55

IS NEPHRON NUMBER REDUCTION SUFFICIENT TO EXPLAIN THE FETAL PROGRAMMING OF HYPERTENSION

C BUFFAT¹, F BOUBRED^{1,2}, JM FEUERSTEIN¹, A DESOBRY¹, M LELIÈVRE-PÉGORIER³, J GUEGEN¹, C OLIVER¹, U SIMEONI^{1,2} ¹FACULTÉ DE MÉDECINE, UNIVERSITÉ DE LA MÉDITERRANÉE, EA 2193, ²SERVICE DE NÉONATOLOGIE, HÔPITAL DE LA CONCEPTION, ³INSERM U356 (FRANCE)

Introduction: Intrauterine growth restriction (IUGR) is associated with increased risk of cardiovascular and metabolic diseases in adulthood. Nephron number reduction has been proposed as a key mechanism for later hypertension.

Aim: to compare the long term effects of two models of IUGR on arterial systolic blood pressure (SBP) and renal function in adult rats.

Methods: 3 groups of animals were investigated: group I, controls: offspring of dams fed normal diet (NP, casein 22 %); group II: offspring of dams fed isocaloric low-protein diet (LP, casein 9 %); group III: offspring of dams that received 3 daily intramuscular injections of betamethasone (0.25 mg/kg) on gestational days 17,18, 19 (BET). SBP, glomerular number, and renal function were obtained in 12 months old animals.

Results: (mean $\pm$ SEM). Glomerular number was significantly reduced in IUGR rats (38 % in LP rats and 50 % in BET rats vs. controls $p < 0.05$). At 2 months, unlike BET rats, LP rats displayed a significant elevated SBP compared to controls (135 $\pm$ 3, 144 $\pm$ 3, 130 $\pm$ 3 mmHg in groups BET, LP, controls; $p < 0.05$). At 12 months, SBP levels were not significantly different between the groups despite an alteration of Creatinine Clearance in BET rats (3.25 $\pm$ 0.2, 4.82 $\pm$ 0.4, 4.88 $\pm$ 0.5, ml/min/kg in groups BET, LP and controls; $p < 0.05$).

Conclusion: Despite no differences in birth weight, maternal low protein diet and short course maternal injections of betamethasone have different effects on SBP, renal function and GT in adult rats, while both reduce nephron number. The hypothesis of an inborn nephron deficit associated with single nephron hyperfiltration appears not sufficient to explain the fetal programming of hypertension.

56

S100B CONCENTRATION IN BLOOD AND URINE IS INCREASED IN NEONATAL INTENSIVE CARE PHYSICIANS ON DUTY

D GAZZOL¹, M BRUSCHETTINI¹, V PERI², V SCIALFA¹, F MICHETTI³ ^{med} ¹MATERNAL AND INFANT DEPT, ²DEPT PEDIATRICS, GASLINI UNIVERSITY HOSPITAL, ³INSTITUTE OF ANATOMY AND CELL BIOLOGY, CATHOLIC UNIVERSITY (ITALY)

Objective. A neonatal intensive care unit is a working environment at high incidence of stressful events and the incidence of neuropsychological disorders in physicians working in these units is high. To date no reliable data are available on cerebral function monitoring. We therefore investigated whether there is a change in concentrations of S100B protein, an established marker of brain distress, in biological fluids (blood, urine) of physicians on duty in a NICU during day and night duty shifts.

Design and Setting. We conducted an observational study in which each case served as control. Participants. Seven physicians out of a total of 10 on duty at the tertiary referral centre for NICUs of the Giannina Gaslini Children's University Hospital (25 beds with a transport service for neonatal emergencies) were admitted to the study. Intervention. Clinical evaluation, standard laboratory monitoring parameters and blood cortisol levels were determined at eight time-points.

Main Outcome Measures. S100B measurements in blood and urine were assessed, using an immunoluminometric assay, at eight predetermined time points (every 4 hours) during day (8 a.m.-8 p.m.) and night (8 p.m.-8 a.m.) 12-hour shifts.

Results. During working hours clinical and laboratory parameters were within normal ranges. S100B levels in urine and blood varied significantly from the protein levels measured at the beginning of each shift, peaking at the end of both day and night time points ($p < 0.001$).

Conclusions. Increased longitudinal blood and urine S100B concentrations measured in physicians during NICU duty could suggest brain distress in the subjects under examination at a time when standard monitoring procedures are silent.

57

ROLE OF NITRIC OXIDE ON OXIDATIVE STRESS OF NEWBORN. EXPERIMENTAL STUDY

E. GITTO, R.J. REITER, C. BUGGÉ, A. ARCO, IGNAZIO BARBERI ¹DEPARTMENT OF MEDICAL PEDIATRICS, NICU, UNIVERSITY OF MESSINA (ITALY)

Background: Therapeutic inhalation of NO (iNO) in various pulmonary diseases is currently under evaluation in several neonatal intensive care units: it is difficult to establish an optimal dose regimen, but the aim should be to use as low an effective dose as possible, minimising the risks of potential toxicity. **Aims:** Aim of this study was to determine effects iNO in newborn with pulmonary hypertension, with extreme hypoxia or with bronchopulmonary dysplasia, in particular, which effects iNO has on inflammatory cascade, on oxidative stress and on clinical outcome.

Methods: Were investigated 70 newborns: 30 newborns of gestational age between 38 and 40 wks with persistent pulmonary hypertension (group 1), 20 newborns of gestational age < 30 wks of birthweight < 1500 gr., with severe respiratory distress and with extreme hypoxia (group 2), 20 newborns of birthweight < 1200 gr., requirement for supplementary oxygen $> 40\%$ at between 10 and 30 days, with radiological findings of Chronic Lung Disease (group 3). Nitric oxide was given at dosage of 20 ppm in newborn, with Pulmonary Persistent Hypertension or with extreme hypoxia, at dosage of 2-3 ppm in babies with CLD.

Results: Newborns of all the three groups presented an amelioration of oxygenation rate and alveolar/capillary rate that permitted to reduce ventilatory parameters (FIO₂, PIP). At time 0 IL-6 blood concentrations were significantly higher in newborn of group 2 and of group 3 than in subjects of group 1. At 72 hours and at 7 days we have a progressive increase of concentration of this interleukin in the group 1 and 2 and a progressive reduction in the newborn of group 3. Also IL-8 concentrations at time 0 were significantly higher in newborn of group 2 and of group 3 than in subjects of group 1. Also IL-8 concentrations were significantly increased from 24 hours to 7 days ($p < 0.01$) in groups 1 and 2 and in the 2 group and significantly decreased in the newborn of group 3. TNF α concentrations at time 0 were significantly higher in newborn of group 2 and of group 3 than in subjects of group 1. Also TNF α concentrations were significantly increased from 24 hours to 7 days ($p < 0.01$) in groups 1 and 2 and in the 2 group and significantly decreased in the newborn of group 3.

Conclusion. In our study we have demonstrated as iNO can ameliorate oxygenation index, alveolar/capillary rate with a reduction of ventilator parameters in all three groups. Our study shows also as iNO can have a pro and antioxidant role on the basis of administered doses: where iNO was administered at dosage of 20ppm have been obtained a progressive rising of blood levels of interleukins; where iNO's dosage was 2-3 ppm have been obtained a progressive reduction of proinflammatory cytokines.

58

PARENTAL EDUCATION AND COGNITIVE PROFILES AT 4 YEARS OF AGE IN HEALTHY VERY PRETERM CHILDREN.

M. BULTRINI¹, B. ROSSIELLO², M. F. COLETTI³, S. PARIS³, M. CUTTINI¹, A. M. DALL'OGGIO² ¹IRCCS PAEDIATRIC HOSPITAL BAMBINO GESÙ - UNIT OF EPIDEMIOLOGY, ²IRCCS PAEDIATRIC HOSPITAL BAMBINO GESÙ - UNIT OF CLINICAL PSYCHOLOGY AND NEUROPSYCHOLOGY, ³IRCCS PAEDIATRIC HOSPITAL BAMBINO GESÙ - NEONATAL INTENSIVE CARE UNIT (ITALY)

BACKGROUND: Improved survival rates for preterm and very low birthweight infants have increased attention towards their long-time neuro-developmental outcome, and particularly cognitive performances. To discriminate the effects of preterm birth from those of its neurological and sensorial consequences, we studied the cognitive function of a sample of healthy preterm children (no IVH stage 3-4; PLV; ROP grade 3-4) at pre-school age.

METHODS: Thirty-five healthy preterm children (gestational age less than 33 weeks) were assessed at mean age of 4.4 years (SD 0.3) together with 50 controls born at term and matched for age and gender. Cases were selected from patients attending follow up at a large tertiary Pediatric Hospital. Griffiths scales were used to measure cognitive development. Multivariate regression analysis was adopted to simultaneously explore the effects of preterm birth and socio-demographic factors on cognitive score: parent age and education.

RESULTS: Ninety-six % of global developmental Griffiths scores of both cases and controls were within 83-116, corresponding to the scale range of low to high average. However, global mean scores were lower for cases (97) than controls (103) and the difference was statistically significant ($p < 0.05$). In particular, scores of preterm infants were significantly lower in four subscales: locomotor, hand and eye co-ordination, performance, practical reasoning. After adjusting for socio-demographic variables in multivariate analysis, the difference in global scores remained statistically significant ($p < 0.01$). Maternal education was also significant predictor of cognitive development ($p < 0.05$) with higher educational level corresponding to better children performances.

CONCLUSIONS: These findings suggest that healthy preterm children at pre-school age, despite a global developmental score in the normal range, still show a lower developmental profile than their term peers, and maternal education also exerts a significant effect. Lower subscale scores point to specific areas of difficulty. These findings have implication for subsequent school performance and therapeutic interventions.

59

A CLINICAL AND GENETIC STUDY OF NEWBORNS WITH CONOTRUNCAL HEART DISEASES AND DEL22Q11.2 SYNDROME

M CAPELLI¹, S GUALDI¹, A PETRACCA¹, A BASTELLI¹, F GIURA¹, A CAPUCCI², P BATTAGLIA², D PRANDSTRALLER³, A BARONCINI², FM PICCHIO³, G COCCHI¹ ¹INSTITUTE OF NEONATOLOGY, ²MEDICAL GENETICS, ³INSTITUTE OF PAEDIATRIC CARDIOLOGY (ITALY)

Background/aims Congenital heart diseases (CHD) occur in 8 per 1000 births. Conotruncal Heart Defects (CTHD) account for 50% of CHD. 22q11 deletion prevalence is high in patients with CTHD (16%). The most common CTHDs in del22q11 patients are Tetralogy of Fallot (ToF), Pulmonary Atresia + Ventricular Septal Defect (PA+VSD), Aortic Arch Interruption (AAI), Truncus arteriosus (TA).

Patients and methods In 1999 a study to determine the prevalence of del22q11 in patients with CTHD, to describe the phenotypic variability and to analyse the familial occurrence of deletion, was designed. The parents of deleted probands were studied too. Caryotype from peripheral blood lymphocytes by fluorescent in situ hybridisation (FISH) using specific probe D22S75 was performed.

Results Over a period of 5 years, 135 patients (M: 70, F: 65) with CTHD were enrolled: 47 (35%) ToF, 39 (29%) Transposition of Great Arteries (TGA), 23 (17%) PA+VSD, 10 (7.5%) Double Outlet Right Ventricle (DORV), 7 (5%) TA, 3 (2%) AAI, 6 (4.4%) other CHDs. 27 (M: 12, F: 15) showed del22q11.2: 14 (30%) ToF, 8 (35%) PA+VSD, 1 (33%) AAI, 1 (14%) TA and 3 other types of CHD. In the familial cases with del22q11.2, we found: an affected father of a child without CTHD, a mother and her daughter with the same CHD, 2 unaffected mothers of affected probands. 26 deleted patients showed dysmorphic facial features (elongated face, micrognathia, hypertelorism, bulbous nose), 1 cleft-palate, 4 velopharyngeal insufficiency, 2 thymic hypo-/aplasia, 2 hypocalcemia, 1 reduced cell CD3+, 9 developmental and speech delay/behavioural problems.

Conclusions del22q11 frequency in patients with CTHD is high (20%) and higher in patients with CTHD and clinical features of del22q11 syndrome. The analysis of del22q11 should not be excluded: in patients with CTHD, including the newborns, and without characteristic phenotype; in parents of deleted children.

60

BIRTHWEIGHT AND MCGOON INDEX PREDICT OUTCOME IN NEWBORN INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA (CDH).

I CAPOLOPO¹, G CASACCIA¹, F CRESCENZI¹, A DOTTA¹, A BRAGUGLIA¹, F CAMPI¹, J RECHICHI¹, L PASQUINI¹, P BAGOLAN¹, C CORCHIA¹, M ORZALESI¹ ¹BAMBINO GESÙ CHILDREN'S HOSPITAL (ITALY)

Background: Birth weight (BW), Gestational age (GA), Apgar score at 5 minutes, prenatal diagnosis (PD), gender (M/F), side of hernia (R/L) and McGoon Index (MGI) (i.e. the ratio between the sum of the diameters of the 2 pulmonary arteries and that of the descending aorta), have been utilized to determine the severity and prognosis of CDH.

Aim: To evaluate the relationship between the above mentioned variables recorded on admission and survival in infants with CDH.

Methods: 34 consecutive newborns with CDH (BW = 2886 g, [range 1500-3620], GA = 37.7 weeks [32-42], M/F = 22/12, Right/Left CDH = 8/26, PD = 29; MGI = 1.31 [0.9-1.85]), all managed according to a standardized protocol (including intubation at birth, gentle ventilation and delayed surgery), were studied. The relationship between the above mentioned variables and mortality was first evaluated by univariate analysis. BW and MGI were classified as high (HBW and HMGI) and low (LBW and LMGI) according to the best cut-off values identified by ROC curves: i.e. 2755 g for BW (sensitivity 70%, specificity 74%), and 1.25 for MGI (sensitivity 73%, specificity 78%). A predictive model of mortality was then developed using a logistic regression analysis.

Results: Only BW and MGI were significantly ($p < 0.05$) and independently associated with mortality at the univariate and multivariate analysis: ORs = 7.2 (95%CI = 1.1-47.8) for BW and 9.1 (95%CI = 1.4-60.1) for MGI. According to the 4 possible combinations of the two dichotomized variables the mortality rates were: HBW+HMGI = 6%; HBW+LMGI = 31%; LBW+HMGI = 36%; LBW+LMGI = 80%.

Conclusions: Since BW and MGI on admission are not influenced by subsequent modalities of care, they can be considered early and reliable severity scores in CDH and utilized for evaluating new therapeutic strategies and/or for comparing performances among different centres.

(Supported by Grant N 02P000631 of the Italian Ministry of Health).