Autumn Meeting, 18th November 2014

Institute of Child Health, London

30 Guilford Street, London WC1N 1EH

09.00 Coffee

Session 1: Chair – Dr Andy Ewer

09.30 B Thomas, Cardiff.
Congenital Diaphragmatic Hernia (CDH): a comparison of regional morbidity and mortality outcomes.

09.45 A Jones, Northwick Park Hospital, Harrow.
A model for implementing routine pulse oximetry screening for congenital heart disease in a local acute hospital: protocol, outcomes and quality improvement.

10.00 S Job, Norwich.
How common is inadvertent lumbar vein catheterisation in the NICU?

10.15 O Sjokvist (Medical student prize), Hull York Medical School.
Integration of cultural beliefs into modern palliative care: a Māori case study

10.30 Morning Coffee

Session 2: Chair – Professor Neena Modi

11.00 G Green, Oxford.
Non-contact vital sign monitoring in the neonatal unit

11.15 G Belteki, Cambridge University.
Discovery of novel non-coding RNAs in the perinatal lung by deep sequencing

11.30 The keynote Lecture: Professor Steve Wilson, University College London. Fishing for answers: zebrafish as a model to study nervous system development in health and disease
12.30 Annual General Meeting for Members of the Neonatal Society

13.30 Lunch Break

**Session 3: Chair – Dr James Boardman**

14.30 F Zhu, Imperial College London.
   Comparison of cranial ultrasound injury score with tract based spatial statistics analysis of whole brain fractional anisotropy in neonatal encephalopathy.

14.45 J Dunne, Barts and the London School of Medicine and Dentistry.
   EEG discontinuity as a predictor of cerebral tissue injury in cooled term neonates with hypoxic-ischaemic encephalopathy.

15.00 P Rogers, King’s College London.
   Consistency of resting state functional networks in the neonatal brain

15.15 I Ng, Cambridge.
   Determining the relationship between thresholds of cerebral tissue oxygenation and adverse outcomes in preterm infants

15.30 I Lingam, King’s College London.
   Constrained spherical deconvolution: a new approach to mapping neuronal highways in preterm and term infants

15.45 Afternoon Tea

**Session 4: Chair – Dr Richard Thwaites**

16.15 J Kimpton, King’s College London.
   Maturation of interhemispheric functional connectivity during a passive wrist motor task in the preterm period

16.30 N Andreas, Imperial College London.
   The diverse human milk oligosaccharide content of human breast milk

16.45 C Heppolette, Imperial College London.
   The effect of maternal protein restriction during lactation on thymic involution and peripheral immunosenescence in adult mice.
17.00 B Ibrahim, Imperial College London. 
Linking electronic records to create a birth cohort of babies admitted to neonatal units in England

17.15 Presentation of prize for best free paper by a trainee

17.20 The Widdowson Lecture: Professor Andrew Prentice, London School of Hygiene and Tropical Medicine. Conceptions, pregnancies and neonates: Lessons from rural Africa
(Introduced by the President of the Society)

18.20 Drinks and Close of Meeting
CONGENITAL DIAPHRAGMATIC HERNIA (CDH): A COMPARISON OF REGIONAL MORBIDITY AND MORTALITY OUTCOMES

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

Dr Bethan Thomas, (ST4 Paediatrics) and Dr Cora Doherty (Consultant Neonatologist)

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Institution(s)

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Introduction (include hypothesis)

Mortality in CDH remains high thus making benchmarking against both standard guidelines and outcomes from other centres important. The South West (SW) of England implemented a clinical pathway and have shown survival rates of 76% for CDH. We aimed to compare our outcomes for CDH in South Wales with the SW and to benchmark our clinical practice against both their clinical pathway and the recent European CDH guidelines (1).

Methods (include source of funding and ethical approval if required)

All cases of CDH in Wales from 1998 to 2010 were identified through the CARIS congenital anomaly register. All live borns managed in South Wales had clinical management reviewed through retrospective case-note assessment. Outcomes from both the International CDH Study Group (2000-2009) and the SW anomaly register (1998-2010) were obtained. Clinical management of South Wales babies was benchmarked against the SW clinical pathway and the European CDH clinical guidelines (1).

Results

176 cases of CDH of which 120 were live born were identified through CARIS. The survival rate for live borns (83) managed in South Wales was 63% (95% CI 0.53-0.73) compared to 69% (95% CI 0.68-0.70) and 76% (95% CI 0.67-0.85) in the CDH Study Group and the SW respectively. There was a difference in pulmonary morbidity with a higher rate of pneumothoraces in babies born in S Wales at 32% (95% CI 0.22-0.42) compared with 13% in SW of England (95% CI 0.06-0.2). Oxygen dependency at 28 days of life in S Wales was 11% (95% CI 0.03-0.19) compared with 22% (95% CI 0.12-0.33) and 38% (95% CI 0.37-0.40) in the SW of England and CDH Study Group respectively. The main difference in the Neonatal Units’ management is the elective use of HFOV ventilation in the SW of England. 90% (95% CI 0.81-0.99) of their cases received HFOV, compared with 64% (95% CI 0.50-0.78) of cases in S Wales.

Conclusions

Survival rates over a 12 year period for CDH in South Wales are lower than the SW. The reasons may be multifactorial however optimising ventilation with permissive hypercapnia (1), may reduce pulmonary morbidity in survivors. More evidence is required to decide whether elective HFOV is associated with better outcomes.

References (include acknowledgement here if appropriate)

A MODEL FOR IMPLEMENTING ROUTINE PULSE OXIMETRY SCREENING FOR CONGENITAL HEART DISEASE (CHD) IN A LOCAL ACUTE HOSPITAL: PROTOCOL, OUTCOMES AND QUALITY IMPROVEMENT

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

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Institution(s)

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Introduction (include hypothesis)

Pulse oximetry is an effective screening tool for CHD in neonates¹, but it has not yet been evaluated if it can be successfully implemented in a local acute hospital without on-site paediatric cardiology services. We introduced routine pulse oximetry in September 2011 with a protocol based on work by de-Wahl Granelli et al² meaning all babies have pre and post ductal saturations measured within 2 hours of age and again pre discharge.

Methods (include source of funding and ethical approval if required)

After introduction of this protocol SEND summaries for all NNU admissions over 24 months were reviewed to determine which were prompted by a positive pulse oximetry screening result. Furthermore 429 neonatal records (gestation >35 weeks) from the postnatal ward were audited for protocol adherence in two cohorts.

Results

Between September 2011 and September 2013, after discounting babies admitted to NNU before screening could take place, there were 10,237 babies suitable for screening. From these 13 babies, 0.12% (95% CI 0.07% – 0.2%) were admitted based on screen positive pulse oximetry recording. Two of the 13 babies, 15.4% (95% CI 4.3% to 42.2%) went on to have echocardiograms and both had critical CHD. Sensitivity of screening in this context is 100% (95% CI 19.3 to 100%), and specificity 99.9% (95% CI 99.8 to 100%). 13.9% of post ductal recordings taken within two hours of birth were abnormal, compared to only 0.7% at discharge (p <0.0001) Two audits were performed; the first cohort indicated protocol was only being followed in 37.4% of cases and 6.7% of babies were not screened at all before discharge, creating the potential to miss babies with critical CHD. After implementing numerous quality improvement measures (based on a fishbone analysis), a subsequent second cohort audited showed 100% (95% CI 96.4 to 100%) of babies were screened at least once before discharge.

Conclusions

Data from the NICOR database⁷ indicates that no babies with critical CHD who needed surgical or catheter intervention were missed by our screening programme. There is currently no national policy for implementing pulse oximetry screening, however at the National Screening Committee’s March meeting it was decided it should be piloted in England⁸. Our experience not only demonstrates effective introduction of such screening in a local acute hospital, but also highlights quality improvement measures that enabled protocol adherence. Furthermore our data suggests an initial saturation check within two hours could be useful to capture early critical CHD, but as the fetal circulation is still in transition we expect more abnormal results that will likely normalise on repeat tests.

References (include acknowledgement here if appropriate)


Title (Upper case)

HOW COMMON IS INADVERTENT LUMBAR VEIN CATHETERISATION IN THE NICU?

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

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Institution(s)

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Introduction (include hypothesis)

Percutaneously-inserted central venous catheters (PCVCs) are vital for successful management of neonates in intensive care. One potential complication of PCVCs is inadvertent lodgement in an ascending lumbar vein (ALV). Associated morbidity of this specific malposition has included epidural extravasation of parenteral nutrition, seizures, quadriplegia, and death.[1] However the incidence of ALV catheter malposition is unknown. The aims of our study were to determine the incidence of PCVC malposition in the ALV, whether left-sided catheterisation has a predilection for this malposition, and the prevalence of routine radiopaque contrast use in UK tertiary-level neonatal units for checking PCVC position after insertion.

Methods (include source of funding and ethical approval if required)

A bespoke in-house clinical database was developed to log details of all PCVCs inserted in our neonatal unit. This ‘long line database’ has been in daily use since 2007 and records catheter insertion date and type, intended use, tip location verified by radiography after routine injection of radiopaque contrast, removal date and reason, and any complications. We interrogated this database for cases of suspected ALV malposition and cross-referenced with a separate, prospectively-maintained list of suspected or reported cases compiled since 2005. All radiographs of suspected or radiologically-reported ALV malposition underwent further independent review by two senior radiologists. In February 2013 we conducted by telephone a national survey of UK tertiary-level neonatal unit practices regarding use of radiopaque contrast for checking PCVC position.

Results

1113 PCVCs were inserted in our NICU over 9.5 years (January 2005 to June 2014). Of the 39 cases of suspected ALV catheter malposition, 9 were excluded after radiological review. 30 cases were confirmed, indicating an incidence of ~3 ALV malposition cases per year in our NICU. 23 (77%) involved the left ALV and 7 (23%) involved the right ALV. Affected babies had a median (range) birth gestational age 27 weeks (24-40 weeks) and birth weight 1099 g (515-3930 g). Of 818 PCVC insertions logged in the long line database, 386 (47.2%) involved lower limb catheterisations and included 25 of the confirmed ALV cases. The incidence of ALV malposition for lower limb-inserted PCVCs (25/386) was therefore 6.5% (95% CI: 4.2% to 9.4%). The risk of ALV catheter malposition was much higher with left lower limb catheterized catheters (left lower limb 19/160 vs. right lower limb 6/226, p=0.0006). Only 27 (52%) centres used contrast (11 routinely for all PCVCs inserted; 16 only after insertion of 28-Gauge catheters).

Conclusion

We present the largest ever reported series of ALV catheter malpositions. Our data derive from a single centre that has routinely used radiopaque contrast to verify the initial position of inserted catheters. ALV malposition affects approximately 1 in every 15 lower-limb inserted PCVCs, and we confirm that left-sided catheterisation has a significantly higher predilection for the ALV. The routine use of contrast may facilitate the early recognition of this potentially-dangerous malposition.

References (include acknowledgement here if appropriate)

INTEGRATION OF CULTURAL BELIEFS INTO MODERN PALLIATIVE CARE: A MĀORI CASE STUDY

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Introduction

There is evidence that attending to cultural and spiritual needs can have a positive influence during dying and bereavement. Historically, New Zealand is a bicultural society with distinct traditions and beliefs differentially held between Māori and Europeans, which are reflected in approaches to health and healthcare. This presentation aims to address challenges that have arisen when Māori based health care is combined with a Western approach to medicine, and how New Zealand health services have attempted to address these challenges as pertaining to neonatal palliative care.

Methods

Cochrane and Medline searches were conducted using keywords “paediatric”, “neonatal”, “palliative care”, “cultural needs”, and “Māori”. Interviews with a palliative care consultant and a specialist nurse with an interest in neonatal palliative care were conducted to identify any specific challenges encountered in the provision of palliative care. A specific case study was discussed that highlighted particular challenges in providing Māori centred neonatal palliative care. A hospital based Māori research advisor was further consulted to understand the origins of various Māori health beliefs and their role of in healthcare provision in New Zealand.

Results

The Treaty of Waitangi is a historical piece of legislation defining the relationship between Māori and Europeans in New Zealand, emphasizing that the values and traditions of both cultures should be reflected in society at large. The He Korowa Oranga further outlines how health services are to be attentive to the cultural needs and health beliefs of Māori. The research conducted suggested that the delivery of culturally appropriate palliative care on the NICU should address the wellbeing and needs of the whānau as well as the need for spiritual protection for the Māori baby. In Auckland, these needs are catered for by having tools to accommodate the shared decision making process of the whānau, the provision of whānau accommodation, access to Māori support services and the creation of a Tupapaku pathway, as highlighted through the case study provided in this presentation.

Conclusions

The literature provides evidence that the delivery of culturally appropriate palliative care, that takes into account the individual spiritual needs of the affected families, is helpful in the dying and bereavement processes. The neonatal palliative care services in Auckland, New Zealand, provide an example of how to integrate biculturalism into health services and highlights various challenges experienced.

References

NON-CONTACT VITAL SIGN MONITORING IN THE NEONATAL UNIT

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Introduction (include hypothesis)

Vital sign monitoring is important in the routine care of the preterm neonate. There have been few advances in neonatal monitoring for more than 30 years. Standard monitoring currently relies on ‘wired’ methods which can increase the need for handling and damage fragile skin. We present a novel non-contact method of monitoring, using a digital video camera positioned over the infant’s incubator which we hypothesise is as accurate as conventional monitoring and will provide entirely new information about the neonate’s physiological status.

Methods (include source of funding and ethical approval if required)

The study received ethical approval and is funded by the Wellcome Trust/EPSRC. Preterm infants in HDU were filmed for a maximum of 4 days each using a digital video camera positioned over a specially modified incubator. Vital sign data from the standard patient monitor was collected concurrently and the camera data was analysed retrospectively. Routine care continued throughout the study. Signal analysis was used to obtain a reflectance photoplethysmogram waveform (PPG) from the raw camera data. Mathematical modelling was then used to identify frequencies corresponding to the physiological parameters of interest from the noisy PPG waveform.

Results

The first two infants were filmed for a total of 39.8 hours during which 24.9 hours of valid camera data was obtained (time periods when the infants was resting quietly inside the incubator). Estimates of heart rate were possible for 80.3% of the valid camera data time with a mean absolute error of <3bpm when compared with ECG heart rate. Data obtained from these first infants have shown that it is possible to continuously monitor heart rate and respiratory rate using this non-contact method. It is also possible to demonstrate and track changes in oxygen saturations. This is the first time that continuous monitoring of vital signs using a non-contact method has been reported in the neonatal population. These initial results which demonstrate feasibility are part of a larger study to evaluate the use of this technology in the neonatal care setting.

Conclusions

Continuous non-contact vital sign monitoring is possible in the neonatal care setting. Our method is not only able to replicate standard ‘wired’ monitoring but in the future is likely to produce novel parameters such as perfusion maps and movement indices.

References (include acknowledgement here if appropriate)

DISCOVERY OF NOVEL NON-CODING RNAS IN THE PERINATAL LUNG BY DEEP SEQUENCING

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

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Institution(s)
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Introduction (include hypothesis)
Perinatal lung maturation is characterized by widespread gene expression changes that are tightly regulated. Recently, a role of regulatory non-coding RNAs in developmental processes has been reported. Short micro RNAs are essential for normal lung development as mice lacking the miRNA processing enzyme DICER die after the birth due to neonatal respiratory failure. The role of longer non-coding RNAs (lncRNAs) in the perinatal lung is unknown. We set out to identify and characterize novel non-coding RNAs in the perinatal lung.

Methods (include source of funding and ethical approval if required)
We isolated both long and short RNAs from mouse lungs at the early canalicular stage of development (embryonic day 16.5, n=5) and at the saccular stage (embryonic day 18.5, n=5). Using Illumina sequencing we sequenced over 200 million small RNA reads and over 500 million paired long RNA reads from both developmental stages. We mapped to sequences to the known mouse protein-coding and non-coding genes. We identified genes differentially expressed at a significance level of p<0.01. Selected genes were validated by real-time quantitative RT-PCR. Our work was supported by Addenbrookes Charitable Trust (ACT).

Results
We found that 424 protein-coding genes were up-regulated and 230 genes were down-regulated over 5-fold during lung maturation. Genes participating in inflammatory and defence responses and in ion transport were significantly (p<0.01) over-represented among up-regulated genes. Genes involved in DNA replication and cell cycle control were over-represented among down-regulated genes. In addition, we found 16 microRNAs and 44 novel long non-coding RNAs differentially regulated. All these non-coding genes are conserved and are also present in humans. Of them, miR-146a and miR-146b attenuate the cytokine response to inflammatory stimuli in adult lung cells and miR-486 is known to have an anti-proliferative effect in lung tumours. Both miR-22 and its host gene (miR22hg), a long noncoding RNA, are turned on in saccular stage lungs. We present an integrative analysis of these non-coding RNAs and their putative regulatory targets.

Conclusions
The transcriptional program of lung maturation includes novel microRNAs and long non-coding RNAs of unknown function. These genes are potential therapeutic targets and warrant further investigations.

References (include acknowledgement here if appropriate)
Thanks for Liisa Chang, Ed Williams and Tom Wright (medical students) for their help with this project.
COMPARISON OF CRANIAL ULTRASOUND INJURY SCORE WITH TRACT BASED SPATIAL STATISTICS ANALYSIS OF WHOLE BRAIN FRACTIONAL ANISOTROPY IN NEONATAL ENCEPHALOPATHY

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

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Institution(s)

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Introduction (include hypothesis)

Although diffusion tensor imaging (DTI) fractional anisotropy (FA) analysed by tract-based spatial statistics (TBSS) is a robust quantifiable biomarker of cerebral microstructural injury, and correlates with early childhood adverse neurological outcomes after neonatal encephalopathy, (1,2), it requires expert input and is not widely available. Here we compared cranial ultrasound (cUS) imaging with whole brain microstructural injury on DTI analysed by TBSS.

Methods (include source of funding and ethical approval if required)

We recruited consecutive term/near term encephalopathic infants admitted to the neonatal unit at Calicut Medical College, India, over a 3 month period. We performed cUS imaging within the first week after birth, and MR imaging (1.5 Tesla, Siemens Avanto) within 2 weeks of birth. Basal ganglia and white matter abnormalities on cUS were scored (0 – normal, 1 – mild, 2 – moderate, 3 – severe), masked to the clinical data. We performed TBSS as previously described (2). Local ethics approval and informed parental consent were obtained prior to recruitment.

Results

Thirty-three newborn infants were recruited; Sarnat staging: 19 (58%) stage I; 10 (30%) stage II; 4 (12%) stage III. Six infants died (4 stage III; 2 stage II) before MR scanning. All 27 survivors had a cUS (mean [SD] age 3 [2.3] days) 24 (89%) of whom had DTI (mean [SD] age 8.8 [1.9] days). Three infants (11%) had moderate basal ganglia/thalami echogenicity (scan days 1, 3 and 5) and 4 infants (15%) had moderate white matter echogenicity (scans on day 1). None had severe injury judged on these early cUS. Reduced white matter FA was associated with moderate basal ganglia injury seen on cUS (29% of white matter voxels) but not with white matter injury. (Figure).

Conclusions

We found that basal ganglia/thalami injury seen on early cUS was associated with reduced whole brain white matter FA on DTI at 2 weeks of age. This was not the case for WM injury but may be because of early cUS scan acquisition. Nonetheless these data support the role of beside cUS imaging in assessing brain tissue injury after neonatal encephalopathy and deserve further investigation.

References (include acknowledgement here if appropriate)

EEG DISCONTINUITY AS A PREDICTOR OF CEREBRAL TISSUE INJURY IN COOLED TERM NEONATES WITH HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

Introduction (include hypothesis)

Neonatal encephalopathy is associated with both high neonatal morbidity and mortality, with therapeutic hypothermia (TH) having a beneficial effect on both outcomes in resource-rich settings. Prior to the adoption of TH, the prognostic value of early EEG recordings in term babies was demonstrated (1,2); continuous limited channel EEG monitoring is routinely used and provides an indication of cerebral function. However, the predictive value of early EEG as a prognostic indicator in therapeutically cooled babies is unclear. We thus tested the hypothesis that early EEG background continuity in term neonates undergoing TH for neonatal encephalopathy is predictive of cerebral tissue injury detectable on later MRI.

Methods (include source of funding and ethical approval if required)

Term neonates receiving 72 hours of TH at three centres were selected for study if they had continuous 2 channel EEG with amplitude-integrated EEG (aEEG) monitoring and cerebral MRI. A two hour seizure-free period, with minimum artefact, at 24 and 48 hours after birth were selected for analysis. Single channel cross-cerebral (P3-P4) EEG data were exported and continuity was analysed in one minute epochs using software that we developed using MATLAB (The MathWorks, Inc., USA). The system detected an interval if the absolute amplitude of the EEG was less than 15 µV with respect to the baseline for at least 6 seconds; the analysis was repeated with a 10 µV threshold. For each recording the mean of the total interval length per epoch, the discontinuity, was calculated. MRIs were graded by the severity of injury using a system that has been shown to provide an indication of cerebral function. However, the predictive value is clear.

Results

Of 49 term neonates receiving TH after HIE, 17 (35%) had cerebral tissue injury on MRI predictive of abnormal outcome. On univariate analysis factors associated with abnormal MRI outcome were high seizure burden (p=0.003), mean discontinuity at 24 hours (p=0.001) and at 48 hours (p=0.001) at 15 µV threshold. In multivariate logistic regression high seizure burden (OR 4.2, 95% CI 1.01–17.48; p=0.05), mean discontinuity at 24 hours (OR 1.04, 95% CI 1.01–1.08; p=0.01) and at 48 hours (OR 1.05, 95% CI 1.01–1.10; p=0.01) were associated with severe cerebral tissue injury on MRI. A mean discontinuity >30s per minute epoch has a positive predictive value of 90% and 86% at 24 and 48 hours respectively (10 µV threshold) and of 75% and 80% at 24 and 48 hours (15 µV threshold) for cerebral tissue injury on MRI.

Conclusions

Our study indicates that, in addition to seizure burden (4), excessive EEG discontinuity in infants undergoing therapeutic cooling after hypoxic-ischaemic encephalopathy is associated with increased cerebral tissue injury on MRI predictive of abnormal neurodevelopmental outcome. The EEG remains a valuable tool for monitoring cerebral function in this group of patients and provides an early prognostic indicator.

References (include acknowledgement here if appropriate)

**Title**

CONSISTENCY OF RESTING STATE FUNCTIONAL NETWORKS IN THE NEONATAL BRAIN

**Authors**

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**Institution(s)**

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**Introduction**

At rest, distinct and highly reproducible spatial patterns of correlated brain activity (known as "resting state networks") can be readily identified with functional magnetic resonance imaging (fMRI). In the neonatal brain, resting state networks emerge during the third trimester in accordance with a period of rapid neural growth, such that a facsimile of adult network architecture can be identified at full term (Doria et al., 2010). Here we investigate the consistency of these networks across the cohort of infants studied at term equivalent age, and study the effects of specific clinical and demographic variables on their formation.

**Methods**

The study population consisted of 62 prematurely born infants who were studied at term equivalent age (38 to 42 weeks PMA, 29 male), all of whom were born prematurely and recruited as part of the NIHR-funded ePRIME study (REC ref: 09/H0707/98). fMRI data was acquired over 6.5 minutes on a 3-T Philips MRI system located on the neonatal unit at the Queen Charlotte and Chelsea Hospital, London. Infants with any evidence of overt brain abnormalities and/or focal brain pathology were excluded from the study group. The majority of infants (50/62) were sedated with chloral hydrate (30-50mg/kg) prior to the MRI scan.

fMRI data analysis was done using FSL (www.fmrib.ox.ac.uk/fsl). A statistical data-driven analysis was done on the fMRI data from all 62 infants using probabilistic independent component analysis (P-ICA) to identify a full repertoire of 14 resting state networks from the group. The consistency of networks was then studied using the dual-regression approach by comparing the effects of key variables (whether they received sedation, sex, age at birth, and age at scan) on the spatial distribution of the empirically derived networks using a general linear model and permutation methods (Filippini et al. 2009). Correction for multiple comparisons was made on a voxel-wise level using the family-wise-error rate, and for overall significance using the Bonferroni correction.

**Results**

As described in the literature, group ICA yielded a total of 14 resting state networks, corresponding to the somatosensory, motor, visual, auditory and cognitive systems. The spatial representation of all networks was not found to be significantly different between any of the study subgroups. In particular, sedation with chloral hydrate did not have a significant effect (example shown in figure is the sensori-motor network in sedated (left) and un-sedated (right) infants).

**Conclusions**

At term equivalent age, infants have consistent and robust resting state networks, which are independent of the effects of sedation, sex, and age at birth. The results suggest that as in adults, resting state networks are reproducible and consistent in neonates at term-equivalent age, and are therefore amenable for systematic studies examining the effects of specific brain pathologies and therapies.

**References**


DETERMINING THE RELATIONSHIP BETWEEN THRESHOLDS OF CEREBRAL TISSUE OXYGENATION AND ADVERSE OUTCOMES IN PRETERM INFANTS

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Introduction

Decreased cerebral perfusion is associated with brain injury in preterm infants. Management that targets cerebral oxygenation requires absolute thresholds of cerebral tissue oxygenation to be defined in the population group. This study investigates the relationship between deviations of cerebral tissue oxygenation beyond set thresholds and outcomes of mortality and intraventricular haemorrhage (IVH) in preterm infants in the immediate perinatal period.

Methods

49 preterm infants born at median (range) gestational age of 26+6 weeks (23+4 – 31+0) were studied at a median (range) age of 11.7 (3.5-64) hours of life, following parental consent. Cerebral tissue oxygenation index (TOI) was measured using a NIRO200NX spectrophotometer and data were stored and analysed using ICM+ software. We calculated burdens of TOI deviation beyond thresholds for hypoxia (< 55%, <60%, < 65%) and hyperoxia (>75%, >80%, >85%). Cumulative burdens of hypoxia were calculated in 6 hour windows in 26 infants who were continuously studied for a median duration of 43 hours. Outcomes were collected from clinical notes.

Results

Of the 49 infants studied, 8 died and 19 had IVH (grade 1 to 4). Burdens of hypoxia/hyperoxia were defined as the magnitude of deviation from thresholds multiplied by the proportion of study time spent outside the thresholds. Logistic regression analysis was used to compare different burden measures and outcomes. Significant log likelihood ratios for mortality were found with all burdens of hypoxia: TOI<55% (p=0.049), TOI<60% (p=0.011) and TOI<65% (p=0.013), as well as with total burden of hypoxia and hyperoxia with thresholds of TOI<60% + TOI>80% (p=0.018) and TOI<65% + TOI>75% (p=0.005). Student's t-test or the Mann Whitney U test was used to compare mean cumulative burdens of hypoxia between infants who developed IVH and those who did not, after testing for normality with the Shapiro-Wilk test. There was significant difference found when hypoxia was defined as TOI<55% and TOI<60%, from 18 hours of life and beyond (p<0.05).

Conclusions

We have defined thresholds of TOI based on burden of hypoxia and adverse clinical outcomes. Cumulative burdens of hypoxia from 18 hours of life have shown significant association with IVH. Therefore, the burden of TOI deviation may be a useful clinical index, especially in the first few days of life in extremely preterm infants.

References

1. Hamamatsu Photonics, Hamamatsu, Japan; 2. Cambridge Enterprise, Cambridge, UK
## Title (Upper case)

**CONSTRAINED SPHERICAL DECONVOLUTION: A NEW APPROACH TO MAPPING NEURONAL HIGHWAYS IN PRETERM AND TERM INFANTS**

## Authors

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## Institution(s)

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## Introduction (include hypothesis)

Magnetic resonance (MR) tractography allows visualisation of white matter tracts by assessing the directional dependence of water molecular diffusion in tissue (anisotropy). Constrained Spherical Deconvolution (CSD) is an approach that better resolves crossing fibres compared to tensor based methods. This project assessed the feasibility of performing CSD of the middle cerebral peduncle (MCP) and corticospinal tract (CST) in the neonatal brain. Results were compared to diffusion tensor based fibre tracking methods used in this population.

## Methods (include source of funding and ethical approval if required)

Ethical Committee permission for this study was granted and parental consent obtained prior to imaging. High angular resolution diffusion images (HARDI) were acquired with a 3 Tesla MR scanner (64 directions, \( b = 2500 \) s/mm\(^3\)). Using the MRtrix software package, CSD and Diffusion Tensor Tracking (DTT) of the MCP and CSTs were performed and compared qualitatively and quantitatively. Secondary analysis included determining the impact of selected perinatal clinical factors on mean fractional anisotropy (FA) values. This study was funded by a Strategic Grant from the MRC.

## Results

Clinical data and images were available for 44 infants, comprising of 41 preterm and 3 term infants. Image acquisition times were approximately 10 minutes. The CSD approach generated significantly more detailed images of the MCP and CSTs. The images of the MCP generated by CSD demonstrated wide fibre bundles spreading across the cerebellar hemispheres. The CST fibres could be seen fanning out across the motor cortex, in contrast to the DTT images that only demonstrated fibres travelling vertically. The mean FA generated by CSD was significantly lower than DTT (\( p<0.0001 \)). Both methods of tractography demonstrated a significant increase in mean FA with post-menstrual age, correcting for gestational age and birth weight (\( p<0.005 \)). In the subgroup of infants born at 33 weeks gestational age and below, this association was significant in the CSD approach (\( p<0.001 \)), but not the DTT method (\( p=0.10 \)).

## Conclusions

CSD has the ability to resolve complex, crossing fibres and provides a richer depiction of neuronal tracks compared to deterministic methods in preterm and term infants. CSD is a more sensitive method of tractography with potential to assess the developing brain in unprecedented detail.

## References (include acknowledgement here if appropriate)

MATURATION OF INTERHEMISPHERIC FUNCTIONAL CONNECTIVITY DURING A PASSIVE WRIST MOTOR TASK IN THE PRETERM PERIOD

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Introduction

Functional neural networks rapidly mature during the preterm period. Resting state fMRI studies show that this process is characterised by marked increases in long-range (and in particular interhemispheric) connectivity 1. At the end point of this period, the specificity of functional connectivity increases, resulting in an adult-like distribution at term equivalent age. However, the maturation of functional connectivity within task-evoked responses is unknown. We hypothesised that, as seen at rest, interhemispheric functional connectivity during a simple motor task initially increases during the preterm period but then decreases as connections become increasingly specific at full term.

Methods

The work was carried out with ethical approval (REC ref: 12/LO/1247) and supported by MRC funding. 62 neonatal subjects between 30+2 to 43+2 weeks post-menstrual age (PMA) were studied. Neonates were excluded if they had focal brain pathology, congenital malformations or if there were severe image artefacts, leaving a study population of 48 infants. fMRI data were obtained with a 3-T Philips MRI system and an EPI sequence lasting 6.5 minutes. Chloral hydrate sedation was administered to neonates >37 weeks PMA. Passive motor stimulation (right wrist extension/flexion) was elicited using a fully automated fMRI-compatible robotic interface and a simple block paradigm 2. fMRI data was analysed using FSL (www.fmrib.ox.ac.uk/fsl) and MATLAB. Functional connectivity was assessed by calculating the partial correlation coefficient (normalised using the Fisher’s z transformation) between the mean BOLD signal time-series within anatomically defined left and right peri-rolandic regions (figure (a)).

Results

The z-transformed partial correlation coefficient between the anatomically defined right (figure (a), red) and left (figure (a) blue) peri-rolandic regions was seen to rapidly increase during the preterm period until approximately 36 weeks PMA. It then steadily decreases towards term equivalent age leading to an inverted U-shape relationship (figure (b)).

Conclusions

The late pre-term period is associated with a significant increase in interhemispheric functional connectivity. This may be driven by the rapid growth of cortico-cortical connections through the corpus callosum. Whilst connectivity appears to decrease at term equivalent age, this may be due to increasing spatial specificity of the functional response during task activity.

References

THE DIVERSE HUMAN MILK Oligosaccharide CONTENT OF HUMAN BREAST MILK

**Authors** (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

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**Introduction (include hypothesis)**

Previous research has identified Human Milk Oligosaccharides (HMO) as a highly variable component of human breast milk. HMO are complex carbohydrates that serve multiple functions, including acting as an anti-infective agent for the infant. HMO biosynthesis is in large part determined by Lewis blood group and secretor status, which are genetically determined [1]. We hypothesised that the diverse profiles of HMO could be assessed using 1H NMR spectroscopy, and that individual HMOs contributing to differences between profiles would be identifiable.

**Methods (include source of funding and ethical approval if required)**

Human milk samples were obtained from 108 mothers, at 7 days and 3 months post-partum. Samples were solvent extracted and 1H NMR spectra acquired for the aqueous fraction. Data were analysed using Principal Component Analysis (PCA) to define clustering of data in relation to the component describing the largest proportion of variation. Data were modelled using Orthogonal Partial Least Squares-Discriminant Analysis (OPLS-DA) to compare different groups of mothers, defined by their spectral profiles. The study has received Research Ethics approval (12/LO/0203) and is funded by Westminster Medical School Research Trust.

**Results**

Large differences in the abundance of HMO were observed between the 7 day and 3 month time points. There was a substantial decrease in HMO quantity at 3 months. Furthermore, large differences in the specific types of HMO were identified. In the PCA plot, two broad groups of mothers were identified, each identified by distinct HMO profiles, known to be determined by maternal genotype. Based on the types of oligosaccharides produced one group, thought to be secretors (Se+), produced a preponderance of HMO known to be products of the gene fucosyltransferase 2, including 2'-fucosyllactose, lactodifucotetraose and lacto-N-fucopentaose 1. The other group, thought to be non-secretors (Se-), did not produce these HMO, but had an increased quantity of other HMO, including 3'-fucosylactose, present in their breast milk. Overlaying the NMR spectra, allows us to identify the types of HMO produced, associated with the Lewis blood groups. The interaction between the Lewis blood group (Le’/Le) and secretor gene status produce four types of breast milk. All four types were present in our cohort, (Se’/Le’), (Se’/Le), (Se/Le’) and (Se/Le).

**Conclusions**

HMO are believed to have important prebiotic properties. Additionally, data show an association between maternal non-secretor status, and increased infant infection risk [2]. We have shown that human milk HMO profile may be characterised rapidly using 1H NMR spectroscopy. This provides opportunity for a stratified medicine approach in future interventional studies involving manipulation of the infant microbiome to reduce infection risk.

**References (include acknowledgement here if appropriate)**


THE EFFECT OF MATERNAL PROTEIN RESTRICTION DURING LACTATION ON THYMIC INVOLUTION AND PERIPHERAL IMMUNOSENESCENCE IN ADULT MICE.

Authors (Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)

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Introduction (include hypothesis)

Environmental factors such as nutrition during early life can influence long-term health, a concept termed developmental programming. Initial studies showed effects on metabolic health but recent studies have also demonstrated effects on ageing, longevity and immunity (1). Given that dysfunction of the immune system is responsible for increased infection, cancer and autoimmune diseases in the elderly, we hypothesise that the adaptive immune system can also be affected by early nutrition, and which may mediate the effect on lifespan.

Methods (include source of funding and ethical approval if required)

C57BL/6 mice were mated and dams were fed an ad libitum diet to establish two groups: Controls (offspring born to and suckled by dams fed a control diet) and the post-natal low protein (PLP) group (offspring of control dams cross-fostered and suckled by dams fed the low protein diet). At 21d, 3m, 18m and 23m fresh thymic and splenic tissues were removed for flow cytometry analysis, confocal microscopy and RNA analysis. All procedures on animals were conducted under the British Animals (Scientific Procedures) Act (1986).

Results

Maternal protein restriction during lactation in mice, that is known to prolong lifespan, slowed ageing of both the central and peripheral immune systems. PLP offspring had a significant increase in thymic cellularity and number of T cells across their lifespan compared to control animals. These animals also demonstrated a less marked age-associated decrease in CD3 expression on thymocytes in old age. Therefore PLP animals demonstrated reducing thymic ageing compared to controls. PLP animals also demonstrated increased relative splenic cellularity, increased naïve: memory CD4+ and CD8+ T cell ratios, increased staining and density of germinal centres, and decreased gene expression of p16 in the spleen, a robust biomarker of ageing. A slower rate of splenic ageing in PLP animals would be expected to result in decreased susceptibility to infection and neoplasia.

Conclusions

In conclusion nutritionally-induced slow postnatal growth leads to delayed ageing of the adaptive immune system, which may contribute towards the extended lifespan that is observed in these animals.

References (include acknowledgement here if appropriate)

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LINKING ELECTRONIC RECORDS TO CREATE A BIRTH COHORT OF BABIES ADMITTED TO NEONATAL UNITS IN ENGLAND

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Introduction
Data on hospital admissions in England are held in an administrative database, Hospital Episode Statistics (HES). Point-of-care clinician-entered information extracted from the Electronic Health Records of all admissions to NHS neonatal units are entered after cleaning into a National Neonatal Research Database (NNRD) at the Neonatal Data Analysis Unit at Imperial College London [1]. The utility of routine data, whether clinical or administrative, for research is limited by uncertainty around the reliability and completeness of key variables [2]. Our aim was to examine data quality and completeness in HES and the NNRD, agreement of key variables, and the feasibility of linking these databases to create a research birth cohort.

Methods
We extracted records from HES and the NNRD of all babies born in England between 1 January 2010 and 31 December 2010. We assessed the completeness of key variables (infant sex, gestational age, birth weight, multiple birth, maternal age and ethnicity) in both sources, and their agreement. We used cut-off values of >+4SDS and <-4SDS to identify potentially erroneous birth weights. We tested linkage using a deterministic approach using the NHS number as common unique identifier. We performed a one to one merge of records from both sources based on the NHS number and created a new dataset with single birth episodes and common key variables from each source included. The data linkage rate was calculated by using the number of true matches divided by the total number of records available for matching.

Results
For the calendar year 2010, 651,703 and 66,403 babies were extracted from HES and NNRD, respectively. NNRD records were over 90% complete for all key variables except maternal age; completeness was higher than HES for all variables except maternal age and ethnicity (Table 1). After data cleaning and removal of duplicates (16,334 records), 651,703 (95.2%) HES records were eligible for linkage to 45,513 (68.5%) records in the NNRD with an NHS number. Although 93% of NNRD records were successfully linked to HES births, this rate dropped to 61.4% when babies with implausible birth weights for gestational age were excluded (1.5% HES; 0.3% NNRD). The final cohort comprised 42,521 babies admitted to NHS neonatal units. The overall agreement between common fields derived from HES and NNRD was >95% for all variables except gestational age (80.7%) and maternal ethnicity (87.1%). For maternal ethnicity and gestational age kappa coefficient values ranged from 0.71 to 0.79; for other variables agreement was almost perfect with kappa values ranging from 0.92 to 0.99.

Table 1  Level of completeness for key variables

<table>
<thead>
<tr>
<th>Key variables</th>
<th>HES (%)</th>
<th>NNRD (%)</th>
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</thead>
<tbody>
<tr>
<td>Infant sex</td>
<td>99.9</td>
<td>99.9</td>
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<tr>
<td>Gestational age</td>
<td>81.2</td>
<td>99.6</td>
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<tr>
<td>Birth weight</td>
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<td>99.6</td>
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<tr>
<td>Ethnicity</td>
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<td>89.5</td>
</tr>
<tr>
<td>Multiplicity</td>
<td>87.4</td>
<td>99.4</td>
</tr>
<tr>
<td>Maternal age</td>
<td>71.8</td>
<td>68.1</td>
</tr>
</tbody>
</table>

Conclusions
We have demonstrated that record linkage between NNRD and HES is feasible. This indicates that identification of long term health outcomes of babies admitted to neonatal units is potentially possible using linked records. The utility of this powerful approach would be enhanced by improvements in data quality and completeness.

References
Self Certificate of Attendance

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Neonatal Society Autumn Meeting 2014
The Institute of Child Health, London
Tuesday, 18th November

Name of person claiming CPD points:
(Blockletters)………………………………………………

Place of Work:........................................................................

Number of CPD points claimed :...........................................

(1 point per hour of attendance – up to a maximum of 5 CPD Points)

Claimant’s Signature……………………

Name and signature of Neonatal Society Committee member

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Howard Clark/Richard Thwaites/Neena Modi/James Boardman
Matthew Hyde/Jane Norman/Andrew Ewer/Topun Austin
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