EFFECTS OF CHORIOAMNIONITIS ON BRAIN DAMAGE IN PRETERM INFANTS OF SMALL GESTATIONAL AGE

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ABSTRACT

Purpose*: This study aims to investigate the effects of chorioamnionitis on brain damage (including periventricular leukomalacia and intraventricular hemorrhage) in preterm infants of small gestational age.*

Methods*: A total of 88 preterm infants born at a small gestational week (28 weeks to 34 weeks) in a hospital between June 2008 and October 2010 are selected as subjects, which are divided into the group with chorioamnionitis (41 cases) and group without chorioamnionitis (47 cases) based on whether their mothers have or do not have chorioamnionitis. The incidence of periventricular leukomalacia and intraventricular hemorrhage are observed and compared between the two groups.*

Results*: The incidence of periventricular leukomalacia is 31.7% in the group with chorioamnionitis of preterm infants, while 6.4% in group without chorioamnionitis of preterm infants. There is a statistically significant difference between the two groups (P<0.05). The incidence of intraventricular hemorrhage is 26.8% and 23.4% in the two groups, respectively, and there is no significant difference between the two groups (P>0.05).*

Conclusions*: Chorioamnionitis can increase the incidence of paraventricular leukomalacia in preterm infants but has little effect on intraventricular hemorrhage.*

Keywords*: Chorioamnionitis, Preterm infant, Brain damage.*

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Introduction

Affected by multiple factors such as the natural environment and social environment, the incidence of preterm infants (as shown in Figure 1) is increasing. With the development of perinatal medicine, the establishment of neonatal care units, the improvement of resuscitation technology and life support technology, the survival rate of preterm infants has increased significantly. However, the incidence of sequelae associated with preterm infant's brain damage has also increased significantly. Preterm infants have become an important issue for perinatal medicine and neonatal medicine in China(1).

Intrauterine infection is the leading cause of premature delivery, while brain damage in preterm infants is an important cause of poor prognosis in preterm infants. The preterm infants' brain damage mainly includes periventricular leukomalacia (PVL) and periventricular intraventricular hemorrhage (PVH-IVH).

Figure 1: Preterm infant.

The mortality rate of severe PVL or severe PVH-IVH can reach 40% and 50%. The survivors have neurological sequelae such as cerebral palsy, epilepsy, mental retardation, hearing impairment and language retardation(2).

Therefore, the sequelae of preterm infants have become a new clinical and social problem. As there is no specific treatment for brain damage, how to take effective measures to prevent the disease is of more important clinical significance[3]. To achieve effective prevention, it is especially important to explore the risk factors that cause brain damage. As for causes of brain damage of the preterm infants, the previous focus mainly lied in hypoxia-ischemia, and other influencing factors, including small gestational age, low birth weight, metabolic acidosis, and ventilator-assisted ventilation, significant fluctuations in blood pressure, hypercapnia and hypocapnia. In recent years, studies have concluded that perinatal infection is an important factor that causes brain damage in addition to the above-mentioned causes.

The relationship between perinatal infection and neonatal brain damage has gradually become a hot topic in perinatal medical research. Recent studies have shown that perinatal infection is the most important risk factor for the occurrence of cerebral palsy, and mothers suffering from chorioamteritis can increase the risk of neonatal development of cerebral palsy 4 times. This study aims to objectively analyze the incidence of PVL and PVH-IVH in preterm infants of small gestational age (28 weeks to 34 weeks) from the clinical point of view through precranial B-ultrasonography and cranial MRI, and explores the effects of amnioticitis on PVL and PVH-IVH, with a view to increasing awareness of the risk factors for brain damage of preterm infants and raising the concern over intrauterine infection, thereby reducing the incidence of preterm infants and improving the prognosis and enhancing the quality of life of preterm infants[4].

Chorioamnionitis is usually secondary to premature rupture of membranes before term, which is closely related to premature delivery. Premature delivery is the direct cause of more than 3/4 deaths of newborns, thus we shall be highly aware of the occurrence of chorioamnionitis, especially subclinical chorioamnionitis which is usually neglected[5]. A large amount of literature has studied the diagnostic value of traditional biological indexes, such as erythrocyte sedimentation rate, leukocyte count, C-reactive protein, and modern molecular biological indexes, such as matrix metalloproteinases, interleukin and tumor necrosis factor in chorioamnionitis[6,7]). Detection of serum biomarkers in pregnant women has the advantages of relatively non-invasiveness, accuracy and rapidness in predicting subclinical chorioamnionitis, thus is recognized by more and more clinical practitioners[8-10]. With the development of the research on inflammatory cytokines, the detection of serum markers is expected to be a reliable and feasible basis for early diagnosis in clinic[11]. Figures 2 and 3 show the cases of brain damage[12,13].

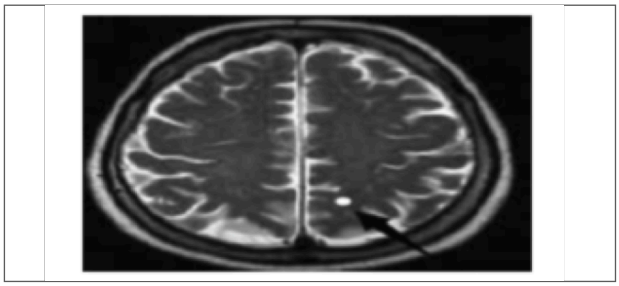

Figure 2: Brain damage by accessory white matter.

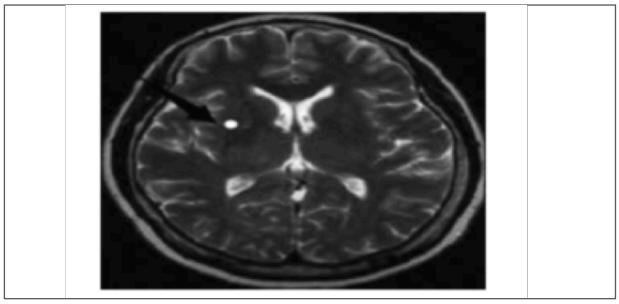

Figure 3: Case of intracerebral hemorrhage in brain injury.

Objects and methods

General data

A total of 88 preterm infants born as the small gestational week (28 weeks to 34 weeks) in a hospital between June 2008 and October 2010 are selected as subjects.

The following cases are excluded:

• The preterm infants whose mothers have pregnancy complications (such as preeclampsia of pregnancy-induced hypertension syndrome, preeclampsia, gestational diabetes, pregnancy complicated with heart disease, placental abruption, etc.;

• Preterm infants with a history of perinatal asphyxia and hypoxia;

• Preterm infants with metabolic disorders, nervous system malformations and other malfunctions. They are divided into two groups based on whether their mothers have or do not have chorioamnionitis.

The diagnostic criteria for chorioamnionitis can be divided into two types:

• Clinical chorioamnionitis. It refers to the infection of the uterus and its contents during pregnancy. The diagnostic criteria of clinical chorioamnionitis: at least two of the following conditions are satisfied, including maternal body temperature > 38

°C, premature rupture of membranes > 24 h, serum C-reactive protein (CRP) > 20 mg / L, leukocyte count > 15 000 / mm3 and fetal heart rate > 160 bpm. Its incidence rate is 10 %~20 %.

• Histologic chorioamnionitis. It refers to the presence of polymorphonuclear leukocyte infiltration in the placenta and fetal membrane, which often lacks clinical manifestations, but appears to be chronic and subclinical.

The 41 patients with chorioamnionitis are taken as the study group, and 47 patients without chorioamnionitis are selected as control group. The study group is composed of 22 males and 19 females (18 cases with clinical chorioamnionitis and 23 cases with histologic chorioamnionitis), with a gestational age of 31.59±2.21 weeks, birth weight of 1,518. 29±440.77 g and PH value of umbilical cord blood of 7.32±0.77 at birth, in which there are 11 cases with mechanical ventilation. In the control group, there are 25 males and 22 females, with a gestational age of 32.06 ± 1.85 weeks, birth weight of 1,558.63 ± 384.65 g, and PH value of umbilical cord blood of 7.33 ± 0.65 at birth, in which there are 9 cases with mechanical ventilation.

Studies have shown that preterm infants treated with ventilators have a higher incidence rate of PVL. Considering factors related to preterm infants' movements, intubation stimulation, and fluctuations in the partial pressure of carbon dioxide, this study also revises the proportion of ventilators used in both groups of preterm infants. There are no statistically significant differences in the clinical data of genders, gestational age, birth weight, umbilical cord blood pH value at birth, and number of cases using ventilator between the two groups (P>0.05), as shown in Table 1.

group	Number of cases	Sex	gestational age	birth weight	Hospitalized blood	mechanical ventilation
		Men and women				
Chorioamnionitis group		41 22	31.5±2.21	1518.29±440.77	7.32±0.77	11
Non chorionic amnionitis group		47 25	32.0±1.85	1558. 63±384.65	7.33±0.65	9
X value		0.0019	10.859	0.4585	0.0661	0.7355
P value		>0.05	>0.05	>0.05	>0.05	>0.05

Table 1: Comparison of two groups' sex composition, gestational age, birth weight, PH and mechanical ventilation at admission.

Methods

Blood routine, serum C-reactive protein (CRP) and blood culture are examined in all pregnant mothers with maternal membranes and placenta pathology, and signs of premature delivery. After birth, the preterm infant is subject to the blood gas analysis of umbilical cord blood. After delivery, regardless of the shape of the amniotic fluid, fetal membranes and placental pathology are promptly submitted to test to determine whether there is a pathological change. The membranes and placenta are obtained by special personnel. If there are premature rupture of membranes, 10 cm×10 cm of fetal membrane tissue is taken with the fetal membrane rupture as the center, which is made into a fetal membrane roll. More specimens shall be taken at the center, and in the middle area and the edge of the placenta, which shall also include the amnion, chorionic plate, villi and decidua. The specimens are fixed with 10% formaldehyde, embedded in paraffin, sectioned and stained with HE, so as to detect whether there is histologic chorioamnionitis. A senior obstetrical physician will take on the evaluation of clinical chorioamnionitis diagnosis[14,15].

All subjects are transferred to the neonatal department for monitoring and treatment due to small gestational age. Clinical medical observations are conducted to monitor the symptoms such as life ability, reaction, dystonia, convulsions, and apnea.

The French Sigma B ultrasonic diagnostic instrument with a probe frequency of 7.5 ~ 10MHz is used by an assigned person for cranial ultrasonic examination through the anterior and posterior fontanelle. The first cranial B-ultrasound is performed on the two groups of preterm infants at bedside within 3 to 7 days after birth. During the neonatal period, review is conducted once a week, and then once every 2 to 4 weeks thereafter until 3 months after birth, with a total of 6 to 8 times. The ultrasonic diagnostic criteria for PVL are as follows: In the coronal section, there is a bilateral symmetric inverted triangle echo area above the lateral ventricle, and in the sagittal section, the echo area is mainly distributed above the lateral ventricle.

According to the degree of lesion, PVL is divided into the following 4 grades, Grade I: increased periventricular echogenicity without any cyst formation persisting for more than 7 days, thereafter there will be no cysts; Grade II: the echogenicity has resolved into small periventricular cysts after several weeks (2 weeks after birth for the earliest); Grade III: increased periventricular echogenicity, that develop into extensive periventricular cysts after several weeks (2 weeks after birth for the earliest), and cysts

can be fused into blocks; Grade IV: increased periventricular echogenicity in the deep white matter developing into periventricular and subcortical superficial white matter diffuse cysts after several weeks (2 weeks after birth for the earliest).

Papile method is used for PVH-IVH classification: Grade I: hemorrhage in subependymal region and/or germinal matrix; Grade II: subependymal hemorrhage with extension into lateral ventricles; Grade III: subependymal hemorrhage with extension into lateral ventricles with ventricular enlargement; Grade IV: intraparenchymal hemorrhage with periventricular hemorrhagic venus infarct.

For some cases suspected with diffuse PVL whose B-ultrasound examination is negative, MRI magnetic resonance imaging (MRI) examination may assist in the diagnosis at the early stage. Diffusion weighted magnetic resonance imaging is a good method for early diagnosis of white matter damage. MRI is of great value in the diagnosis of late PVL. In all cases, MRI is performed at 40 weeks of corrected gestational age to more accurately detect and diagnose late PVL, thus to accurately show the location, extent, and nature of the lesion. It is often manifested by low T1-weighted signal and T2-weighted high signal of periventricular regions (reflecting loss of white matter, reduced volume), enlargement of the lateral ventricles, irregular ventricular wall, and delayed myelination. MRI appearances of PVL are graded with reference to Flodmark standard: (1) Mild: The white mass around the lateral triangle of the lateral ventricle is reduced, the adjacent sulcus is prominent, and the size of the ventricles is normal.

Results

According to B-ultrasound diagnosis, 13 cases (31.7%) of PVL occur in the group with chorioamnionitis, wherein there are 5 cases of Grade I (12.2%), 4 cases of Grade II (9.8%), 3 cases of Grade III (7.3%), and 1 case of Grade IV (2.4%). A total of 3 cases (6.4%) of PVL occur in the group without chorioamnionitis, wherein there are 2 cases of Grade I (4.3%), 1 case of Grade II (2.1%), 0 case of Grade III, and 0 case of Grade IV. There is a statistically significant difference in the incidence of PVL between the two groups ($P<0.01$). Due to the small number of cases studied, the incidence of PVL of all grades is not statistically significant compared with the control group (as shown in Table 2).

There are 11 cases of PVH-IVH (26.8%) in group with chorioamnionitis, wherein there are 3 cases of Grade I (7.3%), 4 cases of Grade II (9.8%), 3 cases of Grade III (7.3%), and 1 case of Grade IV (2.4%). Besides, there are 4 cases with both IVH and PVL. In the group without chorioamnionitis, there are 11 PVH-IVH cases (23.4%), 3 cases of Grade I (6.4%), 5 cases of Grade II (10.6%), 3 cases of Grade III (6.4%), and 0 cases of Grade IV. Besides, there are 2 cases with both PVH-IVH and PVL. There is no significant difference in total incidence between the two groups ($P > 0.05$) (as shown in Table 3). Brain MRI is performed at 40 weeks of corrected gestational age in all cases, as shown in Table 2.

group	I	II	III	IV	Total
Chorioamnionitis group	5	4	3	1	13%
Non chorionic amnionitis group	2	1	0	0	3%
X value					9.44
P value					< 0.05

Table 2: Comparison of two groups of PVL with different degrees.

group	I	II	III	IV	Total
Chorioamnionitis group	3	4	3	1	11%
Non chorionic amnionitis group	3	5	3	0	11%
X value					0.137
P value					> 0.05

Table 3: Comparison of two groups of PVH-IVH with different degrees.

The results show there are 6 mild cases (4 in group with chorioamnionitis and 1 in the group without chorioamnionitis), which are shown by increased T2 signal of periventricular white matter, with small and localized high signal intensity and varying degrees of ventricles enlargement and (or) ventricular wall irregularities. There are 4 moderate cases (3 in group with chorioamnionitis and 1 in the group without chorioamnionitis), which are shown by significantly reduced periventricular white matter, large and many linear and strip-shaped T2 high signal intensity, some of which are fused with the lateral ventricle, and significant ventricle enlargement. There is 1 severe case (in the group with chorioamnionitis), which is shown by the fact that all the white matter is almost replaced by cyst, part of which is fused with the lateral ventricles to cause pronounced ventricle enlargement and abnormal morphology, as shown in Table 3.

References

1) Been JV, Lievense S, Zimmermann LJ, Kramer BW, Wolfs TG. Chorioamnionitis as a risk factor for necrotizing enterocolitis: A systematic review and meta-analysis. Journal of Pediatrics 2013; 162 (2): 236-242.
2) Decembrino L, Pozzi M, Falcone R, Stronati M. Chorioamnionitis and neonatal outcome: early vs late preterm infants. Italian Journal of Pediatrics 2014; 40: A22-A22.
3) Anila K, Bilal A, Atifa M, Hira A, Hafiz MA. Gastroprotective Effe ct Of Avena Sativa (Oat) Seed Grains Against Gastric Ulcer Induced By Indomethacin In Healthy Adult Male Albino Rabbits. Matrix Science Pharma, 2018; 2(1): 14-18.
4) Duran R, Ozbek UV, Ciftdemir NA, Acunaş B, Süt N. The relationship between leukemoid reaction and perinatal morbidity, mortality, and chorioamnionitis in low birth weight infants. International Journal of Infectious Diseases 2010; 14(11): e998-e1001.
5) Ali W, Habib M, Sajid S, Khan RSA, Mazhar MU, Khan IU, Saliha U, Farooq M, Shah MSUD, Muzammil HM. A Reverse transcription-polymerase chain reaction (RT-PCR) based detection of foot-and-mouth disease in District Faisalabad, Pakistan during the Year 2016. Matrix Science Medica 2017; 1(1): 27-29.
6) Fassett MJ, Wing DA, Getahun D. Temporal trends in chorioamnionitis by maternal race/ethnicity and gestational age (1995-2010). Int J Reprod Med 2013; (2): 906467.
7) Zinayyera S, Muhammad S, Muhammad SS, Muhammad N, Hira M. Adverse Effect Of Oxalis Corniculataon Growth Performance Of Broiler Chicksduring Aflatoxicosis. Matrix Science Pharma 2018; 2(1): 10-13.
8) Gillman MW. Predicting Prediabetes and Diabetes: Can We Do It? Is It Worth It? Jama Pediatrics 2010; 164(2): 198-199.
9) Mitra S, Aune D, Speer CP, Saugstad OD. Chorioamnionitis as a risk factor for retinopathy of prematurity: a systematic review and meta-analysis. Neonatology 2014; 105(3): 189.
10) Muhammad QB, Hafiz KM. Phytochemical And Antioxidant Screening Of Zingiber Off icinale, Piper Nigrum, Rutag Raveolanes And Carum Carvi And Their Effect On Gastrointestinal Tract Activity. Matrix Science Medica 2018; 2(1): 09-13.
11) Park HW, Choi YS, Kim KS, Kim SN. Chorioamnionitis and Patent Ductus Arteriosus: A Systematic Review and Meta-Analysis. Plos One 2015; 10(9): e0138114.
12) Gharibreza M, Raj JK, Yusoff I, Ashraf MA, Othman Z, Zakaria W, Muhamad Tahir WM. Effects of agricultural projects on nutrient levels in Lake Bera (Tasek Bera), Peninsular Malaysia. Agriculture, Ecosystems and Environment 2013; 165 (2013): 19-27.
13) Wu YW, Jr CJ. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. Jama 2000; 284(11): 1417.
14) Rodrigo GM, Henríquez GMG, Ospina CG. Morbidity and Mortality Among Very-low-birth-weight Infants Born to Mothers with Clinical Chorioamnionitis. Pediatrics & Neonatology 2014; 55(5): 381-386.
15) Seelbach-Goebel B. Antibiotic Therapy for Premature Rupture of Membranes and Preterm Labor and Effect on Fetal Outcome. Geburtshilfe Frauenheilkd 2013; 73(12): 1218-1227.

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