perception in one or both eyes diagnosed by ophthalmologists or hearing impairment which needs hearing aids. Home health care includes home oxygen therapy, respirator, tracheostomy, tube feeding, gastrostomy, and ventriculoperitoneal shunting. The primary outcome was composite listed above, and the secondary outcome was each of the composite outcome.

Statistical analysis: The Pearson's chi-square test was used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables of clinicodemographic factors between groups. The multivariate logistic regression analysis was used to compare the outcome. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). [17] More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatics. All P values were two-sided and P-values of <0.05 were considered statistically significant.

Results

During the study period, 9,000 patients were eligible, of whom 859 underwent medical follow up at 6 years of age In comparison of characteristics of eligible patients between with and without medical follow up, most of values of standardized differences in in-hospital morbidity and length of hospital stay are less than 0.1 except incidence of chronic lung disease at corrected 36 weeks of gestation (CLD36) and home oxygen therapy (HOT) at discharge from NICU was higher in patients who underwent medical follow up at 6 years of age although those with follow up had younger year of birth, lower gestational age, and smaller birth weight (data not shown).

Comparison of clinicodemographic characteristics between patients exposed to and not exposed to HCA is shown in **Table 1**. Patients exposed to HCA had younger maternal age and gestational age, lower incidence of HDP, NRFS, and SFD, higher incidence of PROM and clinical chorioamnionitis, higher rate of antenatal glucocorticoid administration, cesarean section, and heavier birth weight.

Comparison of neurodevelopmental outcome at 6 years of age is shown in **Table 2**. A multivariate logistic analysis exhibited that exposure to HCA was not associated with worse neurodevelopmental outcome (odds ratio 1.14, 95% confidence interval 0.83-1.57). In the analysis of secondary outcome, exposure to HCA and CCA was also associated with neither of worse neurodevelopmental outcomes.

Discussion

The current study demonstrated that prenatal exposure to HCA was not associated with worse neurodevelopmental outcome at 6 years of age in patients born <29 weeks of gestation.

There are several reports regarding the association between preterm infants exposed to histological and/or clinical chorioamnionitis and worse long-term neurodevelopmental outcome, and that is controversial. This is likely due to differences in study design, patient population, and outcome definitions between studies. In the current study, we evaluated long-term neurodevelopmental outcome of subjects born < 29 weeks of gestation, who were more vulnerable and high-risk population of future neurodevelopmental impairment.

This study has some limitations. First, follow-up rate was low at 9.7% in the study period. In comparison of characteristics between patients who underwent medical follow up at 6 years of age and those lost to follow up, most of values of standardized differences in in-hospital morbidity and length of hospital stay are less than 0.1 except CLD36 and HOT, indicating that the differences in characteristics between the groups with and without follow up might be sufficiently small. Second, our analysis does not have the information about maternal socioeconomic status. Although previous reports suggest that maternal low socioeconomic status is one of a risk factor of lost to follow up, all citizens are covered by national health insurance and even people of low socioeconomic status can get to the hospital in Japan. Third, the study does not have the information about severity of intrauterine inflammation, especially presence or absence of funisitis. There have been some reports that increasing stage of funisitis was associated with increased risk of adverse neonatal outcome. [18-20] Further studies are needed to evaluate the association between the severity of funisitis and long-term outcome of subjects who were born preterm.

References

1. Goldenberg RL HJ, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000;342(20):1500-1507. doi:doi:10.1056/NEJM200005183422007

2. Goldenberg RL CJ, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;Jan 5;371(9606):75-84. doi:10.1016/S0140-6736(08)60074-4.

3. MC M. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med*. 1985;312(2):82-90. doi:doi:10.1056/NEJM198501103120204

4. Soraisham AS, Singhal N, McMillan DD, Sauve RS, Lee SK, Canadian Neonatal N. A multicenter study on the clinical outcome of chorioamnionitis in preterm infants. *Am J Obstet Gynecol*. Apr 2009;200(4):372 e1-6. doi:10.1016/j.ajog.2008.11.034

5. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. *Pediatr Infect Dis J*. Nov 2011;30(11):937-41. doi:10.1097/INF.0b013e318223bad2

6. Wortham JM HN, Schrag SJ, et al. . Chorioamnionitis and Culture-Confirmed, Early-Onset Neonatal Infections..pdf. *Pediatrics*. 2016;137(1):e20152323. doi:doi:10.1542/peds.2015-2323

7. Villamor-Martinez E Á-FM, Ghazi AMT, Degraeuwe P, Zimmermann LJI, Kramer BW, et al. . Association of Chorioamnionitis with Bronchopulmonary Dysplasia among Preterm Infants: A Systematic Review, Meta-analysis, and Metaregression. *JAMA Network Open*. 2019;Nov 1;2(11):e1914611. doi:10.1001/jamanetworkopen.2019.14611

8. Wu YW, Colford JM. Chorioamnionitis as a Risk Factor for Cerebral Palsy. *The Journal of American Medical Association*. 2000;284(11):1417-1424.

9. Pappas A KD, Shankaran S, Stoll BJ, Bell EF, Laptook AR, et al. Chorioamnionitis and Early Childhood Outcomes among Extremely Low-Gestational-Age Neonates. *JAMA*. 2014;168(2):137-147. doi:10.3917/rfsp.676.1041

10. Lahra MM, Jeffery HE. A fetal response to chorioamnionitis is associated with early survival after preterm birth. *Am J Obstet Gynecol*. Jan 2004;190(1):147-51. doi:10.1016/j.ajog.2003.07.012

11. Bersani I, Thomas W, Speer CP. Chorioamnionitis--the good or the evil for neonatal outcome? *J Matern Fetal Neonatal Med*. Apr 2012;25 Suppl 1:12-6. doi:10.3109/14767058.2012.663161

12. Thomas W, Speer CP. Chorioamnionitis: important risk factor or innocent bystander for neonatal outcome? *Neonatology*. 2011;99(3):177-87. doi:10.1159/000320170

13. Miyazaki K, Furuhashi M, Ishikawa K, et al. Impact of chorioamnionitis on short- and long-term outcomes in very low birth weight preterm infants: the Neonatal Research Network Japan. *J Matern Fetal Neonatal Med*. 2016;29(2):331-7. doi:10.3109/14767058.2014.1000852

14. Shuji Ishida HN, Rika Sekiya, et al. . Evaluation of Postnatal Complications in Clinical and Histological Chorioamnionitis in Extremely Preterm Infants: A Japanese Cohort Study. *American Journal of Perinatology*. 2024;41(S 01):e2383-e2389. doi:10.1055/a-2113-4332

15. Wechsler D. Manual: Wechsler Intelligence Scale for Children (4th ed.). *San Antonio, TX: Psychological Corporation*. 2003;

16. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. Apr 1997;39(4):214-23. doi:10.1111/j.1469-8749.1997.tb07414.x

17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. Mar 2013;48(3):452-8. doi:10.1038/bmt.2012.244

18. Van Hoeven KH, Anyaegbunam A, Whitty JE, Distant J, Crawford C. Clinical significance of increasing histologic severity of acute inflammation in the fetal membranes and umbilical cord. *Pediatric Pathology and Laboratory Medicine*. 1996;16(5):731-744. doi:10.1080/107710496175354

19. Pietrasanta C, Pugni L, Merlo D, et al. Impact of different stages of intrauterine inflammation on outcome of preterm neonates: Gestational age-dependent and-independent effect. *PLoS ONE*. 2019;14(2):1-7. doi:10.1371/journal.pone.0211484

20. Nirei J, Kobayashi A, Habuka R, Domon H, Terao Y, Saitoh A. Cord blood granulocyte Colony-Stimulating factor level as an optimal predictor of umbilical cord arteritis associated with brain injury at term equivalent age in preterm neonates. *Cytokine*. Nov 2023;171:156369. doi:10.1016/j.cyto.2023.156369