The Neonatal Society

Autumn Meeting

Royal Society of Medicine, 1 Wimpole Street, London, W1G 0AE

7th November 2019

08.30. Coffee in the Atrium

Session 1: Chair – Professor Lucy Chappell

9.15. C Howarth, Homerton University Hospital NHS Foundation Trust
Can we reliably predict NEC in preterm infants using gut biomarkers and Near Infrared Spectroscopy?

9.30. C Murphy, Homerton University Hospital NHS Foundation Trust
Blood transfusion causes more profound changes in splanchnic oxygenation compared with brain

9.45. I Jones, University of Southampton
Remote ischaemic conditioning as a novel therapeutic intervention for experimental NEC

10.00. E Williams, King's College London
End-tidal carbon dioxide ($ETCO_2$) levels during resuscitation and CO_2 levels in the immediate neonatal period and subsequent cerebral injury

10.15. D Chong, University of Cambridge
The effect of pressure rise time on ventilator parameters and gas exchange during time-cycled and flow-cycled neonatal ventilation

10.30. O Carney, St Thomas' Hospital, London
Incidental findings on brain MR imaging in low risk term neonates in the developing human connectome project

10.45. Tea / coffee

Session 2: Chair – Professor Andy Ewer

11.15. **Keynote Lecture**
Professor Rebeccah Slater. Nuffield Department of Clinical Neurosciences. University of Oxford.
Pain perception in the newborn

12.15. Annual General Meeting for Members of the Neonatal Society

13.15 Lunch break

Session 3: Chair – Dr Ela Chakkarapani

14.45. J Gundersen, University of Oslo
Classical neuropathology shows hypothermic neuroprotection in seven day old rats after a mild hypoxic ischemic insult

15.00. L Hage, Imperial College London
Changing clinical characteristics of infants treated with therapeutic hypothermia for hypoxic ischaemic encephalopathy in England, Wales and Scotland

15.15. M Eyre, King's College London
The developing human connectome project: normal and disrupted functional connectivity across the perinatal period

15.30. B Dean, University of Edinburgh
Eye-tracking for longitudinal assessment of social cognition in children born preterm

15.45. Afternoon Tea / Coffee

Session 4: Chair – Dr Chris Gale

16.15. S Newell, University of Bristol
Neonatal brain volume in twins with discordant birthweight – MRI findings from a multicentre prospective cohort study

16.30. G Toldi, University of Birmingham
Neonatal T cells acquire both pro-inflammatory and tolerant phenotypes in first three weeks of life

16.45. H Wood, University of Birmingham
Breast-fed neonates show increased immune tolerance against maternal antigens

17.00. **Prize for best presentation by a trainee**

17:05. **Widdowson Lecture (Introduced by Professor James Boardman)**
Professor Andrew Copp. UCL Institute of Child Health.
Neural tube defects: developmental biology, prevention and policy

18.05 Drinks reception in the Atrium and close of meeting

Self Certificate of Attendance

Please complete the form below and have it signed by a member of the neonatal society committee if you wish to claim RCPCH CPD points

Neonatal Society Autumn Meeting
London
7th November 2019

Name of person claiming CPD points:

(Block letters)…….

Place of Work:…….

Number of CPD points claimed :……
(1 point per hour of attendance – up to a maximum of 10 **CPD Points**)

Claimant's Signature……

Name and signature of Neonatal Society Committee member

……
Howard Clark/Helen Budge/James Boardman/Andrew Ewer/Karen Luyt/Chris Gale/Ela Chakkarapani/Lucy Chappell/Kevin Goss
(please delete as appropriate)

Can we reliably predict NEC in preterm infants using gut biomarkers and Near Infrared Spectroscopy?

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

Claire Howarth[1,2];Joan Morris[3];Christian Mifsud[4];Jayanta Banerjee[5,6];Terence Leung[7];Simon Eaton[4];Narendra Aladangady[1,2]

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Institution(s)

1.Homerton University Hospital NHS Foundation Trust, London; 2. Queen Mary University of London, London; 3.St George's, University of London, London; 4. UCL,Great Ormond Street Institute of Child Health, London; 5. Imperial College Healthcare NHS Trust, London; 6.Imperial College London; 7. University College London, London.

Introduction *(include hypothesis)*

Survival of very preterm infants has improved[1], but the incidence of NEC has not changed[2]. Progress in the prevention of NEC has been limited by difficulties in clearly defining high risk groups, variable definitions of NEC and a lack of routinely used effective gut biomarkers. Near Infrared Spectroscopy (NIRS) can non-invasively measure regional oxygenation. We aimed to establish if gut biomarkers of tissue injury and measurements of regional oxygenation differ in infants with NEC compared to those without, and whether they could predict the onset of NEC.

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

We examined 48 infants <30w gestational age (GA) admitted to our tertiary level NICU from Oct 2016 to May 2018. Exclusion criteria: birthweight ≤2nd centile, abnormal antenatal dopplers, major congenital anomalies or Twin to Twin Transfusion Syndrome. For 60 minutes each week, splanchnic (sTOI) and cerebral (cTOI) Tissue Oxygenation Index (TOI) were measured simultaneously using NIRO-300 (Hamamatsu KK, Japan). Subsequently splanchnic (sFTOE) and cerebral (cFTOE) Fractional Tissue Oxygenation (FTOE) were calculated. Weekly urinary intestinal and liver fatty acid binding proteins (I- FABP, L-FABP), Trefoil Factor 3 (TFF3) and stool Calprotectin were measured by ELISA and weekly clinical status recorded for the first 8 weeks of life. NEC was defined as ≥ Bells stage 2. Statistical analysis was completed using STATA/SE version 15.1.

Results

Median birthweight was 884g (460-1600), median GA 26^{+3} weeks (23^{+0}-29^{+6}) and 52% were female. 7 infants developed NEC. There was a wide variation in normal ranges of all 4 gut biomarkers and none were affected by confounders. L-FABP had significantly lower values in 28-29w compared to 23w (p=0.01), others were not affected by GA, but for all biomarkers chronological age was important. Cerebral TOI was significantly higher than sTOI over the first 8 weeks of life (p<0.0001). There were no statistically significant differences in any biomarker level between those with, and without NEC (all p>0.05), but there were significant differences in NIRS measurements (Table 1) and these persisted when adjusted for confounders (GA, gender, PDA, enteral feeds, ethnicity and Hb).

NIRS measurements	Non – NEC infants Mean (95% CI)	NEC infants Mean (95% CI)	Mean difference (95% CI)	P value
sTOI (%)	43.6 (41.2-46.0)	33.6 (27.3 – 39.9)	-9.3 (-18.0 to -0.50)	0.038
sFTOE	0.53 (0.50-0.56)	0.64 (0.56-0.71)	0.11 (0.01 to 0.20)	0.031
cTOI (%)	63.9 (62.2-65.5)	56.9 (53.2-60.6)	-6.6 (-11.7 to -1.5)	0.011
cFTOE	0.30 (0.28-0.32)	0.38 (0.33-0.43)	0.08 (0.02 to 0.14)	0.009

Conclusions

Gut biomarker levels in preterm infants demonstrate a wide variation in normal ranges and we did not identify any gut tissue biomarkers that could predict NEC. Infants who developed NEC had significantly lower sTOI and cTOI throughout their neonatal intensive care stay. Further research is needed to examine whether NIRS monitoring coupled with intervention can improve outcomes. Perhaps the future of NEC prediction is an algorithm using machine learning combining clinical, laboratory, and radiological features, as well as NIRS and biomarker information.

References *(include acknowledgement here if appropriate)*

1) Costoloe, K., et al., *Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2996 (EPICure studies).* BMJ, 2012. **345**: p. e7976. 2) Costoloe, K., et al., *Probiotics in Preterm Infants Study Collaborative G. Bifidobacterium, breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial.* Lancet, 2016. **387**: p. 649-660.

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

BLOOD TRANSFUSION CAUSES MORE PROFOUND CHANGES IN SPLANCHNIC OXYGENATION COMPARED WITH BRAIN

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

Ceri Murphy[1,2], Jayanta Banerjee[3,4], Terence Leung[5], Narendra Aladangady[1,2]

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Introduction *(include hypothesis)*

Blood transfusion (BT) improves cerebral[1] and gut[2] tissue perfusion in preterm infants. Retrospective and cohort observational studies have indicated that pre-existing anaemia as well as BT may lead to necrotising enterocolitis.[3] The objective of this study was to measure the relative changes in cerebral and splanchnic tissue oxygenation following blood transfusion using Near Infra-Red Spectroscopy (NIRS) in preterm infants.

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

Preterm infants with clinical indication for BT were studied; pre-existing Grade 3 or 4 IVH or gut abnormality were excluded. Infants were recruited to three postnatal age groups: 1-7 (group 1); 8-28 (group 2) and ≥29 days of life (group 3). Simultaneous cerebral and gut tissue oxygenation index (TOI) and fractional tissue oxygen extraction (FTOE) were measured using NIRS 15 minutes before, during and 15 minutes post-BT. Descriptive analysis and t-tests were performed using SPSS 22.0. Ethical approval and parental consent were obtained.

Results

A total of 59 preterm infants receiving transfusion were recruited to the three postnatal age groups: Group 1; n=20, Group 2; n=21 and Group 3; n=18. The median (range) gestational ages were 26 (23 - 27), 25 (23 - 30) and 26 (24 - 34) weeks and birth weight 763 (600 - 1180), 740 (600 - 1240) and 793 (520 - 1746) grams for the respective postnatal age groups. The cerebral TOI increased significantly ($p<0.05$) by 5%, 11% and 12% following blood transfusion in Group 1, Group 2 and Group 3 respectively; whilst splanchnic TOI increased significantly ($p<0.05$) by 42%, 29% and 30% in those postnatal age groups respectively. Both the cerebral and splanchnic FTOE decreased after blood transfusion in all groups but more so in the splanchnic tissue. On multivariate analysis, changes in TOI following blood transfusion were not associated with PDA, feeding and pretransfusion Hb.

Conclusions

The results indicate that the improvement of splanchnic tissue oxygenation following transfusion was more pronounced compared to cerebral oxygenation. This could be an adaptive mechanism of reduced splanchnic tissue perfusion in response to anaemia and sparing of brain perfusion.

References *(include acknowledgement here if appropriate)*

(1)Banerjee J, Leung T and Aladangady N. Early Hum Dev, 2016; (2)Banerjee J, Leung T, and Aladangady N.Vox Sang, 2016. & (3)Patel R.M., et al. JAMA, 2016.

Check box if presenting author is a trainee: basic science trainee clinical trainee Y

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: Y

Senior author supporting presentation on day of meeting: Professor Narendra Aladangady

Remote ischaemic conditioning as a novel therapeutic intervention for experimental NEC

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)*

Necrotising enterocolitis (NEC) continues to be a cause of significant morbidity and mortality in preterm infants. Novel therapeutic or preventive interventions are desperately needed. We hypothesised that remote ischaemic conditioning (RIC) may be a useful therapeutic intervention for infants with NEC and aimed to evaluate the efficacy of RIC in an experimental NEC model based on intestinal ischaemia reperfusion injury (IRI).

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

With ethical approval (PA813F125), rat pups (10-13 days old) were anesthetised and underwent laparotomy with occlusion of the superior mesenteric artery (SMA) for 40 minutes followed by 90 minutes of reperfusion. RIC was applied by occluding hind limb blood flow for 3 cycles of 5 minutes immediately prior to anaesthesia. Control animals underwent laparotomy and exposure of the SMA without occlusion. Intestinal injury was assessed macroscopically, and microscopically using the Chui-Park scoring system (range 0-8).

Results

Intestine of control animals (n=10) was macroscopically normal. The length of intestine that showed any injury was significantly reduced in animals exposed to RIC prior to IRI (n=13) compared to those who had IRI alone with no RIC (n=14, median 100% [range 0-100] vs 49% [0-100]; p=0.008). The length of intestine with severe necrosis was also shorter in animals exposed to RIC (RIC+IRI 0% (0-55%) vs IRI 40% (0-100%); p=0.002)

Blinded microscopic assessment of intestine demonstrated a significantly reduced injury score in the RIC+IRI group compared to IRI alone. Median score 4 [range 0-6] vs 6 [4-7] (p=0.0013).

Conclusions

In this animal model of NEC, RIC shows a significant protective effect against both the extent and the severity of intestinal injury. RIC should be explored as a potential treatment option for human NEC.

References *(include acknowledgement here if appropriate)*

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☐

Senior author supporting presentation on day of meeting: Nigel Hall

END-TIDAL CARBON DIOXIDE ($EtCO_2$) LEVELS DURING RESUSCITATION AND CO_2 LEVELS IN THE IMMEDIATE NEONATAL PERIOD AND SUBSEQUENT CEREBRAL INJURY

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

E. Williams[1], K. Tamura[1], T. Dassios[2], A. Pahuja[1], K. Hunt[1], V. Murthy[1], P. Bhat[1], R. Bhat[2], A. Milner[1], A. Greenough[1]

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Institution(s)

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Introduction *(include hypothesis)*

Abnormal carbon dioxide (CO_2) levels within the neonatal period are associated with intraventricular haemorrhage (IVH) development in prematurely born infants. The aim of this study was to establish whether CO_2 levels in the first 72 hours post-delivery reflected abnormal levels during resuscitation and hence a prolonged rather than initial insult results in cerebral damage. Furthermore, we determined if those infants exposed to the largest fluctuations in $EtCO_2$ levels during resuscitation would be at greater risk of developing

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

A retrospective study of infants born at less than 33 weeks of gestational age who required resuscitation in the delivery suite was performed. Resuscitation recordings were analysed and the highest and lowest levels of end tidal CO_2 ($EtCO_2$) alongside the degree of fluctuation of $EtCO_2$ (delta $EtCO_2$) were calculated. Blood gases performed in the first three days after birth were analysed and the maximum, minimum and degree of fluctuation in CO_2 levels were calculated. IVH were diagnosed by cranial ultrasound examinations. Ethical approval was given by the Outer London Ethics Committee and registered with the trust research and audit

Results

Fifty eight infants were included with a median gestational age of 27.3 (24.9-29.0) weeks and a birthweight of 0.9 (0.72-1.21) kg. Thirteen infants developed a grade 3-4 (severe) IVH. The highest $EtCO_2$ during resuscitation in the no/non-severe IVH group was 8.2 (7.4-9.9) kPa and 10.2 (8.6-11.1) kPa in the severe group, which remained significant after correcting for differences in gestational age between the two groups ($p=0.037$). There were no strong correlations seen between delivery suite levels of $EtCO_2$ and CO_2 levels on the neonatal unit in the first 72 hours. The delta $EtCO_2$ during resuscitation was significantly different between infants with any grade IVH (6.2 (5.4-7.5) kPa) and those with no IVH (3.8 (2.7-4.3) kPa; $p<0.001$). Delta $EtCO_2$ levels during resuscitation gave an area under the receiver operator characteristic curve of 0.940 for prediction of IVH.

Conclusions

These results emphasize the importance of monitoring $EtCO_2$ levels of prematurely born infants in the delivery suite, as large fluctuations during resuscitation are highly predictive of subsequent IVH development.

References *(include acknowledgement here if appropriate)*

Pahuja A, Hunt K, Murthy V, Bhat P, Bhat R, Milner AD, Greenough A (2018) Relationship of resuscitation, respiratory function monitoring data and outcomes in preterm infants. Eur J Pediatr 177:1617-1624

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Anthony Milner

THE EFFECT OF PRESSURE RISE TIME ON VENTILATOR PARAMETERS AND GAS EXCHANGE DURING TIME-CYCLED AND FLOW-CYCLED NEONATAL VENTILATION

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

David Chong[1,2] Sabrina Kayser[1] , Eniko Szakmar MD[1,3], Colin J Morley MD, FRCPCH[1] & Gusztav Belteki MD, PhD, FRCPCH[1]

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Introduction *(include hypothesis)*

Pressure rise time (PRT), also known as slope time can be set on some modern neonatal ventilators. On other ventilators, PRT is determined by circuit flow implicitly. Changing slope time is thought to affect mean airway pressure, oxygenation and carbon dioxide elimination. We hypothesized that while changing the PRT may affect some ventilator parameters, it does not affect delivery of the target tidal volume and gas exchange.

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

In a cross-over study, 12 infants weighing <2 kg were ventilated with synchronized intermittent positive pressure ventilation with volume guarantee (SIPPV-VG) and pressure support ventilation with volume guarantee (PSV-VG). During both modes PRTs ranging between 0.08 and 0.40 seconds were used in 15-minute epochs. Data from the ventilator and from patient monitors were downloaded with 1 Hz sampling rate and analysed using the Python computer language. Ethical approval and informed consent was obtained. The study was funded by Evelyn Trust.

Results

All participants completed the study without adverse events. During PSV-VG, a shorter PRT was associated with higher flow rate in the ventilator circuit ($p=0.003$); this was not seen during SIPPV-VG. During PSV-VG, a longer PRT was associated with longer inspiratory time ($p<0.0001$) and with lower PIP ($p=0.003$), but the MAP was not different. During SIPPV-VG the PIP was not significantly different in case of different PRTs; however, MAP was lower with a of longer PRT ($p=0.001$). In case of a short PRT (0.08 sec), the PIP was higher during PSV-VG than during SIPPV-VG (19.8 mbar versus 16.5 mbar, $p=0.042$). There was no significant difference in delivery of the targeted tidal volume, in respiratory rate or in minute volume among the epochs using different PRTs. Oxygen saturations (SpO_2) increased slightly with increasing PRT but this was not significant ($p=0.092$). Similarly, there was no signifcant difference in end-tidal CO_2 levels with any PRTs in any of the two modes.

Conclusions

During SIPPV-VG or PSV-VG, using short or long PRTs affects some ventilation parameters but does not significantly change oxygenation or carbon dioxide elimination.

References *(include acknowledgement here if appropriate)*

Bach KP, Kuschel CA, Oliver MH, Bloomfield FH. Ventilator gas flow rates affect inspiratory time and ventilator efficiency index in term lambs. *Neonatology*. 2009; 96(4):259-64.

Check box if presenting author is a trainee: basic science trainee ☐ **clinical trainee** ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

INCIDENTAL FINDINGS ON BRAIN MR IMAGING IN LOW RISK TERM NEONATES IN THE DEVELOPING HUMAN CONNECTOME PROJECT

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)*

Interpretation of incidental image findings on MRI imaging of the Term neonatal brain can be challenging as there is a lack of published normative data on low risk term neonates. The purpose of this study was to determine the prevalence of incidental findings in a large group of normal term infants participating in the Developing Human Connectome project (dHCP) with normal neurodevelopmental outcomes at 18 months.

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

We conducted a retrospective review of the MRI brain image findings in a large cohort of term neonates (n=500; 279M:221F; GA 37+1 - 42+2w)
The MR brain imaging was reviewed by 2 Neuroradiologists and consensus was reached on all reported imaging abnormalities. We also reviewed the results of the Neurodevelopmental assessments (Bayley Scales of Infant and Toddler Development - Bayley III) performed at 18 months as part of the study. No statistical hypothesis was tested.

Results

The main incidental findings included intracranial haemorrhage (23.4%), punctate white matter lesions (PWMLs) (12.4%) and caudothalamic subependymal cysts (9.6%). Subdural haemorrhage was the most common type of intracranial haemorrhage (21.6%). Subdural haemorrhage and PWMLs were more common in ventouse-assisted deliveries compared with Caesarean section deliveries (57% vs 2% and 24% vs 6%, respectively). Acute infarcts were noted in 5 infants (1%). Other incidental findings included mild ventricular dilatation (2%), arachnoid cysts (0.6%) and Developmental venous anomalies (0.8%). The results of the Bayley Scales of Infant and Toddler Development (Bayley III) were: Cognitive score, Mean 99.88 (SD 10.8); Language score: 96.3 (15.2); and Motor score, 101.8 (9.3). Overall 97% of the newborns scored greater than 2SD below the mean.

Conclusions

This study describes the prevalence of incidental findings on MRI brain imaging in a large group of low risk term newborns with normal outcomes. These results can serve as a future reference for the interpretation of incidental findings in clinical and research term neonatal brain MR imaging.

References *(include acknowledgement here if appropriate)*

http://www.developingconnectome.org

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Dr Olivia Carney

CLASSICAL NEUROPATHOLOGY SHOWS HYPOTHERMIC NEUROPROTECTION IN SEVEN DAY OLD RATS AFTER A MILD A HYPOXIC ISCHEMIC INSULT

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

Julia K. Gundersen[1], Else Marit Løberg[1,2], Damjan Osredkar[1], Mari Falck[1], Thomas R Wood[1], Lars Walløe[1], Marianne Thoresen[1,3]

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1. Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway 2. Department of Pathology, Oslo University Hospital, Ullevål, University of Oslo, Oslo, Norway 3.Translational Health Sciences, St. Michael's Hospital, University of Bristol, Bristol, UK

Introduction *(include hypothesis)*

It is unknown whether infants with mild hypoxic ischaemic encephalopathy (HIE) benefit from therapeutic hypothermia (TH), hence we examined this in a mild (50min 8%O2@36°C) rat model of neonatal brain injury. Previously, we demonstrated 30% neuroprotection from TH after a moderate insult (90min 8%O2@36°C). TH was not neuroprotective after a severe HI insult (150min 8%O2@37°C). We aimed to examine, which analysis method, computerized area loss calculations or classical neuropathology scoring, most reliably quantified mild injury.

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

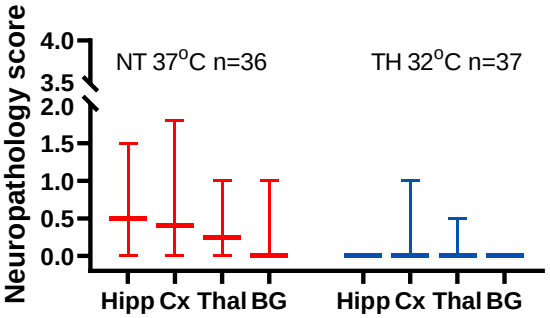
7 day-old rats (n=73) underwent left carotid artery ligation followed by 50min of hypoxia (8%O2@36°C). Pups were randomised to 5h NT 37°C (n=36) or 5h TH 32°C (n=37) followed by 1 week survival. Haematoxylin-Eosin stained slides from 2 sections per animal were assessed for injury using both; 1) ImageJ software calculated percent global area loss in the ligated hemisphere relative to the unligated hemisphere, 2) regional neuropathology scoring from 0.0-4.0 (0.5 increments) of the hippocampus, cortex, thalamus and basal ganglia. The average of all regions was calculated as the global pathology. The non-parametric Wilcoxon-van-Elteren test was used.

Results

ImageJ analysis of global (%) area loss did not show significant differences between treatments: (median, 95% CI) 5h NT 8.4% (4.9-17.9) and 5h TH 5.8% (3.7-9.2), p=0.09, two-sided testing.

Fig. 1 shows the distribution in pathology score in the 4 brain regions (median, 95% CI) in both treatment groups.

TH showed significant neuroprotective effect on global neuropathology (median, 95% CI): NT 0.4 (0.0-1.06) and TH 0.0 (0.0-0.56), p=0.04.



Conclusions

By assessing the brain sections with classical neuropathology scoring, we demonstrated global neuroprotection by TH after a mild (~10%) HI insult. In experiments with mild insults, a sensitive method of identifying injury is required to more accurately demonstrate group differences. Our experimental findings support the hypothesis that immediate TH is beneficial after mild neonatal hypoxic-ischaemic brain injury.

References *(include acknowledgement here if appropriate)*

Thoresen M et al Arch Dis Child Fetal Neonatal Ed. 1996;74(1):F3-9. Bona E et al Pediatr Res. 1998;43(6):738-45. Sabir H et al Stroke. 2012;43(12):3364-70.

Check box if presenting author is a trainee: basic science trainee (medical stud) ☒ clinical trainee ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Marianne Thoresen

Title (Upper case)

CHANGING CLINICAL CHARACTERISTICS OF INFANTS TREATED WITH THERAPEUTIC HYPOTHERMIA FOR HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN ENGLAND, WALES AND SCOTLAND

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

[1]Lory Hage, [1]Dusha Jeyakumaran, [1]Cheryl Battersby, [2]Jon Dorling, [3]Shalini Ojha, [3]Don Sharkey, [1]Neena Modi, [1]Nick Longford and [1]Christopher Gale

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Institution(s)

[1] Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London; [2] IWK Health Centre, Halifax, Nova Scotia, Canada; [3]School of Medicine, University of Nottingham.

Introduction *(include hypothesis)*

Hypoxic ischaemic encephalopathy (HIE) is a leading cause of long-term disability. Standard of care for moderate to severe HIE is therapeutic hypothermia. Therapeutic hypothermia is increasingly used in infants with mild HIE in other parts of the world, despite limited evidence of benefit in mild HIE. Receipt of therapeutic hypothermia is used for surveillance purposes as an indicator of brain injury in the UK[1], therefore any change in the population receiving this treatment has the potential to influence national surveillance programs. The aim of this study is to describe the clinical characteristics of babies diagnosed with HIE who received therapeutic hypothermia in the UK between 2010 to 2017. We tested the hypothesis that there has not been a change of the illness characteristics of babies receiving therapeutic hypothermia for HIE.

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

A retrospective, descriptive, study using deidentified, routinely recorded clinical data held in the National Neonatal Research Database (NNRD). Infants born between 1st January 2010 and 31st December 2017 admitted into a neonatal unit in England, Scotland and Wales, were eligible for inclusion in the study if; (i) they had a recorded gestational age of ≥36^{+0} weeks^{+days} at birth, (ii) were recorded as having received therapeutic hypothermia for 3 days or died during therapeutic hypothermia and (iii) had a diagnosis of HIE as "primary clinical reason for admission" or "principal diagnosis at discharge". Clinical characteristics to describe severity of hypoxia ischaemia were selected *a-priori:* condition at birth, resuscitation characteristics, and condition at admission in the neonatal unit. Continuous variables were analysed using a linear regression analysis and Spearman's rank correlation to eliminate the normality assumption. Ordinal variables were tested using Spearman's rank correlation and binary data was assessed with a Chi-squared test for trend. Research Ethics Committee approval was obtained (17/EM/0307).

Results

In the study period 6031 babies received therapeutic hypothermia for 3 consecutive days or died during cooling, of which 5201 had a diagnosis of HIE. The number of babies diagnosed for HIE who have received therapeutic hypothermia increased from 2010 to 2017. The clinical characteristics of the babies treated for HIE changed over the study period with a decreasing proportion of infants with clinical characteristics of severe hypoxia. These trends were statistically significant and consistent across multiple markers of severity (Figure 1 and 2).

Conclusions

Over the study period, more infants with less severe clinical markers of hypoxia were treated with therapeutic hypothermia for HIE in the UK. Study strengths include population coverage, limitations include missing data and variation in data entry between medical professionals for data items such as seizures. These data highlight the need to investigate the benefit of therapeutic hypothermia in mild HIE and its use as a marker for brain

References *(include acknowledgement here if appropriate)*

1. Gale, C et al. Neonatal brain injuries in England: population-based incidence derived from routinely recorded clinical data held in the National Neonatal Research Database. *ADCFN* 103,4 (2018): F301-F306.

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

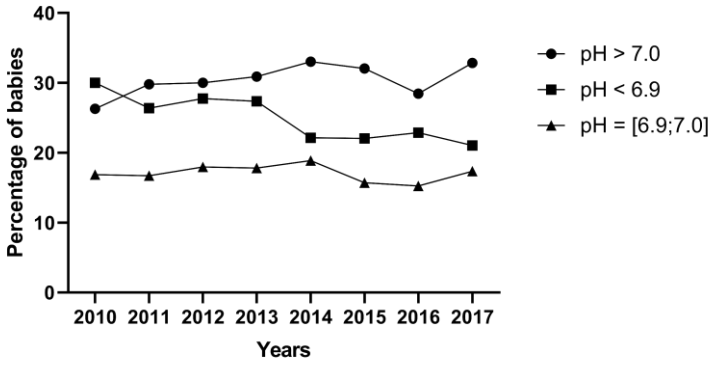

Figure 1. **Line charts of the umbilical cord pH at birth from 2010 to 2017.** The pH values were categorized; over 7.0 (>7.0), between 6.9 and 7.0 ([6.9;7.0]) and under 6.9 (<6.9). Statistical significance of the pH of babies from 2010 to 2017 (linear regression analysis p=0.0003 and Spearman correlation test p≤0.0001).

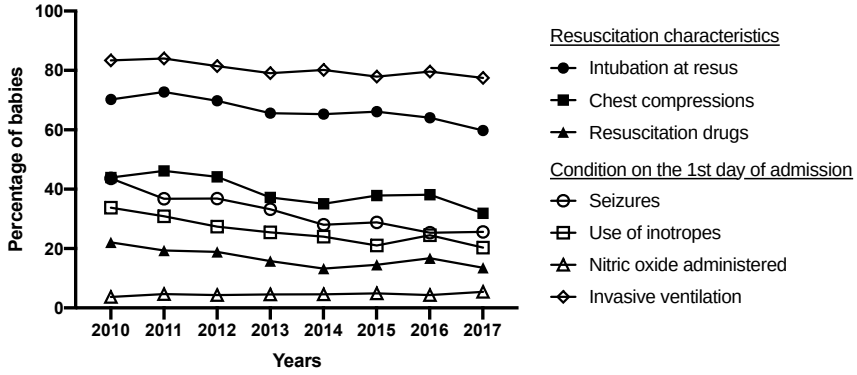

Figure 2. **Line chart of the percentage of resuscitation characteristics and the condition on the first day of admission of babies from 2010 to 2017.** Statistical significance for the three resuscitation interventions (chi-squared test for trend p≤0.0001). Significant difference in the proportion of babies where seizures, inotropes and invasive ventilation were recorded (chi-squared test for trend p≤0.0001, p≤0.0001 and p=0.0016, respectively).

THE DEVELOPING HUMAN CONNECTOME PROJECT: NORMAL AND DISRUPTED FUNCTIONAL CONNECTIVITY ACROSS THE PERINATAL PERIOD

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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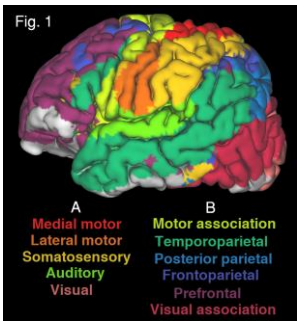
Introduction *(include hypothesis)*

The Developing Human Connectome Project (dHCP) represents the largest open source sample of neonatal functional MRI (fMRI) data ever collected. Using fMRI data collected at rest, the intrinsic functional connectivity of spatially distributed brain regions can be captured as distinct resting-state networks (RSNs). We hypothesised that (i) RSNs undergo active maturation from 37 to 43.5 weeks of postmenstrual age (PMA); and (ii) preterm birth is associated with reduced functional connectivity at normal term age.

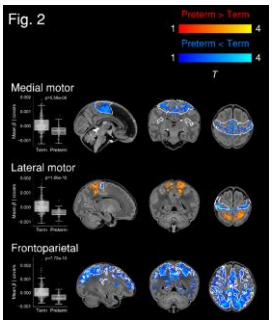
Methods (*include source of funding and ethical approval if required)*

Fifteen minutes of fMRI optimized for neonates was acquired in natural sleep. We first defined normative RSNs in 24 term-born infants scanned at 43.5-44.5 weeks PMA, using probabilistic independent component analysis. We then regressed data from 248 term-born and 65 preterm-born infants scanned at 37-43.5 weeks PMA against these normative networks to test for the effects of age, sex and preterm birth, using dual regression, general linear models and permutation testing. Family-wise error-rate corrected p values < 0.025 were regarded as significant. dHCP was approved by the UK National Research Ethics Authority (14/LO/1160). [Funding below]

Results



Five RSNs encompassing primary cortical areas (Fig. 1A) and six association RSNs (Fig. 1B) were identified. Primary RSNs showed adult-like topology at all ages, while four association RSNs showed areas of increasing functional connectivity with older PMA at scan. Female infants showed increased inferotemporal connectivity within the visual association network. Preterm birth was associated with strikingly reduced functional connectivity across all RSNs studied; conversely, connectivity of the superior parietal lobules within the lateral motor network was increased in



Conclusions

We observed a primary-to-higher-order sequence of brain maturation. Preterm birth was associated with widespread impairments in functional connectivity and aberrant parieto-motor connectivity, with possible implications for understanding developmental coordination disorder and related problems in preterm children.

References *(include acknowledgement here if appropriate)*

dHCP is funded by the European Research Council. Dr Eyre was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust / KCL.

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Dr Tomoki Arichi

EYE-TRACKING FOR LONGITUDINAL ASSESSMENT OF SOCIAL COGNITION IN CHILDREN BORN PRETERM

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)*

Preterm birth is associated with atypical social cognition in infancy[1], and with social difficulties and cognitive impairment in childhood[2]. Socioeconomic deprivation is also known to impact child social development[3]. The stability of an individual's social cognition through childhood and its relationship with neurodevelopment are unknown. We used eye-tracking to investigate social attention over time in preterm and term-born infants, its relationship with standardised tests of neurodevelopment, and the modulating role of socioeconomic deprivation.

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

81 preterm and 66 term infants, with mean (range) gestational age at birth 28^{+5} (23^{+2}-33^{+0}) and 40^{+0} (37^{+0}-42^{+1}) respectively, completed eye-tracking in infancy, with a subset reassessed at 5 years. 3 free-viewing tasks presented social stimuli of increasing complexity. We measured fixation duration to areas of social interest and calculated a social preference score. We collected socioeconomic data and performed neurodevelopmental assessments at 2 and 5 years. We had NRES and NHS R&D approval and received funding from Theirworld. We used t-tests for group comparisons and assessed relationships using correlations and hierachical modelling.

Results

Preterm infants had lower social attentional preference in infancy compared to infants born at term (0.32 vs 0.39, p=0.02). Term infants' social preference scores were stable between the two time points (0.43 vs 0.45, p=0.73), whereas preterm infants showed a significant increase over time (0.29 vs 0.43, p<0.005), reaching equivalent social preference scores to term controls by 5 years. In whole sample multivariate analyses, low gestational age and socioeconomic deprivation were associated with reduced social attention in infancy ($r_s(135)=0.20$, p=0.02 and $r_s(135)=0.21$, p=0.01), explaining a modest but significant proportion of the variance in hierarchical models.

The preterm infants scored lower in neurodevelopmental assessments at 5 years of age (Mullen Early Learning Composite 93 vs 104, p=0.003), particularly in language domains. Social attentional preference in infancy did not correlate with performance on standardised tests of neurodevelopment at 2 or 5 years.

Conclusions

Preterm infants have reduced social attentional preference in infancy compared to term-born controls, but catch up by 5 years. This is influenced by socioeconomic deprivation and gestational age. Further work is required to determine the role of infant social cognition in the ontogeny of cognitive impairment seen in preterm infants.

References *(include acknowledgement here if appropriate)*

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Check box if presenting author is a trainee: basic science trainee ☐ **clinical trainee** ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Professor James Boardman

Neonatal brain volume in twins with discordant birthweight – MRI findings from a multicentre prospective cohort study

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)*

Discordant birthweight in twins has been associated with poorer neurological outcomes. However, the cause of underlying neuromorbidity in growth discordant twins is unknown (1,2). Studies looking at head size in infancy showed that a smaller head circumference is associated with poorer neurological outcomes. Therefore, the aim of this study was to assess the association between birthweight discordance and brain volume.

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

This was a multicentre prospective cohort study over a two-year period. Participants underwent a neonatal MRI scan at term corrected gestational age. A 3T scanner was used to acquire T1 weighed scan images, which were processed and volumetric data extracted. Outcome measures were: absolute brain volume (cm^3) and relative intertwin brain volume discordance (%). Regression analyses were performed to assess the relationship between outcome measures and relative intertwin birthweight discordance (%).

Results

After adjusting for various confounders (including gestational age, birthweight and gender), there was strong evidence that increased birthweight discordance was associated with a reduction in absolute brain volume in: monochorionic twins (p 0.007), gender concordant dichorionic twins (p <0.001) and gender discordant dichorionic twins (p 0.010).

There was also strong evidence that increased birthweight discordance was associated with increased brain volume discordance in: monochorionic twins (p 0.028), gender concordant dichorionic twins (p 0.002) and gender discordant twins (p 0.020).

Conclusions

This is the first study to investigate the association of birthweight discordance with brain volume in twins. Our findings indicate that an increase in birthweight discordance is associated with a reduction in brain tissue volume and an increase in intertwin relative brain volume discordance.

References *(include acknowledgement here if appropriate)*

1. Adegbite, A. et al. Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. *AJOG* (2004). 2. Harper, L. M. *et al.* Significance of growth discordance in appropriately grown twins. *AJOG* (2013)

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Dr Karen Luyt

NEONATAL T CELLS ACQUIRE BOTH PRO-INFLAMMATORY AND TOLERANT PHENOTYPES IN FIRST THREE WEEKS OF LIFE

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

Gergely Toldi[1,2], Hannah Wood[1,2], Richard Powell[2], Paul Moss[2], Andrew Ewer[1,3]

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Institution(s)

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2 – Institute of Immunology and Immunotherapy, University of Birmingham
3 – Institute of Metabolism and Systems Research, University of Birmingham

Introduction *(include hypothesis)*

The neonatal immune system needs to rapidly adapt to environmental changes following delivery in order to fight pathogens and tolerate harmless antigens. The precise kinetics of these changes and the key cellular and soluble components of the immune system remain to be elucidated. We aimed to describe changes in the immune phenotype of neonates in the first 3 weeks of life following delivery.

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

We collected cord blood samples from 19 healthy, term neonates delivered by elective Caesarean sections. A pre-delivery maternal peripheral blood sample was also obtained. The neonates were re-sampled for peripheral blood at 3 weeks of age. Mononuclear cells were isolated from these samples and were measured on 2 flow cytometry panels consisting of a total of 20 intracellular and cell surface markers.

Results

The proportion of IL-8-producing CD4 and CD8 cells was lower in maternal compared to neonatal samples. Intracellular IL-17 production of CD4 and CD8 cells increased by 3 weeks of age compared to cord blood. The proportion of Tregs (CD4+ CD25high FoxP3+) increased by 3 weeks compared to cord blood, but remained lower in comparison to maternal samples. The proportion and cytotoxic activity (CD107a+) of CD8 cells, as well as the proportion of IFN-gamma-producing CD4 and CD8 cells were lower in neonatal compared to maternal samples. The proportion of HLA-DR+ and CD69+ T cells was also lower in neonatal compared to maternal samples.

Conclusions

While neonatal T cells maintain an IL-8 phenotype during the first 3 weeks of life, they also acquire an IL-17 phenotype, possibly contributing to their ability to fight infection. On the other hand, the proportion of Tregs also increase by 3 weeks of age, playing an important role in establishing tolerance towards harmless environmental antigens.

References *(include acknowledgement here if appropriate)*

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Andrew Ewer

BREAST-FED NEONATES SHOW INCREASED IMMUNE TOLERANCE AGAINST MATERNAL ANTIGENS

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

Hannah Wood[1,2], Richard Powell[2], Andrew Ewer[1,3], Paul Moss[2], Gergely Toldi[1,2]

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Institution(s)

1 – Department of Neonatology, Birmingham Women's and Children's NHS FT
2 – Institute of Immunology and Immunotherapy, University of Birmingham
3 – Institute of Metabolism and Systems Research, University of Birmingham

Introduction *(include hypothesis)*

In order to accommodate the developing fetus, a unique symbiosis must be maintained between the maternal and fetal immune systems during pregnancy. Therefore, the maternal immune system is known to be in a suppressed state during pregnancy. We hypothesized that immune suppression in pregnancy may be extended to the neonatal immune system in a bidirectional manner. Our study investigates the interaction of the maternal and neonatal immunological systems by analysing T cell responsiveness in the early postnatal period.

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

We collected cord blood (CB) samples from 37 healthy, term neonates delivered by elective Caesarean sections. A pre-delivery maternal peripheral blood sample was also obtained. All neonates were re-sampled for peripheral blood during a home visit at 3 weeks of age. T cells were isolated and mixed lymphocyte reactions (MLRs) were performed over 5 days (CB or neonatal responders versus maternal antigens and vice versa). In a subset of samples, MLRs were also studied following the depletion of CD25+ cells.

Results

Maternal T cells showed an increased response against neonatal antigens at 3 weeks compared to CB antigens. The neonatal T cell response against maternal antigens decreased by 3 weeks of age. However, this decrease was only observed in breast-fed (n=24), but not in exclusively formula-fed (n=13) infants. When CD25+ cells were depleted from the samples, an increase was observed in the response of maternal and neonatal T cells, but not that of CB T cells.

Conclusions

Although there was no evidence to support the original hypothesis of our study, we identified that breast-fed neonates show a decreased T cell response to maternal antigens at 3 weeks of age compared to birth. This decrease appears to be mediated by regulatory T cells and could be due to on-going antigen load via breastmilk and may reflect postnatal immune tolerance towards maternal antigens.

References *(include acknowledgement here if appropriate)*

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Gergely Toldi