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INTERACTION BETWEEN FETAL PROINFLAMMATORY ACTIVITY, THE INSULIN-LIKE GROWTH FACTOR SYSTEM AND EARLY NUTRITION IN PRETERM INFANTS

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Background: : The fetal inflammatory response has been suggested causal in acute neonatal and chronic neurological morbidity. Insulin-like growth factor 1 (IGF-1) is essential for tissue growth and has protective properties after induced ischemia. Knowledge of the interaction between induced inflammation and the components of the IGF-1 system may be of benefit for therapeutic strategies aiming at promoting growth and tissue protection in preterm infants. Aim: To evaluate the effect of increased levels of proinflammatory cytokines and early nutrition on levels of IGF-1, binding protein –3 (BP-3) and high and low phosphorylated BP-1 (hp BP-1, lp BP-1) in umbilical cord blood and at 72 h of age in preterm infants.

Methods: : A two year prospective cohort study including inborn infants delivered at <32 gestational weeks after antenatal informed consent and excluding infants with major anomalies. 74 infants were enrolled with a mean (SD) gestational age of 27.1 (1.9) weeks. Blood sampling for analysis of proinflammatory (TNF-alpha, IL-1 , IL-2, IL-6, IL-8, IL-12, IFN-gamma) cytokines was performed from umbilical cord and at 6, 24 and 72 h postnatal age. Levels of IGF-1, BP-3, hp- and lp BP-1 were determined in cord blood and at 72 h of age. Enteral and parenteral protein- and caloric intake was prospectively registered during the first 3 days of life.

Results: : Increased levels of IL-8 and IL-6 were associated with a decrease in IGF-1 in umbilical cord blood, r= -0.31 (p=0.017) and r = -0.25 (p= 0.03) respectively, and with an increase in hp BP-1, r =0.39 (p=0.001) and r=0.49 (p=0.000) and in lp BP-1, r =0.38 (p=0.001) and r=0.39 (p=0.002). These associations remained significant after adjustment for gestational age, gender and birthweight. Levels of IGF-1, BP-3 and lf BP-1 at 72 h were decreased by 34, 29 and 50 % (median) as compared to those in the umbilical cord (p<0.001 respectively) whereas hf BP-1 remained unchanged. Parenteral- and enteral protein and caloric intake (0–72 h) were not associated with levels of IGF-1, hp - or lp BP-1 at 72 h whereas BP-3 at 72 h was inversely associated with total caloric intake, r= -0.44, p=0.000.

Conclusion: : Fetal proinflammatory activity is associated with decreased circulating levels of IGF-1 and an increase in hp- and lp BP-1 which may reflect a decreased protective capacity of the endogenous IGF system. Early enteral or parenteral nutrition does not appear to modify the decrease in circulating levels of IGF-1 resulting from preterm birth.

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TEMPORAL PROFILE OF CYTOKINES IN PRETERM INFANTS - IL-6 AND IL-8 ARE ASSOCIATED WITH ARTERIAL HYPOTENSION WHEREAS INTERFERON-Á IS INCREASED IN WHITE MATTER BRAIN DAMAGE

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Background: Antenatal inflammation elicits a fetal inflammatory response which has been suggested causal in acute neonatal and chronic neurological morbidity. Knowledge of temporal changes in levels of proinflammatory and modulatory cytokines during the transition from fetal to neonatal life may improve understanding of the possible relationship between inflammatory response, circulatory impairment and subsequent brain damage in preterm infants. Objective: To evaluate temporal profiles of proinflammatory and modulatory cytokines in fetal and neonatal blood and determine their relationship to arterial hypotension and morphological brain damage in preterm infants.

Methods: A two year prospective cohort study including inborn infants delivered at <32 gestational weeks after antenatal informed consent and excluding infants with major anomalies. 74 infants were enrolled with a mean (SD) gestational age of 27.1 (1.9) weeks. Blood sampling for fluorocytometric analysis of proinflammatory (TNF-á, IL-1 , IL-2, IL-6, IL-8, IL-12, IFN-ã) and modulatory (IL-4, IL-10) cytokines was performed from umbilical cord and at 6, 24 and 72 h postnatal age. Continuous invasive measurement of arterial blood pressure (ABP) was digitally stored during the first 72 h. Ultrasound examinations of the brain were performed at day 1, 3 and 7, at 6 weeks and at term age.

Results: Increased levels of IL-6 at 6h and IL-8 at 24 h were associated with a decrease in mean ABP during the first 72 h (r2=0.28, p=0.002 and r2=0.36, p=0.001 respectively). Level of IL-8 > 85 pg/ml at 6 h was predictive of dopamine treatment for arterial hypotension during the first 72 h (sensitivity 79%, specificity 73%). Infants who developed white matter brain damage (WMD) on ultrasound had increased mean levels of IFN- in umbilical cord and at 6, 24 and 72 hours as compared to those without WMD (p= 0.016, 0.027, 0.003 and 0.022 respectively). MABP during the first 72 h was not associated with development of WMD.

Conclusion: An early postnatal increase in levels of IL-6 and IL-8 was strongly associated with arterial hypotension requiring treatment in preterm infants. However, neither arterial hypotension nor increases in IL-6 or IL-8 were related to development of WMD as defined by ultrasound. Levels of IFN-ã were increased in cord blood and up to 72 h in infants who developed WMD. This suggests an early induction of inflammation with the main part of the inflammatory response taking place before birth in infants developing WMD.

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IDENTIFICATION OF ARTIFACT AND ABNORMAL VARIATION IN NICU MONITORING DATA

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Background: Computerised cotside monitoring has become routine in some neonatal intensive care units. Though a trend display of the vital signs of a neonate has practical benefits, the data is often significantly corrupted by artifact and is difficult to interpret by inexperienced staff.

Aims: To develop a system to reliably identify certain artifacts within monitoring data and to provide a measure of 'abnormality' in the trended physiology of a neonate.

Methods: The study used 10 data channels sampled routinely in our intensive care unit at 1 second intervals, for 6 premature infants. The artifacts modelled were transcutaneous probe (TCP) recalibration, probe dropouts, and the blood pressure spike caused by taking a blood gas sample. A (factorial) hidden markov model (HMM) was implemented to analyse the data, a technique widely used in speech recognition and other machine learning problems. This builds up a probabilistic description of the way a baby's vital signs vary when it is stable or when certain defined events are happening. From this the probability of a particular event happening can be calculated from the observed data. In addition, the system was constructed to flag areas of the data where the signal varied in a way not due to any artifact but also not characteristic of the baby in its stable state.

Results: Probe dropouts are in general easy to identify. The study concentrated on transcutaneous probe recalibration and blood gas sample artifact, both of which frequently occur in monitoring data. Detection performance was evaluated with receiver operating characteristics (ROC) curves. TCP recalibration detection had an area under the ROC curve of 95.8% and an error rate of 3.77%. Blood gas sample detection had an area under the ROC curve of 96.0% and an error rate of 1.54%. Abnormal sections of data can be flagged once the system has been manually given a time where the baby is stable as a reference point.

Conclusion: Machine learning can be reliably used to identify artifacts in NICU monitoring data.

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CHARACTERISTICS OF SKIN MICROCIRCULATION IN CHILDREN AND ADOLESCENTS WITH CONNECTIVE TISSUE DISORDERS MEASURED BY NON-INVASIVE SPECTROSCOPY

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Background/Aims: The differential diagnosis of connective tissue disorders (CTD) is often only possible by skin biopsy as the invasive gold standard. The skin biopsy specimen is then analysed for stages of activity and pathophysiological condition of the capillary bed and surrounding tissue. The clinical examination is confined to observation of skin appearance and capillary refilling time. From this the need of a non-invasive measurement method to assess skin microcirculation in children with suspicion of CTD arises. The aim of this prospective study was to investigate the use of the spectroscopic system Mediscan 2000 (MBR Technik, Herdecke, Germany) as an objective non-invasive tool to measure microcirculation in various CTD and to identify characteristic response patterns for them.

Methods: The Mediscan 2000 measures non-invasively total haemoglobin (tHb) and oxygenated haemoglobin (oxyHb) in the capillary bed. A defined pressure stimulation of 5 seconds was applied after obtaining baseline values and the vasomotion response was recorded afterwards until values return to baseline. A Fast-Fourrier-Analysis (FFT) was used to identify the activity of involved vessels (e.g. capillaries, venoles and arterioles) according to the frequency classes of 1 – 15/min. Vasomotion before and after the pressure stimulation was compared for significant differences by Z-Test (significant > 1.64 at 5% error level).

Results: Measurements at the finger tip and forearm were performed on 36 children and adolescents with CTD aged 2 to 22 years. The CTD types and vasomotion results are listed in the table together with the Z-test results. In juvenile dermatomyositis and systemic lupus erythematodes the vasomotion changed from exclusively higher (capillary) to lower (arterioles) frequencies after the pressure stimulation. In contrast to this children with Morbus Still had overlapping frequencies. The scleroderma patients had a distinct response difference between the finger tip (significant) and the forearm (not significant). Due to low overall activity of vasomotion children with nonspecific vasculitis had no significant difference in vasomotion before and after pressure stimulation.

Conclusion: Even in this small number of patients different response patterns to a well defined pressure stimulation could be identified for five different CTD. Future larger trials might be able to implement this measurement method as a non-invasive tool for assisting in the often difficult differential diagnosis of CTD.

CTD	Measurement location	tHb (Z-test)	oxyHb (Z-test)
Juvenile Dermatomyositis (n = 8)	Fingertip	3.302	2.475
	Forearm	2.646	1.894
Systemic Lupus Erythematodes (n = 10)	Fingertip	2.42	1.34
	Forearm	2.376	1.776
Morbus Still (n = 11)	Fingertip	2.025	2.34
	Forearm	2.477	2.632
Scleroderma (n = 3)	Fingertip	1.67	2.07
	Forearm	1.08	0.59
Non-specific Vasculitis (n = 4)	fingertip/forearm	1.28/1.557	1.44/0

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NEONATAL CRANIAL ULTRASOUND COMPARED WITH CONVENTIONAL MRI AT SCHOOL AGE IN PRETERM BORN CHILDREN, RELATED TO NEURODEVELOPMENTAL OUTCOME

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Background: Cranial ultrasound (US) is the method of first choice to detect brain injury in preterm born infants. Recently Magnetic Resonance Imaging (MRI) has become available. Correlation between US and MRI is excellent for haemorrhages but poor for subtle white matter injury.

Aim: To compare neonatal cranial US with MRI at school age, both related to outcome. **Patients and methods:** 221 (78.1%) out of 283 eligible children (GA< 32 weeks (mean 29.4 wks) and/or BW< 1500 grams (mean 1197 gr)) had a neonatal cranial US and an MRI at school age. Neonatal US findings were classified into group 1 (normal US), group 2 (Intraventricular Haemorrhage (IVH) grade 1/2, periventricular leukomalacia (PVL) grade 1, germinal layer necrosis) and group 3 (IVH grade 3/4, cystic PVL grade 2/3, thalamic lesions, focal infarction). MRIs were classified into group 1 (normal MRI), group 2 (mild gliosis i.e. less than 5 small (2mm) areas of hyperintensity, mild ventricular dilatation (VD), thinning of corpus callosum) and group 3 (extensive gliosis, marked VD, thalamic lesions, cerebellar or cortical atrophy). IQ was estimated by 5 subtests of the WISC-R and motor function was assessed with the Movement ABC.

Results: Of the 96 children in US group 1: 45 (47%) were in MRI group 1, 50 (52%) in MRI group 2 and 1 (1%) was in MRI group 3. Of the 90 children with a mildly abnormal US (group 2): 40 (44%) were in MRI group 1, 46 (51%) in MRI group 2 and 4 (4%) in MRI group 3. Of the 35 children with severe US abnormalities (group 3): 2 (6%) had a normal MRI, 8 (23%) were in MRI group 2 and 25 (71%) had a severely abnormal MRI (group 3). The predictive value of a normal US for a normal or mildly abnormal MRI was 99% (95% CI: 94–100%). The predictive value of a severely abnormal US for a severely abnormal MRI was 71% (95% CI: 54–85%). Mean IQ in US group 1 was not different from mean IQ in US group 2 (p=0.34), but higher than in US group 3 (p=0.02). Mean IQ in MRI group 1 was higher than in MRI group 2 (p=0.026) and in MRI group 3 (p=0.0001). Median Movement ABC scores in US group 1 were similar compared with US group 2 (p=0.59) but better compared with US group 3 (p=0.0001). For MRI median Movement ABC scores were better in MRI group 1 compared with MRI group 2 and MRI group 3 (p=0.0001 each).

Conclusions: A normal cranial US almost guaranteed a normal or mildly abnormal MRI. MRI subgroups differentiated better for neurodevelopmental outcome than US subgroups.

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ANALYSIS OF THE IMMUNOGENICITY OF A NEW PORCINE LUNG SURFACTANT USING THE RABBIT MODEL

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Background: The introduction of foreign proteins from animal lung-based surfactants into the airways of premature infants may provide an antigenic stimulus with a possible immunological response to these proteins. Recently the Butantan Institute (Brazil) produced a porcine pulmonary surfactant preparation obtained by organic extraction coupled with adsorption on a cellulose derivative, composed mainly by phospholipids with two hydrophobic polypeptides, SP-B and SP-C. This new surfactant contains 76% of phosphatidylcholine, 6–8% of phosphatidylethanolamine, 6% of phosphatidylinositol+phosphatidylserine, and 4–6% of sphingomyelin; 30–35% of the phosphatidylcholine was dipalmitoylphosphatidylcholine. The total content of protein is 5.6% of the surfactant preparation. The objective of this study was to analyze in rabbits the immunogenicity of the Butantan Institute surfactant preparation compared with commercial available lung surfactant preparations.

Methods: Study design: 16 1000g-weight New-Zealand-White rabbits were divided into 4 groups according to the type of surfactant administered intratracheally (100mg/kg): Survanta (Abbott Laboratories), Curosurf (Farmalab Chiesi Pharmaceutical) or Butantan. Animals in the control group received no surfactant treatment. All animals were bled immediately before, 60 and 180 days after surfactant administration. Detection of anti-surfactant antibodies: sera were evaluated by enzyme-linked immunosorbent assay (ELISA); after coating ELISA plates with Butantan Institute surfactant preparation, Survanta, and Curosurf, the sera of the animals from the 4 groups were tested in triplicate for each time point. An anti-rabbit peroxidase conjugate was used as second antibody. Statistical analysis: ANOVA one-way was performed to analyze the differences among the mean of the optical densities obtained before, 2 and 6 months after treatment. Student-Newman-Keuls test was performed as a post-disciminatory test. Significant level was set at $p < 0.05$.

Results: The optical densities obtained in the animal sera for each study group are presented in the figure below: INCLUDEPICTURE \d \z "Images\\04090413\\98 1.img"

Conclusion: All the surfactants analyzed did not trigger an immunological response against its components in the animals.