Early Human Development (2005) **81**, 545—553

ELSEVIER

Early Human Development

www.elsevier.com/locate/earlhumdev

Risk factors for cerebral palsy in preterm infants

Ritsuko Takahashi[a,*], Masaaki Yamada[a], Tatsuya Takahashi[b], Takeshi Ito[a], Shingi Nakae[a], Yasuko Kobayashi[c], Akira Onuma[c]

[a]*Neonatal Intensive Care Unit in Perinatal Center, Japanese Red Cross Sendai Hospital, 2-43-3, Yagiyamahonchou, Taihaku-ku, Sendai 982-8501, Japan*
[b]*Department of Public Health, Yamagata University School of Medicine, Japan*
[c]*Takuto Rehabilitation Center for Children, Japan*

Accepted 30 November 2004

KEYWORDS
Cerebral palsy;
Periventricular leukomalacia;
Hypocarbia;
Ritodrine;
Postnatal steroids

Abstract

Objective: To identify crucial factors that precipitate cerebral palsy by controlling confounding factors in logistic regression analyses.
Design and patients: We retrospectively investigated a cohort of all 922 infants with gestational ages of less than 34 weeks (22—33 weeks), who were admitted to our neonatal intensive care unit between 1990 and 1998. Thirty (3.7%) were diagnosed to have cerebral palsy. We analyzed the prenatal and postnatal clinical variables of the cerebral palsy cases and compared them with 150 randomly selected controls.
Results: Risk factors for cerebral palsy identified in univariate analysis were: twin pregnancy, long-term ritodrine tocolysis, respiratory distress syndrome, air leak, surfactant administration, intermittent mandatory ventilation, high frequency oscillation, lowest $PaCO_2$ levels, prolonged hypocarbia during the first 72 h of life, and postnatal steroid therapy. In a conditional multiple logistic model, long-term ritodrine tocolysis, prolonged hypocarbia and postnatal steroid therapy remained associated with an increased risk of cerebral palsy after adjustment for other antenatal and postnatal variables (OR [Odds Ratio]=8.62, 95% CI [Confidence Interval], 2.18—33.97; OR=7.81, 95% CI, 1.42—42.92; OR=21.37, 95% CI, 2.01—227.29, respectively).
Conclusions: Our results suggest that long-term ritodrine tocolysis underlines the development of cerebral palsy. Further assessments of the effect of ritodrine on fetal circulation and nervous system are required. Moreover, possible alternatives to systemic postnatal steroids are needed, and carbon dioxide levels should be more strictly controlled.

* Corresponding author. Tel.: +81 22 243 1111; fax: +81 22 243 1101.
E-mail address: ritsu@sendai.jrc.or.jp (R. Takahashi).

0378-3782/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2004.11.007

1. Introduction

Cerebral palsy is one of the most common developmental disabilities in preterm infants. It is well known that, on cranial ultrasound, certain abnormalities indicative of white matter damage are strongly associated with cerebral palsy in preterm infants [1]. Etiologic studies of periventricular leukomalacia (PVL) seem to be informative about the etiologies of cerebral palsy. However, studies of clinically defined cerebral palsy are needed, because PVL and cerebral palsy are not identical. It appears that a substantial portion of white matter abnormalities is not identifiable using current ultrasound techniques [1—4].

Clinical factors that have been associated with the development of cerebral palsy in previous studies can be divided into two major categories in terms of pathogenesis. The first includes factors associated with ischemia (insufficient cerebral blood flow) [5,6]. The second includes factors associated with inflammatory cytokine production, which has been a major topic in many recent cerebral palsy studies [3,7,8].

To elucidate which factors are the main contributors to the development of cerebral palsy, it is important to simultaneously and extensively analyze the cerebral palsy risk factors belonging to the above two categories.

In this study, we assessed the relationship of both prenatal and postnatal clinical risk factors for cerebral palsy, and in particular, collected as much information as possible regarding the many medical interventions.

2. Subjects and methods

2.1. Subjects

Medical records were reviewed for all the 922 infants of gestational ages of less than 34 weeks (22—33 weeks) who were admitted to the neonatal intensive care unit (NICU) in the Perinatal Center of the Japanese Red Cross Sendai Hospital between January 1990 and December 1998. Of the 922 infants, 48 (5.2%) died in the NICU: 3 had a chromosomal abnormality, 3 had hydrops fetalis, 6 had severe malformations, and others died from common neonatal diseases. Three other infants died after discharge before reaching 18 months corrected age. Three infants were excluded because medical information was not sufficient due to delayed admission after day 1 of life.

The remaining 871 infants received developmental evaluations in our center and 816 (93%) have been successfully followed up. Cerebral palsy was diagnosed in the presence of a definitive abnormality on neurodevelopmental assessment by experienced pediatric neurologists and classified according to the description of function of each limb in children. The categories were diplegia, in which upper-limb function was better than lower-limb function; quadriplegia, in which all four limbs appeared equally affected.

Thirty out of 816 infants were eligible for enrollment in this study (3.7%). The rest of the study population (786 infants) was pooled as potential controls for the study. From the pooled controls, five random controls were selected as individually matched for each case by gestational age, birth weight, and calendar year of admission.

The medical charts of infants and mothers were reviewed and the obstetric and neonatal factors below were compared between cases and controls. This study was approved by the Ethical Committee of the Japanese Red Cross Sendai Hospital.

2.2. Antenatal events

Clinical chorioamnionitis was diagnosed in women with fever 37.8 °C or greater and supporting clinical evidence not explained by another source of infection; which included fetal tachycardia, uterine tenderness, or malodorous vaginal discharge at delivery of the infant.

Antenatal glucocorticoid therapy consisted of the administration of two 12-mg doses of dexamethasone given intramuscularly 12 h apart. If a woman had not delivered and was still at risk for preterm delivery, additional courses of the same regimen were given repeatedly. Other maternal treatments that were analyzed in this study were the use of intravenous tocolysis with ritodrine, magnesium sulfate, and suppositories of indomethacin. The assignment of gestational age was based on the date of the mother's last menstrual period. In cases this was not available an obstetrician's estimation was used.

2.3. Postnatal events

Neonatal infection was defined when a positive blood culture was obtained, or when ≧2 of the following criteria were present within 72 h of delivery: white blood cell (WBC) count ≦5000 cells/mm^3 or ≧24000 cells/mm^3, a ratio of band cells to total neutrophil >0.2, positive result of C-reactive protein assay, or the presence of menin-