77

THE CONTRIBUTION OF COBALAMINE METABOLISM TO GENETIC LIABILITY OF NEURAL TUBE DEFECTS (NTD)

Jacek J.Pietrzyk, Marek Sanak, Magdalena Korecka, Piotr Sucharski. Dept. of Genetics, and Dept. of Biochemistry of the Polish-American Children's Hospital, N.Copernicus Academy of Medicine, Cracow, Poland.

To check the hypothesis that alteration of cobalamine metabolism may contribute to the etiology of NTD, serum and amniotic fluid levels of total transcobalamines (STTC, FTTC) and transcobalamine II (STCII, FTCII) were studied in the pregnancies of high and low risk for NTD development. Material: 79 pregnant women referred for amniocentesis to rule out NTD or chromosomal mutations in fetuses were divided in three groups characterized by: higher risk of NTD (n=19), higher risk of Down syndrome (DS) (n=27), advanced age (>35) (AA) (n=33). Methods: Serum and amniotic fluid samples were collected at the 15-18 wks of gestation. Levels of STTC, STCII FTTC, and FTCII, were determined by using 57Co-Cyanocobalamine (Amersham). For data analysis, Mann-Whitney (z) and Kendall rank correlation (τ) tests were used. Results:NTD women revealed higher levels of FTTC (z= -2.3057 p=0.02) and FTCII (z=-2.469 p=0.014) in comparison to DS and AA. STTC and STCII levels were higher among the NTD vs AA (z= -2.2047 p=0.03), but not vs DS. Significant reversed correlations between FTTC and FTCII concentrations and pregnancy order were observed for NTD (τ= -0.3637, p=0.02; τ= -0.4720, p=0.002). Conclusion: mothers characterized by higher than average risk of NTD development show distinct profile of serum and amniotic fluid transcobalamines. This corroborates the hypothesis that alteration of cobalamine metabolism may represent phenotypic expression of genetic susceptibility to NTD development.

78

GENE EXPRESSION AND ACTIVITY OF ANTI-OXIDATIVE ENZYMES IN RAT EMBRYOS EXPOSED TO A DIABETIC ENVIRONMENT. Henrik Forsberg, Enrico Cagliero, L. A. Håkan Borg, and Ulf J. Eriksson. Department of Medical Cell Biology, University of Uppsala, Uppsala, Sweden.

The aim of this study was to determine if a diabetic environment induces changes in the activity and gene expression of superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). Embryos from control and diabetic rats of gestational day 12, as well as day 9 embryos that were exposed to 10 or 50 mmol/l glucose for 48 h *in vitro* were studied. Total SOD, GPX and CAT activities were determined by chemiluminescence and spectrophotometry. Northern blots of total RNA were hybridized to cDNA probes for human CuZnSOD, human MnSOD, murine GPX, and rat CAT. High glucose induced a significant increase in embryonic SOD activity but not in GPX or CAT activity. A parallel increase in the mRNA coding for MnSOD, but not in the CuZnSOD mRNA was also observed in the high glucose cultured embryos. Furthermore, the embryos of manifestly diabetic rats showed a two-fold increase in MnSOD transcript, and no change in the CuZnSOD, GPX, and CAT mRNAs.

In conclusion, a diabetic environment induces an increase in total embryonic SOD activity and MnSOD mRNA levels, but not in GPX or CAT activity, or in CuZnSOD, GPX, or CAT mRNA transcripts.

INFECTIOUS DISEASES

79

PREVALENCE OF ANTIBODIES TO HELICOBACTER PYLORI (Hp) IN CHILDREN WITH RECURRENT ABDOMINAL PAIN (RAP). E.Curdi, L.Pacifico, F.Nanni, G.Corrado, V.R.Iulianella, A.M. Renzi, C.Chiesa. Inst. Pediatrics,La Sapienza Univ.-Inst. Exp. Med. CNR, Rome, Italy.

Recent studies relied on both invasive (endoscopy and biopsy) and noninvasive (serology) diagnostic procedures have suggested that Hp is a possible cause of RAP in older children and adolescents. It has, however, been argued that serologic testing cannot yet be extended to younger subjects, as the age may influence immune response to Hp. We report the serologic findings of a prospective study in which IgG antibodies to Hp were measured by a quantitative ELISA (Helico-G, Porton Cambridge)in 45 children (mean age 7.6 years) with recurrent bouts of abdominal pain for at least 3 months, as well as in 90 age-matched healthy children with no history of gastric or intestinal complaints. Serum samples were also obtained from 18 parents of children with Hp-associated RAP and 25 parents of age-matched controls. A cut off 10 U/ml appeared more appropriate for screening our population, giving a sensitivity of 86.0% and a specificity of 92.8% when tested on 41 sera obtained from children with known histologic Hp status. Fifteen (33.3%) of RAP patients were seropositive (median, 18 U/ml), while only 4 (4.4%) of the control group showed high antibody titers (median, 18.9 U/ml). Of 18 parents of seropositive children with RAP and 25 parents of seronegative healthy children, 12 (66%) and 6 (24%) had positive serologic results, respectively.

Our data show that systemic immune response to Hp may also be fully established in younger children with RAP. Intrafamiliar spread of Hp may explain the high prevalence of seropositivity among these patients. A definitive answer to the clinical relevance of Hp antibodies in children with RAP will require further studies.

80

INTRACISTERNALLY GIVEN ELASTASE /E/ ENHANCES BLOOD-BRAIN BARRIER /BBB/ PERMEABILITY IN NEWBORN PIGLETS

József Kovács, János Gellén, Csongor Ábrahám, Christian P. Speer*, Péter Temesvári - Dept. of Pediatrics, Med. Univ. Szeged, Hungary and*Göttingen, Germany

Elastase, released during polymorphonuclear phagocytosis, is a potencially tissue damaging enzyme. We investigated its effect on BBB-permeability in newborn piglets. 11 anesthetized animals /Group 1/ were given 1 μg porcine E in 0,5 ml artificial CSF intracisternally, 7 piglets (given mock CSF) served as controls /Group 2/. Through 4 hours after E administration permeability changes of pial microvessels were followed intravitally by fluorescence photomacroscope using an open cranial window. Tracer was 1% Na-fluorescein (NaF). Physiological parameters (HR, MABP, blood gases, acid-base status) were continuously monitored. Spotty NaF extravasation was seen in all animals in Group 1 (meantime elapsed from E administration: 78$\pm$13 min.), but the BBB remained tight in Group 2 till the end of the experiments. α_1-proteinase inhibitor /α_1-PI/ activity was measured in sera and in CSF at 0,2,4 h after E injection. In CSF of Group 1 it increased significantly (0^h: 8,9$\pm$4,1 - 2^h: 173,7$\pm$46,5 - 4^h: 416,8$\pm$132,9 μg/ml), while its activity wasn't elevated in Group 2 (0^h: 8,8$\pm$4,6 - 2^h: 12,8$\pm$3,9 - 4^h: 6,7$\pm$2,4 μg/ml). In the sera measured paralelly, α_1-PI activity remained constant in both groups. Free E wasn't detectable in all samples. White blood cell count elevated in CSF (0^h: 1$\pm$1 - 4^h: 63$\pm$14 μl^{-1}) and in sera (0^h: 2453$\pm$355 - 4^h: 7518$\pm$751 μl^{-1}) in Group 1, but didn't change in Group 2. We conclude that elastase may play an additional role in BBB injury during neonatal meningitis.

All values are: $\bar{x}, \pm$S.E.

81

INTRACISTERNALLY (ic) GIVEN HUMAN RECOMBINANT TUMOR NECROSIS FACTOR (TNFα) RESULTS IN A DOSE DEPENDENT INCREASE IN THE BLOOD-BRAIN BARRIER (BBB) PERMEABILITY IN NEWBORN PIGLETS. Pál Megyeri, Csongor Ábrahám, József Kovács, Christian P. Speer*, Péter Temesvári - Departments of Pediatrics, University of Szeged (Hungary) and *Göttingen (Germany).

There is a growing evidence indicating that TNFα has an important role in the mediation of CNS infections. We have studied the effect of intracisternally given TNFα on the pial-arachnoid microvasculature in vivo in newborn piglets through an open cranial window using a fluorescence photomacroscope by giving 50 U Group 1 (n=6), 500 U Group 2 (n=6), 5000 U Group 3 (n=6), 50000 U Group 4 (n=6) TNFα (10^8U/mg protein) ic in 0.5 ml artificial cerebrospinal fluid (CSF). Control animals (n=6) were given mock CSF. Intravenous Na-fluorescein (NaF) (MW= 376) was used as a BBB permeability marker and brain NaF uptake (BNU) from parietal-, frontal-, occipital cortex, brainstem, cerebellum and periventricular white matter was measured by spectrofluorometer. Start of NaF leakage from the pial microvessels was detected 81$\pm$10.5 (Gr 1), 70.5$\pm$ 7 (Gr 2) 25$\pm$4 (Gr 3), 23$\pm$3 (Gr 4) minutes following TNFα administration. An elevation in BNU: 0.82$\pm$0.15 (controls), 2.97$\pm$0.56 (Gr 1), 3.52$\pm$0.58 (Gr 2), 4.99$\pm$0.49 (Gr 3), 5.81$\pm$1.1 (Gr 4) ug NaF x mg^{-1} protein/ug NaF x ul^{-1} serum was found at the end of observation (4 hours). White blood cell count in the CSF increased from zero (controls) to 25$\pm$6 (Gr 1), 75$\pm$12 (Gr 2), 95$\pm$10 (Gr 3), 780$\pm$143 (Gr 4)/mm^3 by the time of sacrifice (4 hours). In groups 1-4 vasoconstriction of the small pial arteries was also observed. /Values are: $\bar{x}, \pm$ S.E./

Conclusion: ic TNFα results in a dose dependent BBB opening, deterioration in cerebral circulation and pleocytosis.

82

STABLE INCIDENCE OF BIRTHS TO HIV-INFECTED MOTHERS IN SWITZERLAND 1986 TO 1991: APPARENT OR REAL?

Christian Kind* and the Pediatric AIDS Group of Switzerland (PAGS)
*Division of Neonatology, Kantonsspital, CH-9007 St.Gallen

From 1986 to 1991 the Swiss neonatal HIV study, a registry of children of HIV-infected mothers for the whole country, has noted a remarkably constant rate of around 50 new babies registered each year. This study analyses maternal data for possible clues to the underlying dynamics of the female HIV-infected population.

Methods: Data collected at registration to the study were analysed for all 295 children with years of birth 1986 - 1991. 245 children (83%) were registered at birth, the others only later, when their maternal HIV infection became known.

Results: The following variables showed no significant changes during the study period: geographical distribution among the different regions of Switzerland, number of children registered only after detection of symptomatic HIV infection (1986: 3, 1987: 2, 1988: 3, 1989: 3, 1990: 1, 1991: 0), median maternal age (increase from 25 to 27, not significant), proportion of primiparous women (64%). Maternal risk factors for HIV infection changed considerably: Intravenous drug use (IVDU) from 81% in 1986 to 44% in 1991, heterosexual risk factors from 18% to 50% (p = 0.034).

Discussion: Stable geographical distribution and low numbers of children with symptoms at registration do not support the hypothesis that decreasing rates of registration of a really increasing incidence of births to HIV-infected mothers give a false impression of stability. Rather the increasing rates of deliveries of heterosexually infected mothers have been counterbalanced by the decrease among the mothers infected by IVDU. This latter decrease may be related to preventive efforts among drug users.

Conclusion: The stable incidence of births to HIV-infected mothers from 1986 to 1991 seems to be real, but an increasing proportion of deliveries of heterosexually infected women predicts a possible increase in incidence for the nineties, if effective prevention cannot be established in this segment of the population.