

### RANDOMISED TRIAL OF EARLY TAPPING IN NEONATAL POSTHAEMORRHAGIC VENTRICULAR DILATATION: NEURODEVELOPMENTAL OUTCOME AT 30 MONTHS

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Progressive ventricular dilatation after intraventricular haemorrhage (IVH) in preterm infants is associated with unsatisfactory treatment and poor outcome.

157 infants with ventricular width 4 mm over the 97th centile after IVH were randomised to either early repeated CSF tapping or conservative management. Although assessment at 12 months had shown no significant difference in outcome overall, analysis of the subgroup with parenchymal lesions at entry suggested better outcome with early tapping. Therefore, 112 children (90% of survivors) were examined at 30 months by a single experienced examiner. 32 infants had died and 13 were lost to follow-up.

54% scored below 70 on the Griffiths Developmental Scales. 90% had neuromotor impairment with 76% having disability. 56% had multiple impairments. Vision was severely affected in 9% and 27% had a field defect. 6% had sensorineural hearing loss and 14% were taking regular anticonvulsants. Although early CSF tapping reduced the rate of ventricular and head expansion, there was no statistically significant difference (at the 5% level) between the treatment groups in the prevalence of neuromotor impairments, non neuromotor impairments or multiple impairments at 30 months. These findings were consistent regardless of the presence or absence of a parenchymal cerebral lesion at entry to the trial.

In the light of these findings, and the 7% risk of CSF infection associated with repeated tapping, this form of early intervention cannot be recommended.

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ONTOGENY OF NEUROCHEMICAL MARKERS IN THE ADRENAL MEDULLA OF THE PIG. Sabine M. Laroch, Patrick J. Van Reempt, Jef A. Pinksteren, Werner P. De Potter, Karel J. Van Acker (Depts. of Pediatrics and Neuropharmacology, University of Antwerp) and spn. by: P.J. Sauer.

Within the frame of a study on the influence of intra-uterine hypoxia on the maturation of the adrenal medulla, the ontogeny of different neurochemical markers in the adrenal medulla of the pig was studied. Obtained data are the result of measurements on the extract of the adrenals of all piglets from one litter. Gestational age was determined according to the crown-rump length of the piglets (full term being about day 114 of gestation). Adrenals from pig fetuses with 16 different gestational ages between 43 and 100 days were investigated. The amount of adrenaline (A) increases with gestational age. The noradrenaline (NA) content as well as the dopamine- $\beta$ -hydroxylase (DBH) content augment steeply at about day 60, are maximal at about day 75 and decline slightly towards term. The ratio A/NA rises with gestational age. The chromogranin A (CgA) content is maximal at about day 65 and also decreases slightly towards term (Table).

Gestational age (days)	45 <sup>00</sup> *	62 <sup>00</sup> *	74 <sup>00</sup> *	90 <sup>00</sup> *
A ( $\mu$ mol/g tissue)	1.1 $\pm$ 0.1	11.2 $\pm$ 5.4	24.8 $\pm$ 1.4	31.3 $\pm$ 2.9
NA ( $\mu$ mol/g tissue)	7.0 $\pm$ 0.7	40.7 $\pm$ 6.6	59.1 $\pm$ 3.8	45.6 $\pm$ 4.7
A/NA	0.15	0.28	0.42	0.69
DBH ( $\mu$ mol NA/h/g tissue)	2.6 $\pm$ 0.4	3.7 $\pm$ 0.8	4.6 $\pm$ 0.3	3.8 $\pm$ 0.4
CgA (nmol/g tissue)	0.40 $\pm$ 0.01	0.80 $\pm$ 0.19	0.62 $\pm$ 0.06	0.55 $\pm$ 0.07

\*number of fetal adrenals examined

**Conclusion:** In the pig adrenal medulla A, NA and CgA synthesis occurs early in gestation, before adrenal innervation is completely attained (around birth). This suggests an important role of the adrenal medulla in the regulation of hemodynamics prior to and shortly after birth.

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### EDUCATIONAL CAPACITY OF LOW BIRTH WEIGHT CHILDREN UP TO THE AGE OF 24 YEARS

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The attendance to further education after the compulsory education and completion of the further studies was examined among LBW (=low birth weight < 2500g) and NBW (=normal birth weight > 2500g) children. Of the Northern Finland one year birth cohort for 1966 72% of LBW and 92% of NBW alive born children were alive after the compulsory education at the age of 19 in Finland. 8.5% of LBW and 7.0% of NBW children did not enroll in further education. The enrollment of the disabled LBW children compared to the disabled NBW children, however, was significantly worse, 57.1% of the disabled LBW children and 36.8% of the disabled NBW children did not enroll. Especially the disabled LBW girls enrolled poorly, 76.9% of them and 32.5% of NBW disabled girls did not enroll. Completing further studies before the age of 24 was more poor among the LBW children compared to the NBW children. 22.0% of the LBW children and 17.5% of the NBW children did not graduate. However, if disabled children were excluded, healthy LBW children succeeded as well as healthy NBW children. The healthy and especially the disabled LBW girls graduated more infrequently than the LBW boys. When excluding disabled children and controlling for confounding factors by stratification, low birth weight did not affect on enrolling and on nongraduation. Altogether the success of LBW children seemed satisfactory regarding their intermediate-level schooling and their graduation, the exception being the disabled LBW children, especially girls.

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### INTRAPARENCHYMAL, IMMUNOCYTOCHEMICAL DETECTION OF RAT BLOOD-BRAIN BARRIER ANTIGEN.

Michael O Ibiwoye, Paul D Sibbens, Dick van Velzen, Department of Fetal and Infant Pathology, RLCB, Alder Hey, Eaton Road, Liverpool L12 2AP. A rat-specific monoclonal antibody exclusively recognizing the blood-brain and blood-nerve barrier protein has been demonstrated in rat brain from postnatal day 3 (Sternberger and Sternberger, 1987). In the present study, we have employed the anti-endothelial barrier antibody to assess the morphological alterations and the intraparenchymal distribution of barrier competent microvessels in the developing rat brain. At postnatal day 6, the antibody binding endothelia appeared as single round cells with central nuclei and granulated cytoplasm, within which the reaction product was evenly dispersed. These cells appeared over the pial surface of the temporal neocortex. At day 8 postnatally, the endothelial cells were arranged in vascular columns of 2 to 4 contiguous cells within the cerebral cortex and the hippocampus. These reactive cells assumed an oval shape with elongated nuclei. The reaction product was present throughout the cytoplasm although more concentrated on the luminal side of the cell. From postnatal day 10 to 19 months, there was a rapid increase in individual cellular and overall vascular staining intensity and length of stained collaterals arising from reactive parent microvessels. The cerebral cortex is more highly vascularized by barrier competent microvessels than white matter, while vessels in the hippocampus show higher reaction intensity but less vascular network than the rest of the neocortex. The white matter is less vascularized by blood-brain barrier than either the hippocampus or the cerebral cortex.

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### EVALUATION OF SUPEROXIDE RADICAL PRODUCTION IN CULTURED NEURONS. EFFECTS OF HYPOXIA AND HYPEROXIA. Jean Oillet, Jean-François Gheris-Egea, Jean-Claude Eitan, Paul Vert and Jean-Luc Daval, INSERM U272 and Centre du Médicament, Université de Nancy I, NANCY, FRANCE.

The formation of oxygen free radicals, especially superoxide and hydroxyl radicals, leads to hypoxic neuronal damage. In an attempt to investigate the influence of post-hypoxia reoxygenation in a model of primary culture of neurons from fetal rat brain, the production of superoxide radicals (SR) was assessed over 24h in the culture medium. After 8 days *in vitro*, culture medium was replaced by 1ml Krebs-Ringer buffer with acetyl-cytochrome c (ACC). A first set of cultures (n=32) was incubated for 6h in a gas mixture of 95%air-5%CO<sub>2</sub> (normoxia), and a second set (n=32) was incubated with 95%N<sub>2</sub>-5%CO<sub>2</sub> (hypoxia) which reduced the PO<sub>2</sub> by 77% in the culture medium. Half of the two sets of culture dishes was then placed in normoxic atmosphere, and the remaining dishes were incubated for 3h with 95%O<sub>2</sub>-5%CO<sub>2</sub> (hyperoxia) which increased the PO<sub>2</sub> by 250%. All cultures were finally returned to normoxia for 15h. The rate of SR formation was quantified spectrophotometrically by measuring the reduction of ACC at 550 nm. In control cultures (normoxia), about 4% and 8% of ACC per 100  $\mu$ g protein were reduced after 6h and 24h, respectively, indicating a low basal production of SR under standard culture conditions. Hypoxia induced a significant increase in the reduction of ACC (18.7 $\pm$ 3.1%) which was even higher 3h after return to normoxia (44.3 $\pm$ 3.5%). Hyperoxia did not enhance the SR production over basal values and neither aggravated hypoxia-induced production (20.3 $\pm$ 5.5% vs 18.7 $\pm$ 3.1%). The following day, while there was no apparent cell alteration, hypoxia-induced level of SR remained stable (40.8 $\pm$ 1.6%) as well as the SR accumulation induced by the sequence hypoxia-hyperoxia (18.6 $\pm$ 3.9%). Thus, it appears that hypoxia induces an over-production of SR in cultured neurons which may contribute to cell damage. Unexpectedly, post-hypoxia hyperoxygenation tends to limit the SR formation *in vitro*.

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### PLASMA (P) AND CEREBROSPINAL FLUID (CSF) INSULIN (I) CONCENTRATION IS ELEVATED IN PIGLETS WITH EXPERIMENTAL NEONATAL PNEUMOTHORAX (PTX)

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There is a lack of data on the level of I in P and CSF during neonatal cardiovascular collapse. Moreover, disturbances in glucose (G) homeostasis influences brain metabolism profoundly. Therefore, we have studied 10 newborn piglets (Group 1) during the course of PTX measuring I by a RIA method and G concentrations in P and CSF. Stages of the disease were baseline, critical phase 65.0  $\pm$  3.4 min after the beginning of the induction of PTX (MABP: 16.8  $\pm$  0.6 mmHg; HR: 64.7  $\pm$  1.4 min<sup>-1</sup>, pH<sub>int</sub>: 6.89  $\pm$  0.04, pO<sub>2int</sub>: 25.0  $\pm$  2.0 mmHg), when animals were given 10 ml x b.w.kg<sup>-1</sup> 4.2 % v NaHCO<sub>3</sub> iv infusion and recovery (samples were taken 0, 120 and 240 min after the beginning of PTX and in critical phase). Data were compared to results taken from sham operated animals without PTX (Group 2, n=9, sampling at 0, 60, 120 and 240 min); all values are means  $\pm$  SEM; \*p < 0.05 compared to values in Group 2.

	PLASMA		CEREBROSPINAL FLUID	
	Group 1	Group 2	Group 1	Group 2
GLUCOSE (mmol x l <sup>-1</sup> )				
0 min	8.1 $\pm$ 0.9	8.4 $\pm$ 0.6	6.7 $\pm$ 0.7	6.0 $\pm$ 0.6
60 min / critical	10.7 $\pm$ 2.3	9.0 $\pm$ 0.9	5.0 $\pm$ 0.4	5.7 $\pm$ 1.0
120 min	7.7 $\pm$ 1.4	7.5 $\pm$ 1.3	5.5 $\pm$ 0.9	6.2 $\pm$ 1.1
240 min	4.2 $\pm$ 0.9*	6.7 $\pm$ 0.7	3.0 $\pm$ 1.0	4.2 $\pm$ 0.7
INSULIN (pmol x l <sup>-1</sup> )				
0 min	445 $\pm$ 135	330 $\pm$ 127	37 $\pm$ 10	37 $\pm$ 5
60 min / critical	658 $\pm$ 135*	282 $\pm$ 111	30 $\pm$ 3	35 $\pm$ 4
120 min	1358 $\pm$ 495*	132 $\pm$ 25	60 $\pm$ 13*	37 $\pm$ 7
240 min	634 $\pm$ 245*	173 $\pm$ 34	164 $\pm$ 62*	38 $\pm$ 6

**Conclusion:** A significant hypoglycemia develops with a concomitant elevation of insulin levels in P and CSF in piglets with experimental PTX.