September 23rd, 2023 08:00 - 09:00

POSTER WALK – BRAIN 6

ID 955. IMMUNOMODULATION WITH FINGOLIMOD IN NEONATAL HYPOXIC ISCHEMIA IN MICE

Doctor Isabella Schmeh[1,3], PhD Elena di Martino[1], PdD Shanie Saghafian–Hedengren[1], PhD Ulrika Åden[1,2]

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Background

Hypoxic–ischemic encephalopathy (HI) is a major cause of neonatal death and neurocognitive disability. Timing of inflammatory processes is important for neurocognitive outcomes. Treatment with Fingolimod, a sphingosine–1–phosphate receptor agonist with T–cell modulating effects, has been shown to be beneficial in adult models of ischemia–induced neurodegeneration (1) but did exacerbate brain injury in a neonatal model when it was administered directly after HI (2). The effects of delayed and long–term treatment in neonatal HI have not been studied yet.
We investigated the effects of 3 weeks Fingolimod treatment starting 3 or 5 days after induction of neonatal HI in mice.

Methods

We induced HI in term–equivalent 10 days old C57BL/6 mice by electrocoagulation of the left common carotid artery followed by exposure to 10% oxygen/90% nitrogen for 60 minutes at 36˚C +–1˚C. The mice received treatment with 1mg/kg Fingolimod or vehicle (NaCl 0.9%) intraperitoneally once a week starting 3 or 5 days after HI. The

control mice were sham operated. Motor skills were tested with Rotarod and beam walking after 3 injections. In a third group of mice we analysed T-cells in blood and brain 7 or 14 days after HI using flow cytometry.

Results

Weekly treatment with Fingolimod 1mg/kg i.p. led to a relative suppression of T-cells in blood and brain 7 and 14 days after HI (figure 1). The HI groups did not differ in body temperature or weight gain. Fingolimod treatment starting 3 or 5 days after HI did not affect motor skills measured with Rotarod.

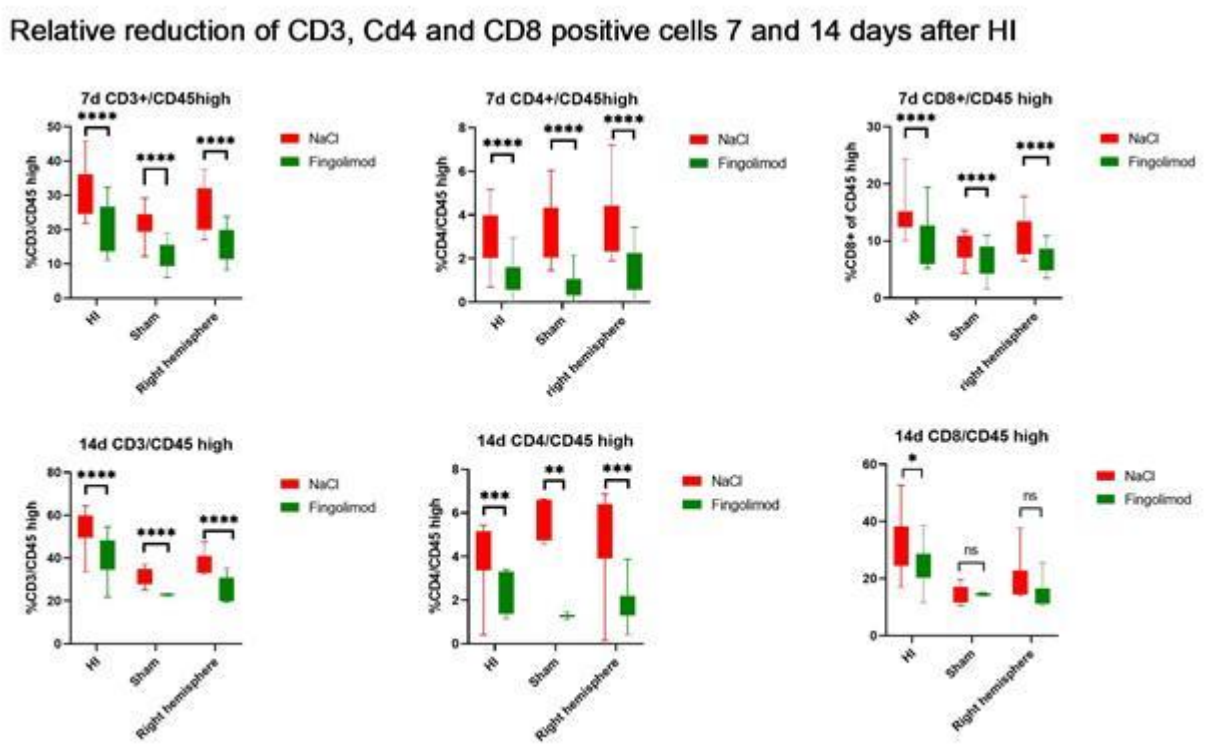
Conclusion

Weekly injection of Fingolimod is sufficient for relative T-cell suppression in blood and brain. Fingolimod treatment in our protocol did neither deteriorate nor optimize motor skills. The results of beam walk testing and morphology evaluation are pending.

References

1. Kraft P, et al. FTY720 ameliorates acute ischemic stroke in mice by reducing thrombo-inflammation but not by direct neuroprotection. Stroke. 2013 Nov;44(11):3202-10.

2. Herz J, et al. Peripheral T Cell Depletion by FTY720 Exacerbates Hypoxic-Ischemic Brain Injury in Neonatal Mice. Frontiers in immunology. 2018;9:1696.



Relative reduction of CD3, CD4 and CD8 positive cells 7 and 14 days after HI after Fingolimod treatment.

Relative reduction of CD3, CD4 and CD8 positive cells 7 and 14 days after HI after Fingolimod treatment.

none declared

ID 817. TESTING OF PROSOPAGNOSIA/ZOOAGNOSIA IN NEWBORN RABBITS: EFFECT OF PRENATAL HYPOXIA-ISCHEMIA USING CONDITIONING IN NEONATAL RABBITS

Dr. Zhongjie Shi[1], Ms. Nadiya Sharif[1], Dr. Kehuan Luo[1], **Professor Sidhartha Tan**[1]
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Background
Higher–animal models for testing cognitive function in the newborn period are sorely needed. Postnatal cerebral palsy–like motor deficits are seen in our rabbit model of prenatal hypoxia–ischemia (H–I). In humans, prenatal H–I often results in intellectual disability and cerebral palsy. An initial video suggested that a 3–week newborn rabbit recognized the human caretaker. We asked the following questions. 1) Is there difference between conditioned and unconditioned kits? 2) Do the kits recognize the human face? 3) Or the lab coat? 4) Do kits with normal motor outcome following prenatal H I manifest cognitive deficits?

Methods
For conditioning, a constant feeder wearing the same lab coat fed and played with the rabbit kits for 9 days prior to the cognitive test. Newborn kits were randomly assigned to the conditioning or unconditioned groups. Fetal H–I via uterine ischemia was induced at 79% or 92% term gestation in pregnant New Zealand White dams. Testing used a simple 6–arm radial maze. Three tests were conducted on postpartum day 22/23 or 29/30, to identify if the fetuses were able to recognize the original feeder from the bystander (Test 1) or the lab coat on bystander (Test 2). The confounding effect of olfactory detection was factored out by the use of masks of feeder/bystander (Test 3). To address the variability in maze–entry, time, and repeated–trial learning, we devised a weighted score for each test. Statistical

significance was determined by Fischer's Exact tests, paired and two-sample t-tests, and Bonferroni correction for multiple comparisons.

Results

Conditioning shows a highly significant effect on cognitive behavior. The rabbits seem to recognize the face of the feeder in Tests 1 and 2. There was no significant preference for the lab coat and the rabbits preferred the human face over the lab coat, confirmed by Test 3. There was no difference between H-I and Naïve groups.

Conclusions

Conditioned kits showed a preference for the human face without the lab coat. Postnatal rabbits with normal motor outcome also have a normal cognitive outcome following prenatal H-I. Testing human face recognition may be useful for testing prosopagnosia/zooagnosia tendencies in newborn animals.

None declared

ID 744. INTRACRANIAL HEMORRHAGES IN FULL-TERM NEWBORNS: RADIOLOGICAL AND CLINICAL RED FLAGS

Doctor Andrea Calandrino[1], Doctor Nicola Sarale[2], Doctor Irene Bonato[1,2], Doctor Carolina Montobbio[1,2], Doctor Gaia Cipresso[1,2], Doctor Francesco Vinci[1,2], Doctor Marcella Battaglini[1,2], Doctor Alessandro Parodi[1,2], Professor Andrea Rossi[3,4], Professor Luca Antonio Ramenghi[1,2]

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Introduction

Intracranial hemorrhage (ICH) is a pathological accumulation of blood within the cranial vault[1]. The perinatal and neonatal period is at high risk of occurrence of ICH. Among term newborns ICH usually presents with non-specific neurological signs, involves mostly the posterior fossa (PCF) but also the dural spaces and the brain parenchyma[2], [3].

Complications during labor and delivery remain the most relevant risk factors for ICH[4]. The use of Susceptibility Weighted Imaging (SWI) MRI, introduced only in the very recent years, represents the most sensitive diagnostic technique[5].

Our aim is to find possible associations in a very large cohort of babies as SWI was pioneered introduced in the daily practice since 2012 at Gaslini Children's Hospital.

Materials and Methods

We enrolled children born at GA≥37w, showing neurological signs within 28 days of life who underwent brain SWI-MRI between 2012 and 2022 and were diagnosed an

ICH. In these subjects, we registered the site of hemorrhage, the total maturation score of the brain (TMS)[6], and we collected perinatal history.

Results

A total of 103 term newborns among 209 scanned for symptoms and 1200 total newborn were included. Median GA was 39w, BW 3274g ± 537g, APGAR 1'–8/ 5'–9, TMS 12. 78,6% were born by vaginal delivery (VD), 15,3% of which needed the use of vacuum. ICH was more frequently detected in VD in compared to the CSs (p=0,04). A subdural hemorrhage was detected in 54, subarachnoid in 7, subpial in 4, intraparenchymal in 25, IVH in 39, a PCF in 53. PCF (p=0,02) and subarachnoid (p=0,04) were most detected in case of vacuum. IVH was associated with serious neurological symptoms (p=0,04) and a lower TMS (p<0,001).

Conclusions

The most frequent form of ICH was subdural. Similarly to other studies, VD remained a significant risk factor for all ICHs. Vacuum was accompanied by an increased occurrence of PCF hemorrhages. IVH was the most frequent form among babies showing neurological symptoms. The association between IVH and a lower TMS with similar gestational age suggests that a more immature structures may favor this form, commonly due to choroid plexus bleeding at term of gestation.

None declared

ID 906. GREY MATTER HETEROTOPIAS IN THE NEWBORN: RELATIONSHIP WITH MEDICALLY ASSISTED PROCREATION AND CASE SERIES

Doctor Irene Bonato[1,2], Doctor Paolo Massirio[1,2], Doctor Marcella Battaglini[1,2], Doctor Samuele Caruggi[1,2], Doctor Chiara Andreato[1,2], Doctor Sara Uccella[3], Doctor Deborah Preiti[1], Doctor Domenico Tortora[4], Professor Andrea Rossi[4,5], Professor Luca Antonio Ramenghi[1,2]

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Introduction: Grey matter heterotopias (GMH) are characterized by interruption of normal neuronal
migration resulting in normal neurons in abnormal locations. The pathogenic mechanisms are unclear.
GMH has a wide spectrum of clinical presentations including epilepsy and mental delay, particularly when
associated with other brain dysmorphic features. The correlation between Assisted Reproductive
Technology (ART) and congenital defects is still unclear but an association between ART and
epigenetic defects appears plausible. In our knowledge there are no data between GMH and ART.

Methods: we retrospectively analyzed data about cerebral magnetic resonances (MRI) performed to our
center from 2013 to 2023. MRI data about presence of heterotopias or other brain malformations,
pregnancy characteristics, use of ART, birth weight, gestational age and neurological outcome were obtained

Results: The population included 1335 patient: 37 patients (2.8%) had GMH at MRI. 17 had prenatal
diagnosis of brain malformation, 9 had neurological symptoms or dysmorphism, 11 were incidental findings
in preterm babies. 26 (70%) had associated cerebral malformation while 11 patients had isolated GMH.
Clinical follow up was available for 21 patients: 6 (28%) had mental delay, 4 (19%) had epilepsy and mental
delay at last visit to our center (mean age 20 months, range 6 – 72 months); 9 of the 10 patients with
mental delay had GMH associated to others cerebral malformation. In our case series 5 patient had ART.
The incidence of GMH in patient that had ART was 2,5% while in patient without ART was 2.8% (p=0,8).

Conclusions: Most patients with GMH carried associated cerebral malformations (70%), with a high
incidence of mental delay. Only the 19% of the patients had epilepsy but the mean age of our
follow up was lower compared to other studies. ART do not seems related to GMH.
To our knowledge,

these are the first data concerning the effects of ART on GMH. We need larger populations to better
understand the outcome of patients with GMH particularly when isolated and in premature babies.

None declared

ID 615. MRI in neonates without sedation in a Neonatal Intensive Care unit (NICU)

A Quality improvement project

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Background and Aim

Successful MRI requires a settled infant to obtain good quality images which can be a major challenge in neonates. Therefore, sedation is often used which may cause potential side effects. Using an infant immobilizer, securely fastens around the infant to restrict movement to help obtain good quality image without sedation. MRI without sedation is not only safe but also facilitates early discharge.

The aim of this Quality Improvement Project (QIP) is to evaluate our experience of performing neonatal MRI without sedation by using the infant immobilizer.

Method

In Epoch 1, we retrospectively reviewed MRI performed in 100 infants admitted in NICU over a period of 4 year (2016 – 2019). Patients who received sedation and non-sedation (feed and wrap) method during MRI were analysed.

In Epoch 2, 66 infants were included and infant immobilizer device was introduced for MRI of infants over a 3 – year time period (2020 – 2022). Patients who received sedation and non-sedation (Infant immobilizer) method during MRI were analysed. Image quality was analysed as optimal (no movement artefact) and sub optimal (movement artefact) images.

Result

In epoch 1, 73 % optimal images were obtained with sedation. With the infant immobilizer, 81 % optimal images were obtained without sedation.

Conclusion

Optimal MRI images can be obtained by using infant immobilizer without sedation and avoid potential side effects of medication.

	Epoch 1	Epoch 2
Non-sedation	33 % (33)	97 % (64)
Sedation	64% (64)	3% (2)
Optimal Images	74% (74)	82 % (54)
Suboptimal Images	26% (26)	18 % (12)
Optimal images with sedation	73% (47)	100% (2)
Optimal images without sedation	57% (19)	81% (52)

Non declared

ID 661. Term-born infants with periventricular haemorrhagic infarction: risk factors, clinical presentation, and venous subtype

Miss Aleksandra Zaykova[1], Dr Jeroen Dudink[1], Dr Floris Groenendaal[1], Dr Maarten H Lequin[2], Prof. Dr Manon JNL Benders[1], Dr Maria Luisa Tataranno[1], Dr Elise Roze[1]
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Background: Periventricular Hemorrhagic Infarction (PVHI) is a rare occurrence in term-born infants, but a more common complication in preterm neonates. It can result in death and long-lasting neurodevelopmental disabilities, including cerebral palsy, cognitive and behavioral impairments. Despite its significance, the risk factors and symptoms associated with PVHI in term-born infants remain largely unidentified.

Methods: This research included infants (GA >36 weeks) admitted to the Wilhelmina Children's Hospital between 2010-2023, diagnosed with PVHI within the first four weeks after birth. We excluded infants with antenatal PVHI. Maternal and neonatal risk factors were gathered from electronic patient records, including pregnancy history, delivery mode, perinatal characteristics, presenting symptoms, coagulation, and genetic tests. The MRIs of the infants were also analyzed, and the PVHI cases were classified based on their venous subtype as seen on susceptibility-weighted images (Dudink et. al., 2018).

Results: A total of 22 infants with PVHI were included (15 males, 7 females, gestational age mean 39.6 wks (SD = 1.4), birthweight mean 3443 grams (SD = 671)). Pregnancy complications e.g., prolonged ruptured membranes, maternal fever, and infection occurred in 46% of the deliveries. Moreover, we identified several potential

neonatal risk factors: being male (68%), hypoglycemia was observed in 41%, thrombophilia with mutation of the genes MTHFR A1298C and MTHFR C677T was observed in 12 out of 13 tested (92%) Additionally, coagulation problems in the neonatal period, e.g., thrombocytopenia, elevated LP(a) and prolonged prothrombin time were observed in 27%. The mean presenting age was 4 days. Seizures were the most frequently presenting symptom (91%), followed by irritability (27%). The most common venous subtypes were caudate vein territory (55%) and partial terminal vein territory (23%), figure 1.

Conclusion: Risk factors for PVHI in term-born infants were pregnancy complications and genetic thrombophilia, however, not tested in all infants. Neonatal seizures around day 4 were the most common presenting symptom. The most frequently affected vein was the caudate vein. More research is needed to fully understand the pathophysiology of this type of brain injury in term infants, and the consequences on long-term outcome.

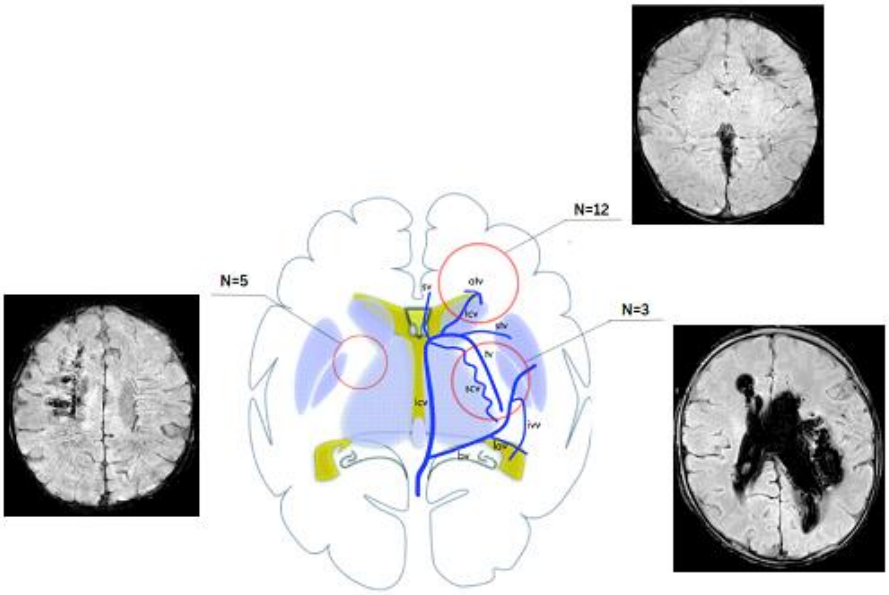

Figure 1. Venous subtype classification, (Left) Right partial terminal vein territory infarction, (Top right) Left caudate vein territory infarction, (Bottom right) Left complete terminal vein territory infarction

Figure 1. Venous subtype classification, (Left) Right partial terminal vein territory infarction, (Top right) Left caudate vein territory infarction, (Bottom right) Left complete terminal vein territory infarction

None declared

ID 936. POSTNATAL SERUM AMINO ACID PROFILES IN NEONATAL HYPOXIC ISCHAEMIC ENCEPHALOPATHY AND PREDICTION OF EARLY MRI FINDINGS

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Background:

We have previously reported alterations in multiple amino acid (AA) pathways, including the Kreb's cycle, tryptophan and pyrimidine pathways in cord blood in neonatal hypoxic–ischaemic encephalopathy (HIE). We wished to examine whether postnatal AAs could aid in the prediction of HIE grade, outcome or MRI findings in a prospectively recruited cohort of term infants with HIE.

Methods:

Term infants with perinatal asphyxia and subsequent evolving encephalopathy at birth were recruited to the MONITOR study (2017–2019). All infants had early Sarnat scoring and EEG monitoring. MRIs were performed on median day 5 of age (IQR 3–5) and scored independently by two reviewers (BW, MM) blinded to grade using the Barkovich scoring system. A subset of recruited infants had serum AAs profiled within 6 hours of delivery. Outcome was assessed using the Bayley's Scales of Infant Development (BSID–III) at 24 months. Only infants with AA analysis, early MRIs, and outcome at 24 months were included in this analysis.

Results:

Of the 62 recruited infants, 31 had complete data available for analysis; mean(SD) gestational age of the cohort was 38.8 (SD=1.66) weeks; (17 male, 14 female

infants) . HIE was graded as Mild(n=11), Moderate(n=16), Severe(n=4), Within this cohort, 52 amino acids were measured. On MRI review 13/31(42%) had abnormal MRIs. Four AAs (Pipecolic Acid (p=0.033), Beta Alanine (p=0.031), Cystine(p=0.004), Glycine (SIR) (p=0.022)) correlated with BSID–III cognitive composite score at 2 years. Four AAs (Carnosine (p=0.02), Homocysteine (p=0.01), Glutamine (p=0.028), Hydroxyproline (p=0.042)) were significantly altered in the group with abnormal MRIs ($p<0.05$) . A Logistic Regression model of 5 AAs had an excellent predictive ability with AUROC = 0.927(0.841–1.000, $p<0.001$, accuracy 83.9%, sensitivity 85% , specificity of 72%, for abnormal MRI findings.

Conclusion:
Multiple AAs involved in the Kreb's cycle, Tryptophan and Hypoxia–inducible Factor (HIF)–1 pathways are altered in the hours following birth in infants with neonatal HIE. AA profiling may aid in the prediction of abnormal MRI findings and later neurodevelopmental outcome.

None declared

ID 770. Normal placental histopathological findings following neonatal encephalopathy are likely to be associated with normal 2-yr neurodevelopmental outcomes

Doctor Olayinka Kowobari[1], Dr. Subhabrata Mitra[1], Dr. Nicola Robertson[1], Dr. Kelly Harvey-Jones[1], Dr. Leigh Dyet[4], Dr. Giles Kendall[4], Dr. Angela Huertas-Ceballos[4], Dr. Hannah Century[2], Dr. Priyal Taribagil[3], Dr. Kelly Pegoretti Baruteau[4], Dr. Vinita Verma[4], Dr. Kirti Gupta[4], Dr. Alan Bainbridge[5], Dr. Magdalena Sokolska[5], Prof. Neil Sebire[6], Dr. Ciaran Hutchinson[6], Dr. Hakim-Moulay Dehbi[7]

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Background:
Neonatal encephalopathy (NE) remains a significant cause of adverse neonatal outcomes. Basal Ganglia-thalamic (BGT) Lac/NAA ratio on MR Spectroscopy is an established MR biomarker of outcome following NE. Placenta histopathology (PH) is promising in evaluating perinatal hypoxic insult aetiology, including infections and inflammatory conditions.

The aim of this project was to review the association of PH findings following NE, monitoring outcomes using DGM Lac/NAA (a short-term biomarker of outcome) and neurodevelopmental outcomes at 2 years of age.

Method:
This retrospective review was part of a service improvement project. PH findings (data acquired from clinical reports) were evaluated in a cohort of 45 term neonates (corrected GA of 36-44 weeks) who underwent HT following moderate to severe NE and were scanned in a 3T MRI scanner within the first 2 weeks after birth. Conventional MR imaging was obtained along with 1H MRS using a single voxel positioned in the left thalamus-basal ganglia (BGT) region. MRS data were analysed using Tarquin. Metabolite ratios were calculated from the fitted data. As previously shown, BGT Lac/NAA cut-off of >=0.39 was used for predicting poor neurodevelopmental outcomes at 2 yrs. 2-year neurodevelopmental assessments were performed using BSID 3rd ed. A combined outcome of death or composite developmental score of less than 85 was marked as adverse outcome.

Results:
Four infants died in the neonatal period. 62% had abnormal PH findings, with a predominance of chorioamnionitis with or without funisitis (61%). All infants with normal PH findings had normal 2-year neurodevelopmental outcomes (Odd's ratio 2.5). The sensitivity of abnormal placenta histopathology for 2-year adverse outcome was 90%, specificity of 50%, a PPV of 45% and NPV of 92%. Inflammatory changes in placental histopathology had an odd's ratio of 2.4 for predicting adverse neurodevelopmental outcomes at 2 yrs.
No direct relationship was noted between abnormal placental histopathology and BGT Lac/NAA. 11% of Babies with abnormal PH had high Lac/NAA >0.39 (indicating poor outcome).

Conclusion:

Normal PH findings after NE was associated with normal 2 yr neurodevelopmental outcomes in this cohort. The presence of inflammatory changes in placental histopathology increased the risk of adverse outcomes following NE.

None declared.

ID 332. SPECTRUM OF TWO-YEAR NEURODEVELOPMENTAL OUTCOMES AFTER PERINATAL ASPHYXIA

Doctor Anna Tuiskula[1], Ms Susanna Stjerna[2], Ms Emma Saure[2], Dr Marjo Metsäranta[1], Dr Leena Haataja[3]

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Introduction

Neurodevelopmental outcome after moderate or severe hypoxic–ischemic encephalopathy (HIE) is well established, but less is known about the outcome profile after mild HIE or perinatal asphyxia (PA) without HIE. Our aim was to characterize neurological outcome and the spectrum of developmental findings after milder sequelae of PA at 24 months.

Methods

A prospective cohort of term infants with PA and a control group of healthy term infants were recruited from Helsinki University Hospital's neonatal units and maternity wards in 2016—2020. Neurodevelopment at 24 months was assessed using Hammersmith Infant Neurological Examination (HINE) and Bayley Scales III. Neurological outcome was defined normal if the global score of HINE was ⩾ 74. Developmental outcome was assessed using 6 subscores of Bayley III. Standard points of ⩽7 in individual subscores were considered as below average. Additionally, neurodevelopmental outcome of children with PA and healthy controls was compared in a subgroup analysis of monolingual children with highly educated parents and no family history of developmental problems.

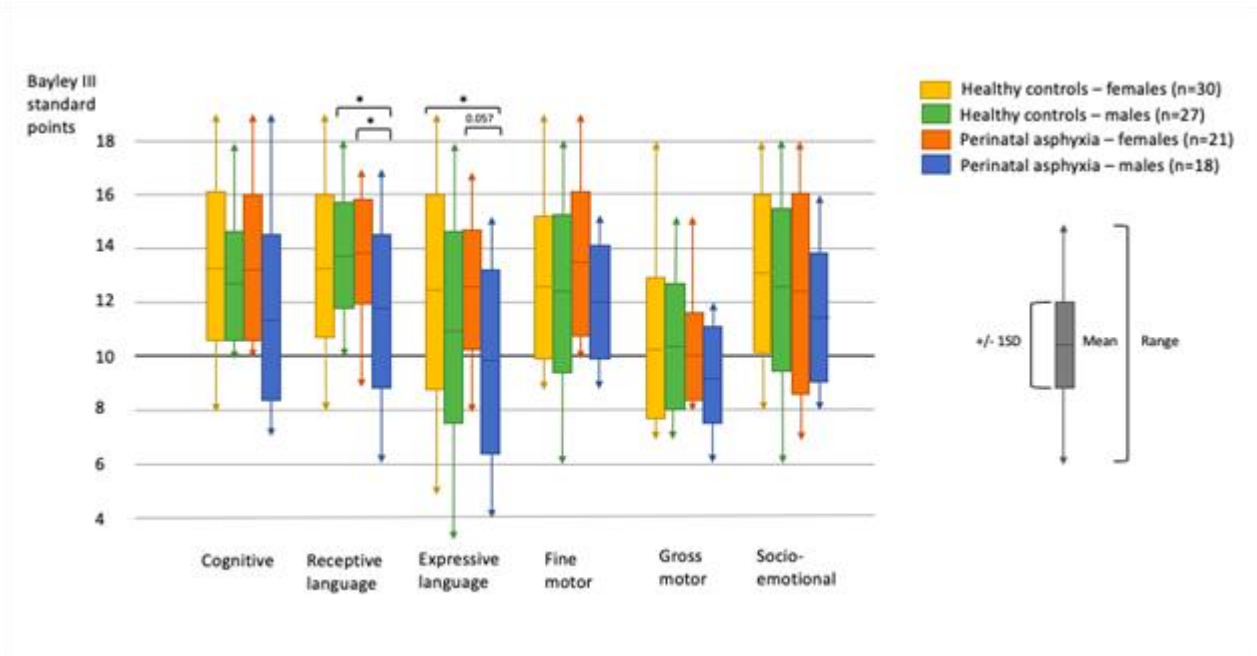
Results

Analysis included 96 infants: 24 displaying PA without HIE, 7 with HIE1, 8 with HIE2 and 57 healthy controls. All infants with PA had a normal neurological examination. In PA group 3 infants had moderately and 1 mildly below average expressive language score. 1 infant had mildly below average cognitive and receptive language scores. All these 5 infants were males. In control group 2 infants had moderately and 5 mildly below average expressive language score (4 females, 3 males).

In receptive language subscore there was a significant difference between male infants in the PA group and healthy male controls. When comparing scores of only monolingual infants with highly educated parents and no family history of developmental problems, infants with PA (n=16) had significantly lower cognitive and receptive language scores than healthy controls (n=25). This difference remained significant even after children with HIE diagnosis (n=7) were excluded.

Conclusion

In this cohort, most infants with PA, with or without HIE, presented with typical neurodevelopmental outcomes at two years. However, male children with PA had lower receptive language scores compared to healthy male controls.



Bayley III subscores (perinatal asphyxia n=39, healthy controls n=57). Asterisks indicate statistically significant differences (*<0.05). Statistical analysis was done using one–way ANOVA and post hoc multiple comparisons.

Bayley III subscores (perinatal asphyxia n=39, healthy controls n=57). Asterisks indicate statistically significant differences (*<0.05). Statistical analysis was done using one–way ANOVA and post hoc multiple comparisons.

None declared.

ID 837. A Systematic Review on the use of Biomarkers to predict Acute Kidney Injury in term neonates with Neonatal Encephalopathy

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Background: Acute Kidney Injury (AKI) is a common complication of Neonatal Encephalopathy (NE) and early diagnosis can be beneficial in indicating those at risk of long-term morbidity and mortality. Therefore, there remains a need for the identification of a statistically robust and reliable biomarker that can assist early detection of AKI in neonates with NE. The aim of this review is to demonstrate the benefit of renal biomarkers in aiding the diagnosis in term neonates with NE.

Method: A systematic review and meta-analysis was performed, using PRISMA, to identify relevant renal biomarkers in the diagnosis of AKI in term neonates with NE through EMBASE, Medline OVID, CINAHL and Web of Science databases. 83 publications matching the search criteria were assessed. Data was extracted based

on population characteristics, biomarker assessment methods, and sampling timeframes, along with predictive values (Sensitivity, Specificity). A quality assessment of included studies was conducted using the Newcastle–Ottawa Scale (NOS) for cohort studies, JBI score for case control and case series, AXIS tool for cross sectional studies and the GRACE checklist for observational studies.

Results: 14 studies that met the eligibility criteria were included in this review for data extraction and analysis. A meta–analysis was performed on day 1 urinary NGAL, which found that it was significantly increased in neonates with NE + AKI. Differences in the following biomarkers: IL–18, Human Cystatin C, Albumin, Beta–2–Microglobulin, NGAL, EGF, Serum Creatinine, Uromodulin, Osteopontin, and Renal Fractional Tissue Oxygenation fraction were found to be statistically significantly increased between neonates with NE +AKI and their non–AKI counterparts.

Conclusion: Biomarkers have a pertinent and promising role in the early diagnosis and treatment of AKI in neonates, potentially facilitating better long–term outcomes. Promising biomarkers include Neutrophil Gelatinase Associated Lipocalin, Serum Creatinine, and Human Cystatin C; all of which had high diagnostic sensitivity and specificity. Further information on the relevance of long–term renal function would be valuable.

Ethical approval: None required
Conflict of interest: None
Keywords: Neonatal Encephalopathy, Perinatal asphyxia, Acute Kidney Injury, Neonate, Biomarker, NGAL, CysC

None declared

ID 802. HINDSIGHT IS 20/20: COULD THE DOSE IN THE HIGH DOSE ERYTHROPOIETIN FOR ASPHYXIA AND ENCEPHALOPATHY (HEAL) TRIAL HAVE BEEN TOO HIGH?

Dr. Zhongjie Shi[1], **Professor Sidhartha Tan**[1]

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Background

Erythropoietin (EPO) has been shown to be neuroprotective for neonatal encephalopathy (NE) in numerous animal and clinical studies. Yet, death and neurodevelopmental disability following a total dose of 5000 U/kg erythropoietin (EPO) over 5 doses in the High Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) trial involving 500 babies, was 52.5% vs. 49.5% in saline controls. Serious adverse events were also higher in the EPO group (relative risk, RR, 1.01–1.57, 95% C.I.). Post treatment intracranial hemorrhage (ICH) was significantly elevated after EPO in the 5–day MRI (1.02–2.34). Post–treatment thrombosis was found in 6 babies in the EPO group vs. 1 in controls. We hypothesized that the non–improvement and even slight worsening with EPO may be related to the choice of the dose given to term newborn babies with hypothermia.

Methods

We reviewed the clinical outcome and pharmacokinetics literature using the search terms of EPO, newborn, encephalopathy (or hypoxia) and found 26 human and 93 animal studies.

Results:

The range of total dose of EPO used in human trials was 300–12,500 U/kg in single or divided doses. The range of total dose in animal trials was 1,000–90,000 U/kg).

The inverted U–shaped brain damage response of EPO has been demonstrated in the rat Vannucci model with the best histopathological improvement at 15,000 U/kg but no effect with 35,000 to 90,000 U/kg. In mice, the same dose showed histopathological improvement only in female mice but not at 60.000 U/kg. A dose of 10,000 U/kg showed neurobehavioral improvement in the rat Vannucci model. Using placental insufficiency model, neonatal EPO was neuroprotective only in male rats in long–term neurobehavior following the same total dose of 10,000 U/kg. However, clearance of EPO is approximately three times faster in rats, suggesting that equivalent dosages in humans should be approximately one third that of the dose given to rodents, 3333–5000 U/kg.

Conclusions

EPO has a bimodal distribution in neuroprotection. Neuroprotective effect had been demonstrated in humans using lower than HEAL trial–dose. HEAL trial dose was optimal using histopathological criteria improvement in rodents as a reference, but too high using neurobehavioral improvement in rodents, by about 1/3.

None declared