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LUNG-TO-HEAD RATIO AND LIVER POSITION TO PREDICT OUTCOME IN EARLY DIAGNOSED ISOLATED LEFT SIDED DIAPHRAGMATIC HERNIA FETUSES: A MULTICENTER STUDY.

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Objective: In utero diagnosed congenital diaphragmatic hernia (CDH) is associated to high antenatal and neonatal loss rates. Accurate prediction of outcome is crucial in counselling parents about management options. We evaluated Lung-to-Head Ratio (LHR) and liver position in prediction of outcome of isolated Left CDH.

Methods: Retrospective review of consecutive patients diagnosed with isolated LCDH prior to 28 weeks, evaluated at 6 tertiairy units from 1995 onwards. Only patients with LHR measurements, obtained by experienced sonographers and with determined liver position by ultrasound or MRI, both <or=28 wks, were included. Outcome measure was survival at discharge from NICU.

Results: 134 cases were available for review; LHR was obtained at a mean of 24.4+/- 2.8 wks. Eleven patients (8%) opted for termination after being evaluated, all having LHR<1.4. There were no postnatal diagnoses of chromosomal anomalies. Overall survival rate was 43% (58/134), after substraction of antenatal losses it was 47% (58/123). LHR correlated to survival irrespective of liver position. In case of liver herniation survival was 35 %. Combination of both variables predicted neonatal outcome better: liver up & LHR<1 predicted a survival of 9%. When LHR<0.8 & liver up, there were no survivors, but with liver down (37% of cases) survival was 40%. When LHR<0.6 there were no survivors irrespective of liver position.

Conclusion: Combination of liver up & LHR <1 at <or=28 wks predicts a <10 % chance of survival, dropping to 0% if LHR<0.8. 8% of patients opted for termination after second opinion, all with LHR<1.4, but only in half this coincided with the above poor prognostic indicators.

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IS THE SEVERITY AND OUTCOME OF RESPIRATORY ILLNESS OF PRETERM NEONATES WITH GENERALISED, MINIMAL SUBCUTANEOUS EDEMA DIFFERENT?

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Background: Clinical observation suggested that ventilated preterm neonates with generalised minimal edema (GMSE) not amounting to hydrops fetalis, had severe respiratory disease with poor outcomes.

Aim: To compare the severity and outcome of the respiratory illness on admission (primary outcome) between ventilated preterm neonates with and without GMSE.The secondary outcomes of interest included non-respiratory outcomes such as IVH and ROP. Design: Case control study in a tertiary neonatal nursery.

Methods: Data on all ventilated preterm neonates (gestation<32 weeks)with GMSE (cases) was collected prospectively from 1/1/1999 to 31/12/2000.Two controls mathched for gestational age and sex were selected for each case. Severity of the respiratory illness on admission was assessed by maximum ventilatory-oxygen needs,and need for supplemental oxygen at day 28 and 36 weeks corrected age respectively. Statistics: As Bivariate test procedures, exclusively exact approaches were applied. Fisher's exact tests, linear trend tests and exact non-parametric procedures were used for comparisions between cases and controls.

Results: Data on 8 identified cases were compared with 16 controls. Demographic characteristics did not differ significantly in cases vs controls except for the place of birth (outborn:5/8vs2/16, p=0.02). Need for multiple doses of surfactant (Two doses: 50% vs 37.5%,Three doses: 37.5%vs 0%,p=0.005) duration of oxygen supplementation (36(11–51) vs (1–26) days,p=0.036) and postnatal dexamethasone therapy for CLD (2(2–17) vs 0(0–2) days, p=0.007) was significantly more in cases vs controls.There was no significant differences in other variables including the incidences of mild and severe CLD.

Conclusion: GMSE in ventilated preterm neonates is associated with significant respiratory illness necessiating multiple doses of surfactant and a longer duration of oxygen and glucocorticoid therapy for CLD.

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TREATMENT OF RDS USING AEROSOLIZED KL4 LUNG SURFACTANT IN COMBINATION WITH NCPAP

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The leading treatments for premature infants suffering from respiratory distress syndrome (RDS) include 1) intratracheal instillation of lung surfactants, and 2) nasal continuous positive air pressure (nCPAP). Both approaches have shown clinical promise. An ideal therapy would combine the benefits of lung surfactant treatment and nCPAP (i.e., no intubation). Previous attempts to deliver aerosolized lung surfactants yielded discouraging results, largely due to inefficient delivery of the aerosol. Therefore, a patient interface was engineered to efficiently direct aerosolized KL4 lung surfactant to the lungs of neonates in conjunction with nCPAP. Two custom components were designed which linked the aerosol generator to the nasal prongs: 1) an aerosol Conditioning System (CS) to modulate the aerosol and control deposition, and 2) a Prong Adapter (PA) to integrate the CS with ventilator circuits and nasal prongs. These components were cGMP produced by injection molding. An Aeroneb Professional Nebulizer System (Aerogen Inc.) and cGMP produced KL4 lung surfactant at 20mg/ml total phospholipid were the aerosol generator and lung surfactant studied, respectively. The interface components were evaluated in vitro using an InfantStar ventilator. A Harvard Ventilator was used to simulate infant breathing. This novel interface was able to direct 17 +/-2 mg/min of lung surfactant (0.4 mg-total phospholipids per minute) aerosolized by the Aeroneb Pro to the infant-simulator. In contrast, only 8 mg/min was delivered to the simulated infant using an aerosol generator in-line with the CPAP circuit for the same operating conditions (p<0.005). Ventilator gas flow rates, temperature, and nasal prong size were all examined and not found to have a significant impact on the efficiency of aerosol delivery to the simulated infant. In short, this system holds promise to combine the life saving benefits of lung surfactant replacement with nCPAP therapies for infants with RDS and is currently undergoing clinical testing.

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ERYTHROPOIETIN IS NEUROPROTECTIVE IN 10 DAY OLD MICE SUBJECTED TO HYPOXIA ISCHEMIA (USA)

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Erythropoietin (Epo) is neuroprotective in many models of brain injury. We developed a model of hypoxia-ischemia (HI) in P10 mice that results in consistent, moderate, brain injury with minimal acute mortality. Our objectives were to determine whether Epo is neuroprotective by comparing the degree of injury in sham, Epo and placebo-treated animals, and to catalog the time course of HI-induced changes in gene expression. We hypothesized that early changes in gene expression will mediate Epo neuroprotection. The right carotid artery of anesthetized P10 BALB/c mice was cauterized under direct visualization (n=100 total). Animals were then exposed to alternating hypoxia (8% oxygen x 15 minutes) and hyperoxia (100% oxygen x 10 minutes) for a total of 45 minutes of hypoxia, 20 minutes of hyperoxia at 34 C. Shams underwent anesthesia and visualization of the carotid artery only. After injury, mice were treated with either daily rEpo (5000 U/kg) SQ x 3, or placebo. RNA was extracted from the right hippocampus, cortex and diencephalon 1, 2, or 7 days after injury. The Code-link platform was used to compare gene expression. Triplicate RNA samples from each condition were pooled for analysis. Results: 18 of 33 rEpo-treated animals were grossly normal (55%), as compared to 8 of 35 placebo-treated animals (23%), p<0.01. The brain injury scores of Epo-treated animals were lower than placebo controls (1.76 vs 2.83, p < 0.001), indicating less severe injury. There were differences in the magnitude, timing and nature of the injury response across brain regions at all time points. Changes in gene expression included apoptosis, angiogenesis, and inflammatory genes. We conclude Epo is neuroprotective in this mouse model, that Epo significantly alters gene expression when compared to placebo control, and that acute changes in gene expression in response to neonatal HI differ across brain regions. NIH - R21 HD042213–01

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THE EFFECTS OF NEONATAL THYMECTOMY ON THE HISTOLOGY OF THE HIPPOCAMPUS AND THE COGNITIVE FUNCTION OF ADULT RATS

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AIMS: Previous studies in mammals have shown that there is a reciprocal interaction between the thymus and the neuro-endocrine system. However, the influence of the thymus on the central cognitive function is largely unknown. This study aims to investigate the effects of neonatal thymectomy on the histology of the hippocampus as well as the cognitive function of adult rats.

METHODS: Wistar rats were thymectomized 2 days after birth (Tx2). Sham thymectomized rats (D2), were used as control. A year later, the animals were processed for nerve tissue electron microscopic examination of the hippocampus. Cognitive function was tested in an active and passive avoidance tasks, which conducted for 5 consecutive days. The parameters used in the active avoidance were: Lat: total latency time in 1:10 of sec, Re: number of crossing during the shock, St : number of crossing during light/sound stimulus and Itc: interstitial crossing.

RESULTS: Hippocampal formation showed minor focal alterations, compared to the control group. Only some dilation of the endoplasmic reticulum was observed, a few alterations in mitochondria and expansion of the perinuclear membrane of the nerve cells. A few myelinated nerve fibers appeared some vacuolar spaces in their cytoplasm, while some myelinated nerve fibers showed a disorganization of the myelins sheath. Finally, some glial cells revealed only a partial degeneration of their cytoplasm and some unmyelinated nerve fibers showed disorganization of their cytoplasm. Minor differences in the active and passive performance were also observed between sham-operated and thymectomized rats.

CONCLUSIONS: According to our data, thymectomy at the neonatal period results in minor focal alterations of hippocampus, which was accompanied with limited impairment in learning and memory abilities at the adulthood. It is possible that early removal of the thymus may act as a triggering event, which initiates a decline in homeostatic potential that characterizes the aging process.

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HUMAN MECONIUM CONTAINS ANTIMICROBIAL PEPTIDES/PROTEINS

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Background: Meconium is a greenish substance that accumulates in the fetal intestines and is expelled after birth. After the transition from a sterile environment to a world full of microbes, the newborn baby needs to be protected against microbial invasion. Since the adaptive immunity of the newborn is immature, the neonate must rely on its innate immunity. Antimicrobial peptides/proteins are effector molecules of the innate immune system and form a chemical barrier at epithelial surfaces that prevent infection.

Aim: To screen for antimicrobial activities in meconium extracts and to isolate and characterise the components giving rise to these activities.

Methods: Meconium from 12 newborns was collected and peptides/proteins were extracted. Antimicrobial activities were measured with an inhibition zone assay. Bactericidal components were isolated utilizing cationic and reverse-phased chromatographies and identification of peptides/proteins was performed with N-terminal sequence analysis, peptide mass fingerprinting, mass spectrometry and immunodetection.

Results: Antimicrobial activities were detected against Group B Streptococci (GBS), Bacillus megaterium (Bm11), Escherichia coli (D21), but not against Candida albicans. The antimicrobial activity against GBS, Bm11 and D21 was salt sensitive, where high salt concentration diminished the activity. After treatment of the extracts with pepsin, the activity against Bm11 decreased, indicating that a part of the activity is derived from peptides/proteins. In several extracts, lysozyme was detected. So far, we have identified five antimicrobial peptides; the cathelicidin LL-37 and four alpha-defensins, the human neutrophil peptides 1, 2 and 3 (HNP1–3) and human defensin 5 (HD-5). Furthermore, two histones, i.e. H2A and H4, were isolated and found to exhibit antibacterial activity.

Conclusions: These results suggest that meconium exhibit protective function against microbes in the gastrointestinal tract of the foetus and the newborn baby.