304

DETECTION OF VASCULAR EXPRESSION OF E-SELECTIN IN VIVO BY MR IMAGING

PR REYNOLDS[1], DJ LARKMAN[2], DO HASKARD[3], JV HAJNAL[2], NL KENNEA[1], AJT GEORGE[4], AD EDWARDS[1] [1]DEPARTMENT OF PAEDIATRICS, IMPERIAL COLLEGE LONDON, HAMMERSMITH HOSPITAL , [2]ROBERT STEINER MR UNIT, IMAGING SCIENCES DEPARTMENT, IMPERIAL COLLEGE LONDON, HAMMERSMITH HOSPITAL, [3]DEPARTMENT OF CARDIOVASCULAR MEDICINE, IMPERIAL COLLEGE LONDON, HAMMERSMITH HOSPITAL, [4]DEPARTMENT OF IMMUNOLOGY, IMPERIAL COLLEGE LONDON, HAMMERSMITH HOSPITAL (UK)

Background: We aimed to develop a contrast agent suitable for targeting to E-selectin expressed on activated vascular endothelium in an in vivo model of inflammation and detection by magnetic resonance (MR) imaging.

Methods: Anti-murine E-selectin F(ab')2 monoclonal antibody (mAb) (MES-1) was conjugated with ultrasmall superparamagnetic iron oxide nanoparticles (USPIO). Flow cytometry, PERL staining for iron, and MR imaging were performed using CHO cells expressing mouse E-selectin (CHO-E) to detect binding of the conjugate in vitro, and a mouse model of contact hypersensitivity to oxazolone in the ear was used to investigate the in vivo characteristics of the MES-1-USPIO, with serial imaging being performed using an Oxford/Varian 9.4T MR imaging system with a custom receive-only coil. Tissue sections were stained to define the distribution of E-selectin expression and the localisation of the MES-1-USPIO conjugate.

Results: The MES-1-USPIO was shown to bind to CHO-E in vitro. Following injection of MES-1-USPIO in vivo, distinct changes in the R2 relaxation rate (1/T2) characteristics could be detected in inflamed ears compared to controls. Histological analysis confirmed the vascular endothelial distribution of the MES-1-USPIO.

Conclusions: E-selectin expression in vivo can be selectively and directly imaged non-invasively with magnetic resonance. This molecular imaging tool has the potential to be useful for the diagnosis and monitoring of early or occult inflammation, and may provide an attractive alternative to established clinical investigations such as the use of radiolabelled leukocytes. In addition, such an agent may have value in the investigation of some solid tumours and metastases, either by targeting tumour-associated neovasculature or tumour cells expressing E-selectin.

305

REGIONAL CEREBRAL BLOOD FLOW IN ASPHYCTIC FOETAL LAMBS AFTER RESCUE WITH MGSO4

MC REY-SANTANO[1], E GASTIASORO[1], VE MIELGO[1], B LOUREIRO[1], A AGUINAGA[1], E HILARIO[2], A ALVAREZ[2], F GOÑI-DE-CERIO[2], S GOMEZ[3], A VALLS-I-SOLER[1,4], FJ ALVAREZ[1] [1]RESEARCH UNIT ON PAEDIATRICS OF CRUCES HOSPITAL , [2]DEPT. OF CELL BIOLOGY AND HISTOLOGY OF UNIVERSITY OF BASQUE COUNTRY, [3]DEPT. OF NEUROSCIENCES OF UNIVERSITY OF BASQUE COUNTRY, [4]DEPT. OF PAEDIATRICS OF CRUCES HOSPITAL (SPAIN)

Background: Hypoxic-ischemic (HI) injury induced by partial cord clamping produces brain damage. MgSO4 infusion has been used as a neuroprotector, but it produces haemodynamic and cardiac changes.

Aim: To determine the effects of MgSO4 infusion on cerebral oxygenation, cardiovascular parameters and regional cerebral flow (RCBF) in preterm lambs with perinatal asphyxia induced by umbilical cord occlusion.

Methods: 18 preterm lambs (80–90% GE) were used. Lambs were randomly assigned to receive magnesium sulphate (MGSO4) or not (SHAM) after HI injury induced by partial cord clamping. Non-injured group was used as (CONTROL). Carotid blood flow (CBF), systemic arterial pressure (SAP), heart rate (HR), arterial oxygen content (CaO2) and O2-uptake were measured. RCBF by microspheres and previous parameters were determined at fetal point (F), post-injury (P-I), 1h and at the end of the experiment. Frontal, parietal, temporal and occipital cortex were grouped (C), and striatum, thalamus, hypothalamus and hippocampus as periventicular zones (P). One factor ANOVA, $p<0.05$

Results: After injury, H-I injured groups developed acidosis, hypoxia and hypercapnia in comparison with control group. Also, they demonstrated an increase in HR without change on SAP. MgSO4 infusion did not showed significant changes in SAP, HR, CBF and O2-uptake in comparison with other groups.

RCBF summarised in table: (*) vs Control group

RCBF	F		P-I		1h		End	
mL/100g/m	C	P	C	P	C	P	C	P
CONTROL	186±70	146±48	186±70	146±48	136±48	116±26	174±46	120±41
SHAM	166±40	178±81	220±68	246±90*	140±20	150±38*	194±81	182±50*
MGSO4	210±48	198±38	238±61	282±48*	178±32	160±20*	158±48	156±24*

Conclusion: In our model of perinatal asphyxia by partial occlusion of umbilical cord in premature foetal lambs, MgSO4 infusion does not compromise the cardiovascular adaptation to asphyxia. However, histopathological analysis of brain tissue and neuronal metabolic status must be study to evaluate the neuroprotective effect of MgSO4. Supported by grants: FIS 03/987 and RESPIRA net of RITC, FIS C03/11.

306

DIFFERENTIAL EXPRESSION OF CYCLOOXYGENASES DURING DEVELOPMENT OF HUMAN DUCTUS ARTERIOSUS

C RHEINLÄNDER[1], SCT WEBER[1], N SARIOGLU[2], M OBLADEN[1], P KOEHNE[1] [1]DEPT. OF NEONATOLOGY, CHARITÉ VIRCHOW HOSPITAL, [2]DEPT. OF PAIDOPATHOLOGY, CHARITÉ VIRCHOW HOSPITAL (GERMANY)

Background: During fetal life ductus arteriosus Botalli (DA) is the shunt blood vessel between pulmonary artery and aorta, bypassing pulmonary circulation. Due to its fate of closure it undergoes a different development compared to the main arteries. This programmed proliferative degeneration underlies a large developmental variation. Prostaglandines regulate ductal tone during pregnancy and mediate closure after birth. Cyclooxygenases (COX) catalyse the first committed step in prostaglandine synthesis. Numerous studies have been carried out on ductal expression of COXs in different species but very few studies exist on human tissue. The aim of this study was to investigate gestational age dependent protein expression of COX1 and 2 in developing human DA and the corresponding main arteries.

Measurements: Specimens of the DA and corresponding main arteries from 71 human foetuses were collected. For determination of histological maturity of the DA in comparison to gestational age all 71 specimens were scored after a new maturity score system. For examination of COX-expression specimens suspicious for inflammatory events and malformation of the main arteries were excluded. The 50 cases included were examined for COX-expression using immunohistochemical techniques.

Results: In 63 out of 71 cases gestational and histological age corresponded. COX1 staining intensity rose steadily during development and was strong from the 28th week on, while COX2 staining remained weak during development. As for the main arteries moderate staining for COX1 and 2 was seen throughout development.

Conclusion: For the first time data based on a huge number of cases can be provided for COX1 and 2 protein expression in human developing ductus arteriosus and corresponding main arteries. The findings on COX1 and 2 expression in DA are consistent with results found in other species.

307

DISTURBED CARDIAC FUNCTIONAL PARAMETERS AND BLOOD FLOW PARAMETERS OF PERIPHERAL ARTERIES IN PREMATURE SGA NEONATES

E ROBEL-TILLIG, M KNUEPFER, F PULZER, C GEBAUER, CHR VOGTMANN [1]UNIVERSITY CHILDREN'S HOSPITAL , [2]UNIVERSITY CHILDREN'S HOSPITAL, [3]UNIVERSITY CHILDREN'S HOSPITAL, [4]UNIVERSITY CHILDREN'S HOSPITAL, [5]UNIVERSITY CHILDREN'S HOSPITAL (GERMANY)

Problem: Small for gestational age preterm neonates (SGA) are at higher risk for early postnatal morbidity and cardiovascular and metabolic diseases in later childhood. The aim of the prospective study was to determine the cardiac adaptation and the organ blood flow in growth retarded neonates after intrauterine hemodynamic disturbances in comparison to appropriate for gestational age preterm infants (AGA).

Patients and methods: 25 AGA neonates (29.1 ± 1.4 wks, 1420 ± 243 g) and 25 small for gestational age neonates (30.1 ± 1.2 wks, 985 ± 167 g) were examined during the first five days. By Doppler sonographic measurements the cardiac left ventricular systolic time intervals, peak systolic velocities, end diastolic velocities and pulsatility indices of anterior cerebral artery (ACA), superior mesenteric artery (SMA) and renal artery (RA) were investigated.

Results: Significantly increased left ventricular pre ejection period was observed in SGA neonates. Systolic peak velocities and end diastolic velocities of ACA, SMA and RA were significantly decreased in SGA neonates in relationship to AGA neonates. The pulsatility indices were significantly increased in SGA neonates during the first five days.

Conclusions: Disturbed left ventricular time intervals were observed as a sign of myocardial dysfunction in SGA neonates. In relationship to the diminished myocardial contractility there were demonstrated pathologically diminished blood flow parameters of peripheral vessels and an increased pulsatility caused by a vasoconstriction in the regional vascular bed. For that reason it seems possible, that the disturbed intrauterine perfusion persists into the postnatal life and could cause later cardiac and metabolic problems.

308

IMPLEMENTATION OF PEDIATRIC ASPECTS INTO THE GLOBAL DRUG DEVELOPMENT PROCESS

K ROSE, (SWITZERLAND)

In the 1960ies children were described as therapeutic orphans, but without consequence until the 1990ies. Today pharmaceutical industry is expected to consider potential use of new drugs in children. Pediatric assessments are mandatory in US and a comparable EU legislation is discussed. In 2002, implementation of pediatric aspects into drug development was analyzed in Novartis by a cross-functional team. A pediatric strategy was decided. An internal pediatric advisory group was established spring 2003. It coordinates implementation of pediatric aspects into standard development plans and has built up an internal training program in pediatric drug development. The EU commission wants pediatric data at submission. We analyzed this in the content of ICHE11 (guideline on drug development in children), which lists serious diseases in children only, serious diseases affecting both adults & children, and other diseases. The first two scenarios justify early development in children. Exposure of children to new experimental drugs is ethical only for life threatening conditions without acceptable therapeutic alternative. In this case, major development blocks are shifted to earlier stages, e.g. preclinical safety & toxicology and pediatric formulation. Higher investments at early project stages increase overall drug development costs. Project teams have to carefully balance potential therapeutic value, ethical concerns, risks and business considerations. Scenario (3) with deferral at registration point and a commitment to pediatric development later will mostly be the routine. In the complex modern drug development the introduction of pediatric thinking is a major challenge. It requires internal training and organized exchange of knowledge & experience. The decision for early pediatric development will probably be the exception reserved for therapeutic brake-throughs, but a careful analysis of pediatric aspects at several development decisions points is becoming integral part of drug development.

309

HEALTHY PRETERM CHILDREN BORN AT LESS THAN 33 WEEKS GESTATIONAL AGE AND TERM PEERS: NEUROPSYCHOLOGICAL OUTCOMES AT 4 YEARS OF AGE

B ROSSIELLO[1], MF COLETTI[1], M BULTRINI[2], C DE MARCHIS[3], L RAVÀ[2], M CUTTINI[2], MC CASELLI[4], AM DALL'OGLIO[1] [1]UNIT OF CLINICAL PSYCHOLOGY AND NEUROPSYCHOLOGY - IRCCS PAEDIATRIC HOSPITAL BAMBINO GESÙ , [2]UNIT OF EPIDEMIOLOGY - IRCCS PAEDIATRIC HOSPITAL BAMBINO GESÙ, [3]NEONATAL INTENSIVE CARE UNIT - IRCCS PAEDIATRIC HOSPITAL BAMBINO GESÙ, [4]INSTITUTE OF COGNITIVES AND TECHNOLOGIES SCIENCES - CNR (ITALY)

BACKGROUND The long term outcomes (neurodevelopmental disabilities) in preterm children of less than 33 weeks gestational age have an incidence of about 15%. Cognitive and developmental difficulties, and consequent lower school performance, have been described in this category of children also when free from frank disability. This study aims at evaluating the peculiarities of the neuropsychological profile in a sample of healthy preterm children at pre-school age compared with their peers born at term.

METHODS Thirty-five Italian preterm children born between January 1989 and July 1999 at less than 33 weeks, with no congenital malformations and no significant neurological damage were compared at a mean age of 4.4 years (SD 0.3) with a group of 50 full-term children matched for age and gender. Neuropsychological tests were carried out in both groups to evaluate the prerequisite areas for the school learning abilities: language (Category, Boston, Borel Maisonny, and Rustioni tests); visual-motor competence (Visual Motor Integration test); constructive abilities (Block Building); verbal and spatial short term memory (Digit and Corsi); attention and visual processing (Bell).

RESULTS All children had a cognitive level within the normal range (Griffiths General Quotient over 80). Significantly lower neuropsychological scores were recorded in preterm children with respect to the fullterm group. The differences involved spatial abilities, linguistic function (except for Boston test), and the verbal and spatial working memory ($p<0.01$). Attention and visual processing difficulties were more evident in infants weighing less than 1000 gr. at birth.

CONCLUSIONS Even when healthy, children born at less than 33 weeks gestation show at pre-school age a disadvantaged neuropsychological profile compared with their peers born at term. Follow-up at four years of age should therefore include an assessment of the neuropsychological development in order to provide, when required, timely psycho-pedagogical and therapeutic support.