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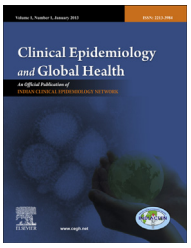

Original Article

Cerebral blood flow velocity in asymptomatic premature neonates exposed to clinical chorioamnionitis

Sriparna Basu [a,*], *Shashikant Dewangan* [b], *Sandeep Barman* [b], *Shampa Anupurba* [c], *Ram Chandra Shukla* [d], *Ashok Kumar* [e]

[a] *Associate Professor in Neonatology and Perinatology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India*

[b] *Resident, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India*

[c] *Professor, Department of Microbiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India*

[d] *Professor, Department of Radiodiagnosis, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India*

[e] *Professor, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India*

ARTICLE INFO

Article history:
Received 6 June 2013
Accepted 8 August 2013
Available online 31 August 2013

Keywords:
Cerebral blood flow velocity
Chorioamnionitis
Interleukin-6
Newborn
Transcranial doppler ultrasound

ABSTRACT

Aims: To test the hypothesis that cerebral blood flow velocity (CBFV) is altered in asymptomatic premature neonates exposed to clinical chorioamnionitis.

Methods: This prospective observational study included 30 premature (<34 weeks) neonates who were exposed to clinical chorioamnionitis but did not develop any feature of early-onset neonatal sepsis. Thirty gestational-age matched healthy neonates served as controls. Cord blood interleukin (IL)-6 concentrations were measured at birth. Resistance index (RI), pulsatility index (PI), peak systolic flow velocity and vascular diameter of internal carotid, vertebral and middle cerebral arteries were measured by transcranial color doppler ultrasonography within 48 h of delivery. The infants were followed up clinically after discharge and magnetic resonance imaging (MRI) was done at the corrected age of 6 months.

Results: Conventional sepsis screen and blood culture was negative in all. Significantly higher cord blood IL-6 concentrations, lower resistance (RI and PI) and higher blood flow with vasodilation were recorded in all cerebral arteries of the chorioamnionitis group. Significant correlation was observed between the increase in CBFV and the increase of IL-6 concentrations. At the age of 6 months, two cases showed features of delayed developmental milestone and periventricular leucomalacia in MRI.

Conclusions: Asymptomatic premature neonates exposed to clinical chorioamnionitis had significantly increased cord blood IL-6 concentrations and CBFV. The utility of increased

* *Corresponding author.*
E-mail address: drsriparnabasu@rediffmail.com (S. Basu).

http://dx.doi.org/10.1016/j.cegh.2013.08.003

CBFV as a predictor of adverse neurodevelopmental outcome may be tested in a well designed longitudinal study with larger sample size.

1. Introduction

Prematurity and sepsis are the two important causes of neonatal mortality all over the world, including India.[1] Preterm birth is a well known risk factor for the development of a spectrum of neurodevelopmental disorders including intracranial hemorrhage, periventricular leukomalacia (PVL), cerebral palsy (CP), autism and schizophrenia.[2–4] Chorioamnionitis is one of the most common causes of preterm delivery accounting for 30% of preterm births.[4] Intrauterine inflammation, occurring in approximately 20% of all pregnancies is dramatically increased to approximately 85% in very preterm births.[5]

Recent studies have shown that chorioamnionitis (intrauterine infection and inflammation) is more common than intrapartum hypoxia to cause brain damage in preterm neonates.[4,6] Infection-induced maternal immune activation leading to fetal inflammatory response (FIRS) has been implicated in fetal neurological damage.[7] Animal experiments have also shown that despite an absent or limited maternal immune response in low grade intrauterine inflammation, the immune activation of placenta is sufficient to induce a FIRS and subsequent brain injury.[4]

Though it is well known that chorioamnionitis is the forerunner of early-onset neonatal sepsis (EOS), in the resource-limited setting of a developing country, little attention is paid to the neonates who are exposed to chorioamnionitis but do not develop signs and symptoms of EOS. Because of the burden of high patient load, most of them are discharged early and never been followed up. There is no easily available, bedside measure to identify the effects of intrauterine inflammation on developing brain. Measurement of sophisticated cytokines, which are well known parameters for confirming the diagnosis and extent of chorioamnionitis, is beyond the capacity of most of the centers of India. In a previous study, we have seen that neonates with symptomatic EOS develop increased cerebral blood flow velocity (CBFV), which can be utilized as a predictor of brain damage with reasonable accuracy.[8] The present study was conducted to test the hypothesis that CBFV may also be altered in asymptomatic premature neonates exposed to clinical chorioamnionitis. We have measured the alteration of CBFV in this group and correlated it with cord blood interleukin (IL)-6 concentrations.

2. Methods

This prospective observational study was conducted in Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu over a period of 15 months. It was approved by the Institute Ethics Committee. The study group comprised of premature (<34 weeks of gestation) inborn neonates delivered to mothers with clinical chorioamnionitis who did not develop any feature of EOS within 72 h of birth. Gestational-age matched healthy neonates without any exposure to clinical chorioamnionitis formed the control group. Informed consents were taken from all the parents. Clinical chorioamnionitis was defined as prolonged (>18 h) rupture of membrane and intrapartum maternal fever (>37.8 °C in the period from onset of labor to delivery) with two or more of the following features: fetal tachycardia, uterine tenderness, malodorous vaginal discharge or maternal leucocytosis (>15,000 leucocytes/μL).[9] Infants requiring delivery room resuscitation, perinatal asphyxia (1 and 5 min Apgar score ≤5), intrauterine infections (TORCH, congenital syphilis, infective hepatitis, Human Immunodeficiency Virus), other systemic or metabolic diseases and congenital malformations were excluded. Those who had any intracranial pathology/malformation since birth, developed signs of sepsis, patent ductus arteriosus or were discharged from hospital before 72 h of life were also excluded.

2.1. Sample size calculation

Since there was no similar publication in literature, the present study was conducted as a pilot trial with a convenient sample size of 60 (30 cases and 30 controls).

2.2. Clinical work-up

Detailed antenatal and natal history were recorded and thorough clinical examination was made at birth. Cord blood was collected for the measurement of IL-6 concentrations. Enrolled subjects were followed up for development of clinical signs of sepsis till 72 h of birth. Blood culture and conventional sepsis screen comprising of total leucocyte count (TLC), absolute neutrophil count (ANC), serum C-reactive protein (CRP) and micro-erythrocyte sedimentation rate (μESR) were sent after birth. Cut-off values for the parameters of positive sepsis screen were defined as TLC $\leq 5 \times 10^9$/L, ANC $\leq 1.8 \times 10^9$/L, CRP ≥10 mg/L and micro-ESR ≥10 mm in 1st hour. Neonates were provided supportive management as per our unit protocol. Progress during hospital stay and outcome was noted. The infants were followed up clinically after discharge and magnetic resonance imaging (MRI) was done at the corrected age of 6 months.

2.3. Collection of samples and laboratory analysis

After complete delivery of the neonate, 10 mL of free flowing cord blood was collected for quantitative estimation of IL-6 in sterilized test tubes from the placental end of the umbilical cord without milking. Plasma was separated immediately by centrifugation and stored at −20 °C until analyzed. IL-6 concentrations were determined by Human IL-6 ELISA kit as per