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Abstracts

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ABS 1

PRETERM BIRTH AND THE TIMING OF PUBERTY

E. James[1], C. Wood[2], H. Nair[3], T. Williams[4]

[1]University of Sheffield Medical School, Sheffield, UK

[2]Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

[3]Centre for Population Health Sciences, University of Edinburgh, UK

[4]Institute of Genetics and Molecular Medicine, University of Edinburgh, UK

INTRODUCTION

An estimated 11% of births occur preterm, and survival is improving. Early studies suggested an association between preterm birth and earlier puberty. Given the adverse outcomes associated with early puberty this could have significant public health implications. The objective of this review was to assess the timing of puberty after preterm birth.

METHODS

Pubmed, Embase, Popline, Global Health and Global Health Library were searched using terms relating to "premature birth", "menarche", "puberty" and "follow up studies". Inclusion criteria were a population consisting of pubertal or post-pubertal adolescents and adults; studies which defined preterm delivery in participants and compared outcomes to those after term delivery; and a quantitative assessment of pubertal onset. Assessment of risk of bias was conducted using principles from the Critical Appraisal Study Process.

RESULTS

Our search identified 1,050 studies, of which 15 met the inclusion criteria. In females, 8 studies found no association between preterm birth and the timing of menarche. Five studies found earlier onset in preterm infants, 1 found later onset, and 1 showed both earlier and later menarche, depending on birth weight. The range of effect of studies showing earlier menarche was -0.94 to -0.07 years in the preterm group, with a median of -0.3 years. In males, 2 studies showed earlier onset of puberty in the preterm group, 4 showed no difference, and 1 showed later onset. The majority of studies did not present outcomes in the form of a mean, precluding a meta-analysis. There was insufficient data to address potential confounding factors.

CONCLUSIONS

The published evidence does not suggest that being born preterm leads to a significant acceleration in the onset of puberty. This should prove reassuring for public health purposes, and for clinicians counseling parents of infants born preterm.

ABS 2

NEONATAL PAIN, OPIOID AND ANAESTHETIC EXPOSURE; WHAT REMAINS IN THE HUMAN BRAIN AFTER THE WHEELS OF TIME?

G.E. van den Bosch[1], D. Tibboel[1], J.C. de Graaff[2], H. El Marroun[3], A. van der Lugt[4], T. White[3,4], M. van Dijk[1,5]

[1]Intensive Care and Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

[2]Department of Anesthesiology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

[3]Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

[4]Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

[5]Division of Neonatology, Department of Pediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

INTRODUCTION

Not only early exposure to anaesthetics, but also pain and opioids are associated with negative outcome at least in animals. These consist of cell death in the brain as well as alterations in pain sensitivity after neonatal pain and apoptosis in brain regions along with impaired cognitive functioning after neonatal opioid exposure. While these negative effects occurred in the absence of pain, protective effects of opioid exposure in the presence of pain are observed as well. The question rises whether these findings hold true for humans. Therefore our main objective was to evaluate possible long-term effects of neonatal exposure to pain, opioids and anaesthetics in children and adolescents.

METHODS

To obtain a comprehensive view on the potential individual and combined effect of these factors in human, we studied five unique groups of children recruited from well-documented neonatal cohorts with a history of neonatal exposure to pain, opioids or anaesthetics at different points along the

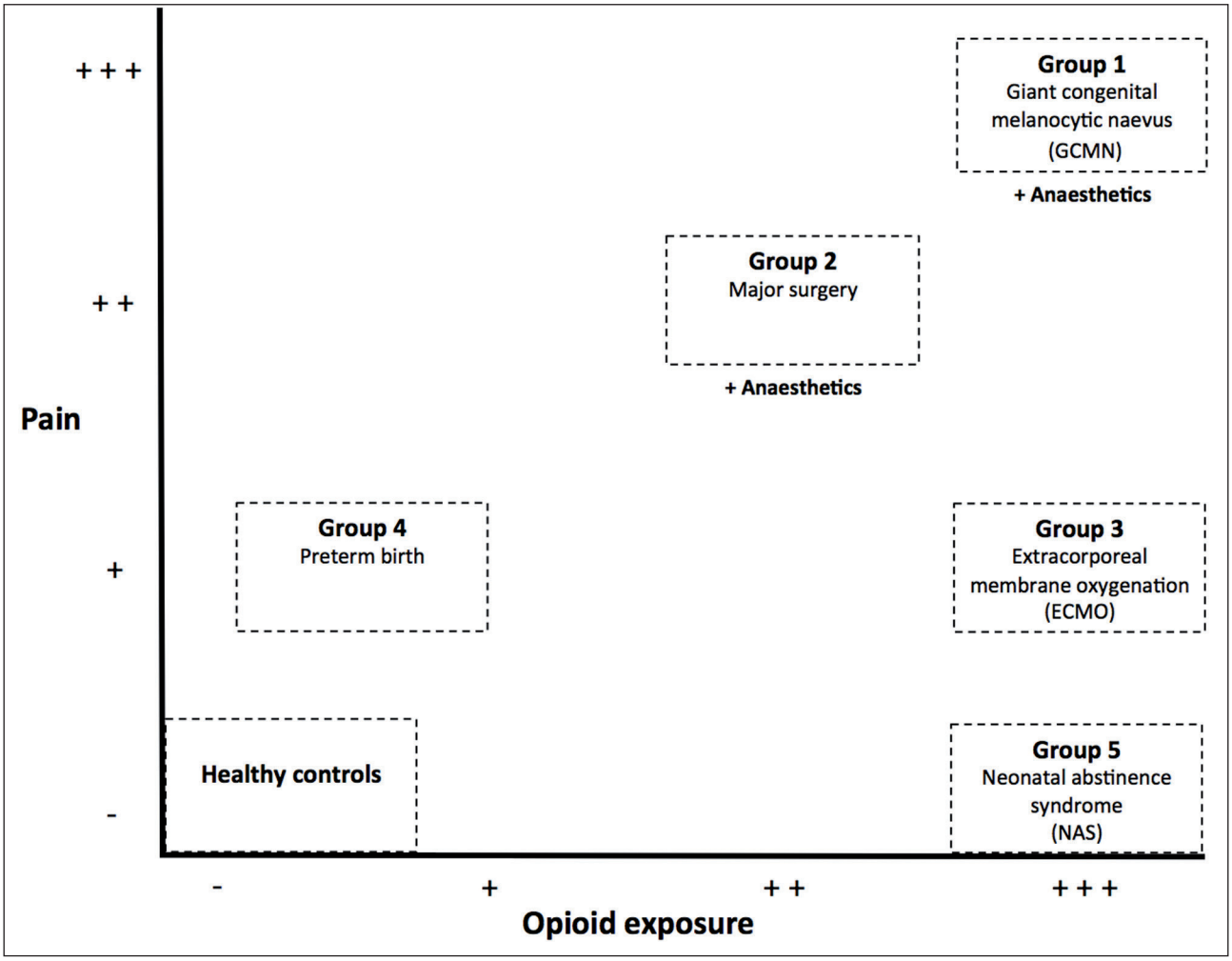

Figure 1 (ABS 2). Study groups: children who underwent major surgery (group 1 and 2), ECMO (group 3), preterm birth (group 4) and prenatal opioid exposure (group 5) in comparison to healthy controls.

continuum from no pain to intense pain and from no opioid exposure to high opioid exposure in the presence or absence of anaesthetics. We evaluated children who underwent major surgery (group 1 and 2), ECMO (group 3), preterm birth (group 4) and prenatal opioid exposure (group 5) in comparison to healthy controls (**Fig. 1**). Neuropsychological functioning, thermal detection and pain thresholds and high-resolution structural and task-based functional magnetic resonance imaging during pain were assessed.

RESULTS

In total 94 cases were included and were compared to healthy controls. Children and adolescents in groups 3 and 5 showed worse neuropsychological functioning after high opioid exposure. A thicker cortex was found in group 1 (pain, opioid and anaesthetic exposure) in only the left rostral-middle-frontal-cortex compared to controls. But most importantly, we found no differences in cortical thickness or volumes of other brain volumes, pain thresholds or brain activity during pain in pain related brain regions between the other groups and their controls.

CONCLUSIONS

In conclusion, we show no major effects that remain in the human brain after neonatal pain, opioid or anaesthetic exposure some 8-19 years later. We conclude that besides specific neuropsychological effects in humans that warrant further investigation, no major clinical relevant effects with respect to thermal and pain sensitivity, brain functioning during pain or brain morphology is observed.

ABS 3

DEPRESSION DURING PREGNANCY AND DNA METHYLATION CHANGES IN CORD BLOOD

A.-C. Viuff[1], G. Sharp[2], D. Raj[3], K.J. Kyng[4], L.H. Pedersen[1,5], T.B. Henriksen[1,4], C.L. Relton[2]

[1]Department of Clinical Medicine, Health, Aarhus University Hospital, Aarhus, Denmark
[2]MRC Integrative Epidemiology Unit, Bristol University, Bristol, UK
[3]School of Social and Community Medicine, Bristol University, Bristol, UK
[4]Department of Paediatrics, Aarhus University Hospital, Aarhus, Denmark
[5]Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus Denmark

INTRODUCTION
Many women are affected by depression, especially during particularly vulnerable periods of their lives as in pregnancy. Up to 13% of women may experience symptoms of depression during pregnancy and in the postpartum period. Maternal depression during pregnancy has been associated with an increased risk of adverse neurodevelopmental outcomes in the children. Epigenetic pathways could be one of the biological pathways to explain this association. Epigenetics is the study of molecular modifications of gene expression that do not change the underlying DNA sequence. The aim of this study was to investigate the association between prenatal maternal depression and methylation changes in the cord blood of the newborn, under the hypothesis, that maternal depression during pregnancy may cause a change in the transcription of genes in the developing infant brain that could lead to alterations in the structure of the brain and thereby to an altered susceptibility to later neurodevelopmental problems or psychiatric illness.
METHODS
877 mother-child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) were included in our study. We ran an epigenome-wide association study (EWAS) between maternal depression during pregnancy and DNA methylation changes in cord blood samples. Maternal depression was defined as an EPDS score ≥ 12 at any time during pregnancy. We performed a single-site regression analysis. P-values were adjusted for genome-wide significance using False Discovery Rate (FDR) adjustment, and adjusted for multiple comparisons using Bonferroni correction. CpG-sites with an FDR corrected P-value < 0.05 were considered significant. We also performed a regional analysis where a Sidak corrected p-value < 0.05 was considered significant.
RESULTS
We discovered 2 CpG-sites in our single-site analysis associated with maternal depression in the early part of pregnancy: cg08667740 (β = -0.025; p = 3.9 x 10-8) and cg22868225 (β = -0.005; p = 5.89 x 10-8). 39 differentially methylated regions (DMRs) survived correction for multiple testing (Sidak p-value < 0.05). We found 184 different significantly (p < 0.01) enriched biological process GO terms and 44 KEGG pathways among the DMRs. Replication was attempted in the GenR Study. 49 out of 68 (72%) within DMRs identified both in ALSPAC and GenR showed the same direction of effect, but none survived correction for multiple testing.
CONCLUSIONS
This study is to our knowledge the first of its kind studying epigenome-wide DNA methylation changes in children exposed to maternal depression during pregnancy. In this study we discovered several DNA methylation changes in the cord blood of newborns exposed to maternal depression during pregnancy. These changes are related to genes that have previously been associated with adult mental illness. Future studies with larger sample sizes are needed and it also remains to be established whether this is a causal pathway leading from methylation change to disease.

ABS 4

PREVENTION OF CEREBRAL PALSY: FEASIBILITY OF UMBILICAL CORD BLOOD STEM CELLS AND UMBILICAL CORD MESENCHYMAL STROMAL CELLS

H. Shintaku[1], M. Nabetani[2], T. Hamazaki[1], S. Kusuda[3], M. Tamura[4], S. Watabe[5], M. Hayakawa[6], Y. Sato[6], M. Tsuji[7], A. Taguchi[8], H. Ichiba[9], O. Akira[10], R. Mori[11], A.Taki[12], T. Mukai[13], T. Nagamura-Inoue[13]

[1]Paediatric Department, Osaka City University Graduate School of Medicine, Osaka, Japan
[2]Paediatric Department, Yodogawa Christian Hospital, Osaka, Japan
[3]Neonatology Department, Tokyo Women's Medical University, Tokyo, Japan
[4]Neonatology Department, Center for Maternal, Fetal and Neonatal Medicine, Saitama Medical University, Kawagoe, Saitama, Japan
[5]Neonatology Department, Kurashiki Central Hospital, Kurashiki, Okayama, Japan
[6]Neonatology Department, Center for Maternal-Neonatal Care, Nagoya University Hospital, Nagoya, Japan
[7]Regenerative Medicine & Tissue Engineering Department, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
[8]Regenerative Medicine Research Department, Institute of Biomedical Research and Innovation, Kobe, Hyogo, Japan
[9]Neonatology Department, Osaka City General Hospital, Osaka, Japan
[10]Paediatric Department, The Tokyo University, Bunkyo, Tokyo, Japan
[11]Health Policy & Clinical Epidemiologic Department, National Center for Child Health and Development, Setagaya, Tokyo, Japan

[12]Paediatric Department, Tokyo Medical and Dental University, Bunkyo, Tokyo, Japan
[13]Cell Processing & Transfusion Department, Institute of Medical Science, University of Tokyo, Shinagawa, Tokyo, Japan

INTRODUCTION
Regeneration therapy for prevention of cerebral palsy (CP) has been initiated in Japan. Not only hypoxic-ischemic encephalopathy (HIE) but also periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) lead to CP. We have already started umbilical cord (UC) blood stem cells (UC-BSCs) therapy for neonatal HIE in addition to therapeutic hypothermia (TH). Also, we have been preparing to start a clinical trial of UC mesenchymal stromal cells (UC-MSCs) therapy for patients in whom the effect was insufficient or who could not take UC blood.
METHODS
UC-BSCs were collected aseptically and prepared by using SEPAX. UC-MSCs were collected aseptically from UC and cryopreserved after culture. Infants admitted to the NICU of 6 hospitals in our research group will be eligible if they are ≥ 36 weeks' gestational age and birth weight ≥ 1,800 g with HIE and meet the cooling criteria.
RESULTS
UC-BSCs therapy for neonatal HIE in addition to TH was performed in 5 newborn patients. All of them have survived from 7 months for 2.2 years. UC-MSCs have been defined and characterized as follows; (1) abundant sources and ease of collection, storage, and transport; (2) little ethical controversy; (3) multi-potency to differentiate into various cell types; and (4) low immunogenicity with significant immunosuppressive ability.
CONCLUSIONS
Good results in combination therapy of UC-BSCs and TH for newborn HIE were obtained in our 5 patients. UC-MSCs therapy will enable the possibility of treating patients who could not take UC blood.

ABS 5

NO GENDER-RELATED DIFFERENCES IN FETAL CORPUS CALLOSUM THICKNESS: *IN-UTERO* MRI STUDY

R. Bercovitz[1], R. Achiron[2], C. Hoffmann[1], A. Achiron[2]

[1]Department of Radiology, Sheba Medical Center, Ramat Gan, Israel
[2]Department of Obstetrics and Gynecology, Sheba Medical Center, Ramat Gan, Israel

INTRODUCTION
Gender-related differences in the size and shape of the human corpus callosum (CC) are a matter of ongoing dispute. Callosal size and shape have been extensively studied in adult brains in relation to gender. Only a few studies examined gender effects on the CC during prenatal development. We have previously reported using high-resolution ultrasonography that, during the second trimester, female fetuses have a thicker CC as compared to males. The objective is to investigate whether there are gender related differences in the fetal CC thickens during late gestation using brain magnetic resonance imaging (MRI).
METHODS
We have studied the CC thickness by MR I3T in 29 male and 12 female fetuses during the third trimester of pregnancy. Measurements were performed in axial and sagittal plains and the thickness of three regions of the CC were obtained: rostrum, body and splenium.
RESULTS
No differences were demonstrated in CC measurements between male and female fetuses at a mean gestational age of 33 weeks. The mean thickness of the splenium in female fetuses was 3.66 ± 0.25 mm compared to male fetuses 3.8 ± 0.23 mm, p = 0.36; the mean thickness of the CC body was in females 2.97 ± 0.18 mm compared to male fetuses 3.08 ± 0.14 mm, p = 0.33; and the mean thickness of the rostrum in female fetuses was 3.17 ± 0.21 mm, compared to male fetuses was 3.48 ± 0.2 mm, p = 0.19.
CONCLUSIONS
CC development in late pregnancy did not differ between female and male fetuses.

ABS 6

NEUROMOTOR PROFILE OF HIGH-RISK INFANTS AT TERM OR NEAR TERM

I. Ereno, W.Y. Teh

Department of Neonatal and Developmental Medicine, Singapore General Hospital, Singapore

INTRODUCTION
It is well established that infants born preterm are at increased risk of neurodevelopmental

impairment and subsequent disability, its incidence increases as birth weight and gestational age decrease. Early identification is therefore essential in the determination of neurological integrity and the potential risk for these sequelae so that early developmental intervention is initiated. Our objectives are to assess the neuromotor performance of infants born ≤ 34 weeks' gestation, birth weight (BW) < 1,500 g and other high-risk infants to identify developmental delay, set goals and establish early intervention.

METHODS

A retrospective study was done from January 2013 to October 2015 for premature infants born < 34 weeks' gestation and high-risk term infants using Test of Infant Motor Performance (TIMP). A term infant is considered high-risk for neurodevelopmental impairment if one of the following criteria is met: perinatal asphyxia/HIE stage 2 or 3, perinatal stroke, any neuroimaging abnormalities, abnormal neurological examination and medical problems resulting in abnormal neurology. TIMP was administered at 36-42 weeks' postconceptional age as part of the routine neurodevelopmental assessment prior to discharge. Each infant was medically stable and was assessed by trained neonatal physiotherapists. Infant is required to be at least a state 3 as defined in Brazelton Neonatal Behavioural Scale and test is completed within 24 hours.

RESULTS

There were 20 extremely low birth weight (ELBW), 40 very low birth weight (VLBW), 26 low birth weight infants (LBW) and 5 with BW > 2,500 g infants assessed. 26 infants were born < 28 weeks, 41 28-32 weeks, 20 33-36 weeks and 4 37 weeks' gestation. In the 91 infants studied, 67% performed average with TIMP. 33% who had poorer performance includes low average (16.5%), below average (12.2%) and far below average (4.4%). Study shows a trend of suboptimal TIMP performance with decreasing gestation and birth weight among preterm infants while only 1 of 4 high-risk term infants perform satisfactorily. Among all risks factors of prematurity, history of IVH is significantly associated with poor TIMP raw score ($p < 0.05$). The 4 infants with far below average performance in TIMP are shown in **Tab. 1**.

CONCLUSIONS

Thirty-three percent (33%) of infants born < 34 weeks' gestation assessed at term or near term have delayed neuromotor development. Majority of high-risk term infants have abnormal neuromotor profile. Among all risk factors, history of IVH and HIE are associated with impaired neuromotor development. Therefore, TIMP is an important assessment too, to identify infants who would benefit from early developmental intervention.

Table 1 (ABS 6). Summary of all 4 infants with far below average performance in the Test of Infant Motor Performance (TIMP).

Characteristics	Neurological findings	PT management and follow-up	Current progress
Baby boy, term • moderate HIE with multiple haemorrhages in subcortical and deep cerebral white matter, PPHN	• increased tone and abnormal reflexes • clonus, fisting, abnormal movements	• early infant stimulation in inpatient • parents education • home program exercises for developmental therapy, stretching exercises etc.	• GMFCS level II • bilateral lower limbs hypertonia • possibly spastic diplegia CP
Baby boy, ex-prem 33/52 • IVF, twin 1 DCDA, idiopathic preterm labour, NNJ, hypoglycaemia	• appropriate tone and reflexes • reduced alertness in inpatient	• developmental care and early infant stimulation in ward • parents education • developmental therapy and assessment • 4th month TIMP: average performance	• baseline gross motor development • age-appropriate fine motor skill
Baby girl, ex-prem 27^{+5}/52 • VLBW, CLD, PPHN, grade 1 IVH, thrombocytopenia, dysmorphism	• general hypotonia • minimal spontaneous limbs movements	• positioning and developmental care in NICU • appropriate infant stimulation • development assessment and therapy	• 6th month PDMS results – average gross and fine motor skill • noted visual nystagmus and reduced head control
Baby boy, term • HIE with seizures, LMSL, acute renal impairment, raised TSH level	• increased tone in lower limbs • abrupt upper limbs movements present • sucking and gag reflexes present	• parents education and home program exercises • developmental therapy i.e.: stretching exercises, neck muscle activation	• referral to EIPIC centre for more intensive therapy sessions

ABS 7

THE PREDICTIVE VALUE OF SEVERE BRONCHOPULMONARY DYSPLASIA FOR NEUROLOGICAL IMPAIRMENT IN 2-YEARS-OLD VERY PRETERM INFANTS IS HIGHER WHEN DIAGNOSED AT 40 THAN AT 36 WEEKS' POSTMENSTRUAL WEEKS

A.M. Malavolti[1,2], D. Bassler[1], R. Arlettaz-Mieth[1], G. Faldella[2], B. Latal[3], G. Natalucci[1,3]

[1]Department of Neonatology, University of Zurich and Zurich University Hospital, Zurich, Switzerland

[2]Department of Gynaecological, Obstetric and Paediatric Sciences, University Hospital of Bologna, Bologna, Italy

[3]Child Development Centre, Zurich University Children's Hospital, Zurich, Switzerland

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is among the most frequent respiratory neonatal morbidities and a good predictor of neurodevelopmental impairment (NDI) in very preterm infants. However, it is unclear what the contribution of the severity of BPD and of the time of its diagnosis is to the prediction of neurologic outcome. This study aimed to assess to what extent the time of diagnosis and the severity of BPD does contribute to the prediction of neurodevelopment of very preterm infants at 2 years.

METHODS

Retrospective single-centre study of a cohort of 754 very preterm children with a gestational age 0.21 for > 28 days and its severity grade was classified as mild (FiO_2 = 0.21), moderate (FiO_2 0.21-0.30%), and severe (FiO_2 ≥ 0.30% and/or positive pressure support) at 36 (according to the 2000 NICHD consensus) and at 40 weeks' postmenstrual age (PMA). Multivariable regression models were used to calculate the association (OR [95%-CI]) between BPD and its severity grade with the occurrence of an NDI, defined as one of following: cognitive or motor development score < -2 SD, severe cerebral palsy, deafness, or blindness.

RESULTS

Among 754 eligible infants, 610 (81%) were assessed at 2 years corrected age (50% females, mean [SD] gestational age 27.9 [1.2] weeks, birth weight 1,050 [230] g): 357 (58%) needed supplemental O_2 for > 28 days and 98 (16%) displayed an NDI. Additional O_2 for > 28 days as well as mild and moderate BPD at 36 and 40 weeks' PMA were not associated with NDI, while severe BPD (5.6 [2.0; 16.0], 16.6 [4.6; 59.9]) increasingly was. Mental development score of infants with severe BPD at 36 or 40 weeks' PMA was lower than that of infants without BPD (mean difference -11.4 [-18.5; -4.3], -25.7 [-35.9; -15.5]). Results remained similar after adjustment for variables that were significantly unequally distributed among groups as well as for known neonatal predictors of poor neurodevelopment in accordance with previous reports.

CONCLUSIONS

In this cohort of very preterm children, severe BPD was a better independent predictor of NDI at the corrected age of 2 years than mild or moderate BPD. The diagnosis of severe BPD provided better identification of children at high risk for poor neurodevelopment when made at 40 than at 36 weeks' PMA.

ABS 8

PSYCHOSOCIAL OUTCOME OF INFANTS WITH CONGENITAL MALFORMATIONS AFTER POSTNATAL SURGICAL REPAIR

N. Doberschuetz[1], A. Allendorf[1], R. Dewitz[2], B. Wittekindt[1], U. Rolle[3], R. Schloesser[1]

[1]Department of Neonatology, J.W. Goethe University Hospital, Frankfurt am Main, Germany

[2]Department of Neuropediatrics, J.W. Goethe University Hospital, Frankfurt am Main, Germany

[3]Department of Pediatric Surgery, J.W. Goethe University Hospital, Frankfurt am Main, Germany

INTRODUCTION

Survival rates of children with congenital malformations of the gastrointestinal tract have risen dramatically over the last decades. While scientific interest on the neurodevelopmental outcome of these patients increased in recent years, little is known on their psychosocial development. Information on this topic might be of high relevance for the pre- and postnatal counselling of affected parents as well as the medical and psychosocial care of affected patients. Therefore, we decided to perform a study on the psychosocial outcome of children with congenital malformations of the gastrointestinal tract, which required surgical repair under general anesthesia within the neonatal period.

METHODS

This bidirectional cohort study examined patients with major gastrointestinal malformations, which

required surgery within the neonatal period. Based on information on parents' socioeconomic status (SES), number of siblings and languages spoken at home, every patient was compared to a healthy peer of same gender, birth weight and gestational age at birth. All participants were tested with the Bayley Behavior Rating Scale at the corrected age of 24 months. This scale evaluates the categories "orientation/engagement", "emotional regulation", and "motor quality", resulting in a score with a maximum of 99. The results of patient and control group were compared by Wilcoxon Mann Whitney U test. These outcome data and neonatal exposure to general anesthesia were correlated by Spearman correlation.

RESULTS

We included 40 patients treated at our center from June 2008 through April 2011 and matched every patient to a healthy peer. The two groups did not show significant differences in birth weight ($p = 0.76$), gestational age ($p = 0.82$), age at testing ($p = 0.38$), SES ($p = 0.22$), number of siblings ($p = 0.99$) and number of languages spoken at home ($p = 0.40$). Regarding the psychosocial outcome, the differences between the two groups in the categories "orientation/engagement" ($p = 0.66$), "emotional regulation" ($p = 0.29$) and "motor quality" ($p = 0.73$) did not show statistical significance. The same applied to the total behavioral score ($p = 0.55$). Relevant anesthesia data (overall number and duration of exposure to anesthesia, age at first anesthesia) were evaluated. A possible correlation between these parameters and psychosocial outcome was analyzed as well and did not show any statistical significance either.

CONCLUSIONS

The psychosocial outcome of infants with major gastrointestinal malformations is not significantly distinct from healthy matched peers at the age of 24 months. A significant correlation between these outcome data and relevant anesthesia parameters could not be found. Possible impairments of the psychosocial development within further infancy are not studied yet, which emphasizes the importance of long-term follow-up programs for these patients.

ABS 9

THERAPEUTIC HYPOTHERMIA AND HEARING IMPAIRMENT: INCIDENCE AND ASSOCIATED FACTORS

M.P. Fitzgerald, G. Norman, C. Mc Garvey, A. Reynolds, M. King, B. Hayes

Neonatal Department, Rotunda Hospital, Dublin, Ireland

INTRODUCTION

Therapeutic hypothermia for neonates with moderate to severe hypoxic ischaemic encephalopathy (HIE) has been shown to reduce death and disability without increasing disability in survivors. A recent study found hearing impairment to be common finding among cooled infants. The objective of this study was to establish the local incidence of hearing loss in newborns with HIE and to identify associated risk factors.

METHODS

A retrospective case note review was conducted between June 2012 and March 2016 in a tertiary neonatal intensive care unit in Dublin, Ireland. Eligibility criteria were HIE and enrolment in the National Newborn Hearing Screening Programme (AOAE and AABR). Information collected included demographic data, labour and delivery details along with detailed neonatal history including resuscitation, ventilation, seizures and medication history. Measures of renal function, gentamycin levels and brain magnetic resonance imaging (MRI) findings were reviewed. Fishers exact test and both Kruskall Wallis rank and Pearson's r correlation coefficient were used to analyse continuous and categorical variables respectively.

RESULTS

Fifty-seven newborns received therapeutic hypothermia for HIE. Fifteen infants were excluded from the study (12 died and 3 had incomplete data). Complete data was available for 42 babies, 4 of whom had significant hearing impairment. The development of hearing loss was associated with abnormal blood glucose levels ($p = 0.006$), low Apgar score at 1 minute ($p = 0.0219$), high creatinine on days 1 and 2 of life ($p = 0.0172$ and 0.0198) and raised liver function tests (AST $p = 0.0012$, ALT $p = 0.0037$). An association with gentamicin was not found.

CONCLUSIONS

Hearing impairment is common in survivors of term HIE treated with hypothermia. Developmental surveillance should include formal audiology. In attempts to minimize the risk of hearing impairment, glucose should be monitored very carefully in this population. Larger studies are required to fully identify underling risks for hearing impairment in this population.

ABS 10

PRETERM INFANTS 33-35 WEEKS' GESTATION WITH SEVERE HYPOXIC-ISCHEMIC ENCEPHALOPATHY TREATED WITH HYPOTHERMIA DO NOT PRESENT MORE ORGAN DYSFUNCTION THAN TERM NEWBORNS

M. Alsina[1], A. Martin-Ancel[1], M. Leon[1], G. Arca[1], E. Perez[2], A. García-Alix[1,3]

[1]*Hospital Sant Joan de Déu, Barcelona, Spain*

[2]*Hospital Clínic de Barcelona, Barcelona, Spain*

[3]*Fundación de Alcorcón, Madrid, Spain*

INTRODUCTION

The benefits of hypothermia on neurodevelopment of newborns ≥ 36 weeks' gestation with hypoxic-ischemic encephalopathy (HIE) have been widely demonstrated. The absence of clinical trials limits its extension to infants of 33-35 weeks' gestation, although the feasibility has been suggested in several studies. Aims: 1) To describe organ damage in infants of 33-35 weeks' gestation with HIE evaluated for hypothermia. 2) To compare this data with newborns ≥ 36 weeks' gestation.

METHODS

Retrospective observational study of prospective data collected between April 2009 and December 2012. Patients: Consecutive newborns of 33-35 weeks' gestation, ≥ 1,800 g birth weight and moderate or severe HIE were included. Data were compared with newborns ≥ 36 weeks' gestation. Outcome measures: A total of 24 clinical and laboratory variables of organ damage were studied daily in the first 3 days of life.

RESULTS

Eight preterm newborns with severe HIE were enrolled and compared with 31 term neonates with severe HIE. All infants presented with moderate-to-severe organ injury. Transaminases were less altered in the preterm group compared with term newborns, while sodium levels were lower in the preterm group. There were no differences in the rest of variables or the number of affected organ-systems (**Tab. 1**).

CONCLUSIONS

Organ injury in infants of 33-35 weeks' gestation with severe HIE evaluated for hypothermia is not more severe regarding newborns ≥ 36 weeks'

Table 1 (ABS 10). All infants presented with moderate-to-severe organ injury. Transaminases were less altered in the preterm group compared with term newborns (GPT, UI/l day 1: 94 ± 105 vs 285 ± 303, p = 0.035; day 2: 66 ± 6 vs 347 ± 424, p = 0.015), while sodium levels were lower in the preterm group (Na^+, day 1: 130 ± 3 vs 135 ± 5, p = 0.005). There were no differences in the rest of variables or the number of affected organ-systems (continues on the next page).

Organ-Systems	Severe HIE			≤ 35 weeks	≥ 36 weeks	p-value
	N	Day 1		8	31	
	N	Day 2		7	27	
	N	Day 3		4	23	
Cardiovascular	Troponin T, mean (SD), μg/mL	Day 1		1.07 ± 2.14	1.08 ± 1.63	0.98
		Day 2		1.05 ± 0.04	1.11 ± 1.85	0.78
		Day 3		0.46 ± 0.46	0.49 ± 0.71	0.68
	Need for vasoactive drugs, N (%)	Day 1	None	1 (13)	5 (16)	0.31
			1	5 (62)	10 (32)	
			2	2 (25)	16 (52)	
		Day 2	None	1 (14)	3 (11)	0.90
			1	4 (57)	13 (48)	
			2	2 (29)	11 (41)	
		Day 3	None	1 (25)	4 (17)	0.64
			1	1 (25)	11 (48)	
			2	2 (50)	8 (35)	
Renal	Plasma creatinine, mean (SD), mg/dl	Day 1		1 ± 0.28	1.16 ± 0.38	0.29
		Day 2		1.03 ± 0.57	1.25 ± 0.57	0.48
		Day 3		0.68 ± 0.44	1.13 ± 0.73	0.20
	Diuresis, mean (SD), ml/kg/h	Day 1		1.2 ± 0.9	1.3 ± 1.6	0.64
		Day 2		2.5 ± 0.5	2 ± 1.7	0.25
		Day 3		2.4 ± 1	2.4 ± 1.7	0.87
	Need for renal replacement therapy, N (%)	Day 1		0 (0)	0 (0)	1
		Day 2		1 (14)	2 (7)	0.51
		Day 3		1 (25)	2 (9)	0.40

Table 1 (ABS 10). All infants presented with moderate-to-severe organ injury. Transaminases were less altered in the preterm group compared with term newborns (GPT, UI/l day 1: 94 ± 105 vs 285 ± 303, p = 0.035; day 2: 66 ± 6 vs 347 ± 424, p = 0.015), while sodium levels were lower in the preterm group (Na^+, day 1: 130 ± 3 vs 135 ± 5, p = 0.005). There were no differences in the rest of variables or the number of affected organ-systems (continues from the previous page).

Respiratory	Mechanical ventilation due to other causes than central apnea N (%)	Day 1	7 (88)	26 (84)	1
		Day 2	6 (86)	23 (85)	1
		Day 3	3 (75)	19 (83)	1
	$FIO_2 \geq 0.4 \geq 24$ h, N (%)	Day 1	2 (25)	9 (29)	1
		Day 2	3 (43)	9 (33)	0.68
		Day 3	1 (25)	5 (22)	1
	Nitric oxide, N (%)	Day 1	0 (0)	3 (10)	1
		Day 2	0 (0)	4 (15)	0.56
		Day 3	0 (0)	2 (9)	1
	HFV, N (%)	Day 1	1 (13)	7 (23)	1
		Day 2	0 (0)	8 (30)	0.16
		Day3	0 (0)	6 (26)	0.55
Hematologic	Leukocytes < 4.5, N (%)	Day 1	0 (0)	1 (3)	1
		Day 2	0 (0)	1 (4)	1
		Day3	1 (25)	1 (5)	0.31
	Leukocytes > 30, N (%)	Day 1	2 (25)	7 (23)	1
		Day 2	0 (0)	0 (0)	1
		Day 3	0 (0)	0 (0)	1
	Platelet count, mean (SD), (mm^3)	Day 1	181 ± 107	140 ± 73	0.41
		Day 2	183 ± 57	131 ± 69	0.24
		Day 3	148 ± 20	110 ± 71	0.58
	Platelet or fresh frozen plasma concentrate (units), median (IQR)	Day 1	0.5 (0-1.75)	1 (0-3)	0.23
		Day 2	0 (0-0.38)	0 (0-2)	0.15
		Day 3	0 (0-3)	0 (0-1)	1
	TTPA > 45, N (%), sec	Day 1	6 (75)	18 (62)	0.69
		Day 2	2 (33)	8 (35)	1
		Day 3	1 (25)	4 (29)	0.33
Hepatic	GOT, mean (SD), (UI/l)	Day 1	433 ± 531	784 ± 934	0.223
		Day 2	218 ± 52	809 ± 1.087	0.12
		Day 3	96 ± 43	455 ± 677	0.32
	GPT, mean (SD), (UI/l)	Day 1	94 ± 105	285 ± 303	**0.035**
		Day 2	66 ± 6	347 ± 424	**0.015**
		Day 3	47 ± 13	202 ± 207	0.1
	Prothrombin activity, mean (SD), %	Day 1	33 ± 15	24 ± 20	0.53
		Day 2	51 ± 21	44 ± 24	0.45
		Day 3	70 ± 70	52 ± 27	0.8
pH and electrolytic imbalance	pH, lower limit, mean (SD),	Day 1 ≥ 12 hours of life.	7.17 ± 0.16	7.13 ± 0.13	0.23
		Day 2	7.26 ± 0.12	7.2 ± 0.14	0.32
		Day 3	7.23 ± 016	7.23 ± 0.16	0.66
	Na^+ lower limit, mean (SD), mmol/L	Day 1	130 ± 3	135 ± 5	**0.005**
		Day 2	131 ± 9	133 ± 6	0.55
		Day 3	131 ± 5	135 ± 6	0.15
	Na^+ upper limit, mean (SD), mmol/L	Day 1	137 ± 4	140 ± 7	0.10
		Day 2	131 ± 3	135 ± 6	0.24
		Day 3	133 ± 3	136 ± 5	0.50
	K^+ lower limit, mean (SD), mmol/L	Day 1	3.6 ± 0.4	3.5 ± 1.1	0.20
		Day 2	3.6 ± 0.8	3.6 ± 0.8	0.38
		Day 3	3.8 ± 0.8	3.8 ± 0.8	0.64
	K^+ upper limit, mean (SD), mmol/L	Day 1	4.4 ± 0.5	4.4 ± 1.1	0.55
		Day 2	4.0 ± 1.1	4 ± 1.1	0.94
		Day 3	4.0 ± 0.8	4 ± 0.8	0.37
	Ca^+ lower limit, mean (SD), mmol/L	Day 1	1.0 ± 0.1	1.0 ± 0.2	0.38
		Day 2	1.0 ± 0.2	1.0 ± 0.2	0.63
		Day 3	1.0 ± 0.2	1.0 ± 0.2	0.94
	Ca^+ upper limit, mean (SD), mmol/L	Day 1	1.6 ± 0.5	1.3 ± 0.3	0.1
		Day 2	1.2 ± 0.2	1.2 ± 0.2	0.39
		Day 3	1.2 ± 0.2	1.2 ± 0.2	0.81

gestation. Therapeutic hypothermia appears feasible in this group of gestational age. Organ injury in infants of 33-35 weeks' gestation with severe HIE evaluated for hypothermia is not more severe regarding newborns ≥ 36 weeks' gestation. Therapeutic hypothermia appears feasible in this group of gestational age.

ABS 11

IMPACT OF ENVIRONMENTAL FACTORS ON MOTOR AND COGNITIVE PERFORMANCE OF LATE PRETERM INFANTS

M.M. Santos, C. Corsi, A.C. Campos, N.A.C.F. Rocha

Physiotherapy Department, Federal University of São Carlos (UFSCAR), São Carlos, Brazil

INTRODUCTION

Preterm infants are at greater developmental risk than term infants. In general, preterm infants present poorer motor and cognitive performance, even those who are classified as late preterm infants. Although the influence of environmental factors (either positive or negative) is acknowledged, their role is still controversial. This study aimed to investigate the impact of environmental factors (maternal education, monthly income and characteristics of home environment) on motor and cognitive performance of late preterm infants.

METHODS

34 late preterm infants (mean corrected age 15.6 months) were enrolled in this study. A survey collected information on environmental factors such as maternal education (years), monthly income and enrollment in day care (yes or no). The Infant/Toddler HOME Inventory was used to evaluate the home environment. Infants' fine motor, gross motor and cognitive performance were evaluated with the third edition of Bayley Scales of Infant and Toddler Development. Correlation tests (Pearson/Spearman) were performed according to data distribution. Statistical significance was set at $p < 0.05$.

RESULTS

Higher fine motor scores in late preterm infants correlated to higher family income and enrollment in daycare, while no association was found between gross motor performance and environmental factors. Higher cognitive performance of late preterm infants correlated to higher maternal education, higher income and better home environment (greater parents' acceptance, organization of care, more variety of learning materials, better involvement of parents on stimulation and better variety of stimuli). Besides the characteristics of HOME inventory may be sensitive only for cognitive performance of late preterm infants, fine motor performance was affected other environmental factors such income and day care center enrollment. We believe that motor performance is affected by stimulus of the environment and must be part of a family-centered early intervention programme. Bayley domains and environmental factors correlation are presented in **Tab. 1**.

CONCLUSIONS

Late preterm infants' performance is positively influenced by different environmental factors such as maternal education, income and home environment.

Table 1 (ABS 11). Bayley domains and environmental factors correlation.

	Bayley domains					
	Fine Motor		Gross Motor		Cognitive	
	r	p	r	p	r	p
Maternal Education	0.148	0.411	0.091	0.614	**0.405**	**0.019**
Income	**0.469**	**0.006**	0.163	0.364	**0.614**	**0.001**
Day Care Center	**0.377**	**0.031**	0.164	0.362	0.303	0.087
Responsivity [a]	0.021	0.910	-0.201	0.262	0.254	0.154
Acceptance [a]	-0.033	0.857	-0.152	0.400	**0.345**	**0.049**
Organization [a]	0.211	0.239	0.107	0.555	**0.509**	**0.002**
Learning Materials [a]	0.195	0.277	0.218	0.223	**0.468**	**0.006**
Involvement [a]	0.293	0.098	0.010	0.955	**0.594**	**0.001**
Variety [a]	0.271	0.128	0.109	0.546	**0.593**	**0.001**
Total HOME Score	0.225	0.209	0.031	0.864	**0.536**	**0.001**

[a] HOME subscales.
r values between 0.4 and 0.69 were considered moderate correlation.

Follow-up programs should emphasize family-centered interventions to optimize development, once these interventions will promote the development of this population.

ABS 12

THROMBOCYTOPENIA IS ASSOCIATED WITH SEVERE RETINOPATHY OF PREMATURITY CLINICALLY; IN MICE PLATELET TRANSFUSION SUPPRESSES RETINOPATHY

P. Lundgren[1], R. Liegl[2], S. Klevebro[3], G. Hellgren[1], C. Löfqvist[1], C. Mannheimer[1], Y. Sun[2], Z.-J. Liu[4], M.C. Sola-Visner[4], B. Hallberg[3], L.E.H. Smith[2], A. Hellström[1]

[1]Section for Ophthalmology, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2]Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Neonatology, Karolinska Institute and University Hospital, Stockholm, Sweden

INTRODUCTION

Retinopathy of prematurity (ROP), a potentially blinding disease of preterm infants, is characterized by abnormal retinal vascularization. Platelets regulate angiogenesis and may play a role in ROP.

METHODS

We correlated ROP with platelet counts, from birth to postmenstrual age 36 weeks, in preterm infants born at gestational age < 27 weeks (n = 202). We retrospectively reviewed 237 infants born at GA < 27 weeks and screened for ROP in Stockholm (2008-2011; n = 176) and Gothenburg (2013-2015; n = 61). International guidelines for ROP classification and ROP treatment were followed. We retrieved ROP data from the Swedish national register for ROP (SWEDROP). We defined the initial phase of ROP, with suppressed vascularization, as < 30 weeks PMA and the later proliferative phase as 30-36 weeks PMA. Platelet counts and platelet transfusions from birth until 36 weeks PMA were recorded. Briefly, mouse pups (with nursing dams) are exposed to 75% oxygen from P7-P12 to induce retinal vessel loss and returned to room air at P12-P17, when hypoxic retina stimulates neovascularization. Maximum retinal neovascularization (and remaining vaso-obliteration) at P17 was quantified. To deplete platelets in mice with oxygen-induced retinopathy, anti-GPIbα antibody was injected intraperitoneally.

RESULTS

Any episode of thrombocytopenia (platelets < 100 × 10^9/L) at ≥ 30 weeks post-menstrual age (at onset

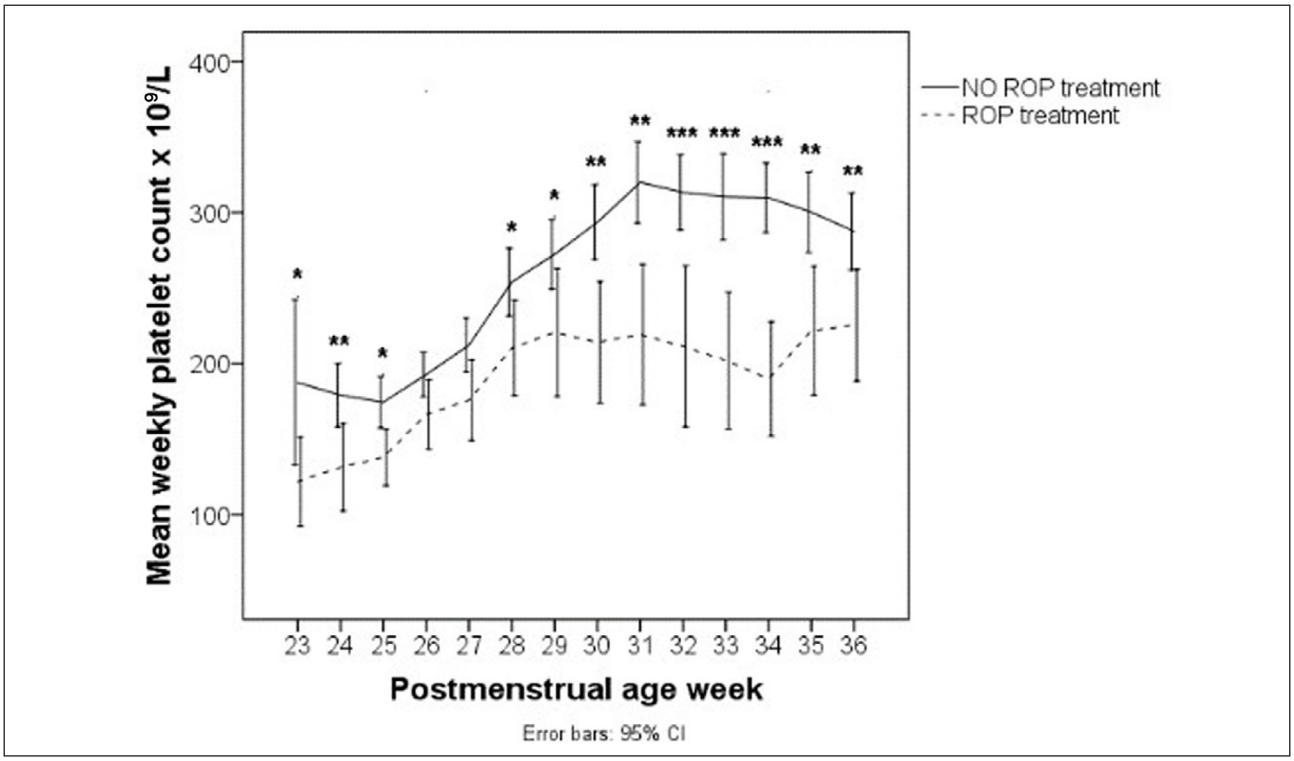

Figure 1 (ABS 12). Infants with severe ROP requiring treatment have a lower weekly median platelet count compared to infants with less severe ROP not requiring treatment at different postmenstrual ages.

of ROP) was an independent risk factor for severe ROP requiring treatment (OR 2.97, CI 95% 1.37-6.46, p = 0.006). Infants with severe ROP requiring treatment also had a lower weekly median platelet count compared to infants with less severe ROP not requiring treatment (193 × 10^9/L, range: 14-695 vs. 262 × 10^9/L, range: 17-786; p < 0.001) (**Fig. 1**). In a mouse oxygen-induced retinopathy model of ROP, platelet counts were 30% lower at P17 (p = 0.008) (the peak of neovascularization) compared to controls. Platelet transfusions at the onset of retinopathy, P15-P16, suppressed neovascularization by 25% (p = 0.0026) and platelet depletion increased neovascularization by 65% (p = 0.0011).

CONCLUSIONS

Low platelet count is a risk factor for preterm infants developing severe ROP requiring treatment and, in a murine model of retinopathy, platelet transfusion suppressed retinopathy.

ABS 13

COGNITIVE AND BEHAVIORAL ASPECTS OF EXECUTIVE FUNCTIONING AT AGE 6.5 YEARS IN CHILDREN BORN EXTREMELY PRETERM: A SWEDISH NATIONAL PROSPECTIVE STUDY (EXPRESS)

A. Farooqi[1], F. Serenius[2], M. Adamsson[1], M. Hafström[3], U. Åden[4], K. Stjernqvist[5]

[1]Unit of Pediatrics, Institute of Clinical Sciences, University of Umea, Umea, Sweden

[2]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[3]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

[4]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[5]Division of Developmental Psychology, Department of Psychology, Lund University, Lund, Sweden

INTRODUCTION

Executive functioning has been considered to be one of the crucial mechanisms related to academic and behavioral problems in very preterm or extremely preterm children (EPT). We examined cognitive and behavioral aspects of executive functioning (EF) in EPT children born between 2004-2007 at 22-26 weeks' gestation in all of Sweden within the EXPRESS study (EXtremely PREterm infants in Sweden Study), and compared these with term-born control children. We also assessed whether group differences in EF would persist among EPT children without major neurodevelopmental disability and the relation of EF with the sociodemographic factors was examined

METHODS

A total of 360 of 441 (82% of all eligible survivors) EPT children born in all of Sweden (mean age = 6.5 years, mean birth weight = 780 g, and mean gestational age = 24.9 weeks) and 371 matched term controls were assessed. General intelligence was assessed using the Wechsler Intelligence Scale for Children (WISC-IV), and cognitive aspects of EF were analyzed using EF-sensitive subscales of the WISC-IV. Behaviors related to EF were assessed using the Five to Fifteen questionnaire, a validated parent instrument. Analyses performed included multivariate analyses of covariance (ANCOVA and MANCOVA) and logistic regression analyses.

RESULTS

The EPT children displayed significant deficits in cognitive aspects of EF compared with the controls, exhibiting decreases on the order of 0.6 SD to 1.2 SD for tasks of verbal conceptual reasoning, verbal and non-verbal working memory, spatial conceptualization, processing speed and planning ability (p < 0.001 for all). After excluding the children with major neurosensory impairment or a Full Scale Intelligence Quotient of < -2 SD compared with the controls, significant differences in the cognitive aspects sensitive to EF were observed on all tests. Compared with controls, parents of EPT children reported significantly more EF-related behavioral problems. MANCOVA of the 5 subsets of WISC-IV sensitive to EF revealed significant main effects for the group status (EPT vs control), sex and mothers education, for which all effect sizes were medium to large (6% to 23%).

CONCLUSIONS

EPT children who received active perinatal care are at an increased risk of executive dysfunction, even after excluding children with major neurodevelopmental disabilities. These findings suggest the need for timely interventions that address specific cognitive vulnerabilities and executive dysfunctions.

ABS 14

EARLY AMPLITUDE INTEGRATED ELECTRO-ENCEPHALOGRAM AS A PREDICTOR OF BRAIN INJURY IN NEWBORNS WITH VERY LOW BIRTH WEIGHT: A COHORT STUDY

R.C. Silveira[1], L.V. Magalhaes[2], M.I. Winckler[3], J.A. Bragatti[4], R.S. Procianoy[1]

[1]Department of Pediatrics, Federal University of Rio Grande do Sul, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

[2]Postgraduate Program in Child and Adolescent Health, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

[3]Pediatric Neurology Section, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

[4]Clinical Neurophysiology Unit, Neurology Section, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

INTRODUCTION

Very low birth weight newborns are at increased risk of brain injury. The amplitude integrated electroencephalogram (aEEG) can assist in early diagnosis and detect patients at risk. The aim is to evaluate the relationship between aEEG performed in very low birth weight preterm infants during the first 48 hours of life and severe alterations in imaging tests performed during the neonatal period.

METHODS

Prospective cohort study conducted over a period between February 2013 and September 2015 including preterm newborns with birth weights between 750 and 1,500 g clinically stable at the time of enrollment. An aEEG (NicoletOne monitor with 2 channels C3-P3, C4-P4, according to the 10-20 system) was performed during the first 48 hours of life and analyzed for the background activity, sleep wake cycle, and epileptic activity. Concomitant with the aEEG, cEEG and video EEG were performed for the detection of electrographic epileptic seizures. Severe lesions on imaging tests (grade 3 or 4 periventricular hemorrhage, leukomalacia and other white matter changes, and hydrocephalus) during the neonatal period were considered as adverse conditions. Sample size was calculated based on the results from the Hellström-Westas study.

RESULTS

A total of 70 patients with a mean birth weight of 1,226 g and mean gestational age of 30 weeks participated in the study. Adverse outcomes were observed in 7 patients (10%). There was a significant relationship ($p < 0.001$) between moderate to severe changes on the aEEG and severe alterations observed on the imaging tests, for both ultrasonography (US) and magnetic resonance imaging (MRI) with high evidence of brain injury on US or MRI (OR = 48, CI 95% 5-460).

The aEEG showed a sensitivity of 85%, specificity of 89%, positive predictive value of 46%, and negative predictive value of 98% for serious lesions detected on the US or MRI during the neonatal period.

CONCLUSIONS

In very low birth weight preterms, early aEEG with moderate to severe background activity is associated with severe structural changes detected in imaging studies conducted during the neonatal period. This method should be considered as an auxiliary screening tool for the detection of brain lesions in this population.

ABS 15

NEONATAL ADMISSIONS FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY: WEEKEND AND OUT OF HOURS EFFECT

F. Ceroni, M. Parmar, S. Narayanan, N. Merchant

Neonatal Department, West Hertfordshire NHS Trust, Watford General Hospital, London, UK

INTRODUCTION

Healthcare studies have shown that there is evidence of sub-optimal care and outcomes when patients are admitted on weekends (weekend effect) or outside usual working hours (out of hours effect). Hypoxic ischemic encephalopathy (HIE) is a leading cause of acquired neonatal brain injury and may result in death or long-term neurodisability. Intrapartum care for women often involves time critical decisions dependent on access/input from senior professionals. Very limited information is available that explores out of hours/weekend effect on HIE. The aim of this study was to compare the incidence and variation of neonatal HIE in relation to working hours.

METHODS

Retrospective targeted data collection was performed over a period of 6 years (Jan 2010-Dec 2015) from a busy district general hospital with approximately 5,500 deliveries per year. Data obtained from the neonatal Badgernet included day and time of birth and grade of HIE. Total number of deliveries was obtained from local birth registry. Weekend was defined from Friday 17:00 - Monday 08:59 and out of hours as 17:00-08:59. Time stratified analysis was done to look for any peaks in incidence of HIE in relation to time of birth. Results were collated and analysed using STATA® 12 and Microsoft® Excel® 2016. Logistic regression analysis and Pearson chi^2 test was used. A p-value of less than 0.05 was used as the cutoff for significance.

Table 1 (ABS 15). Hypoxic ischemic encephalopathy (HIE) and hour of birth. Showing no difference in gestation, birth weight gender and HIE grade and time of delivery, however significant increase in incidence of HIE out of hours.

	In Hours (n = 13)	Out of Hours (n = 62)	p-value
Mean gestation (SD), weeks	39.07 (1.8)	39.5 (1.47)	0.36
Mean birth weight (SD), g	3,274.07 (743.33)	3,405.44 (634.81)	0.51
Gender M:F	7:6	32:30	0.86
Grade of HIE 1:2:3	5:6:2	31:24:7	0.46
HIE incidence (per 1,000 live births)	**1.2**	**2.6**	**0.01**

HIE: hypoxic ischemic encephalopathy.

RESULTS

Over the 6 year study period, 75 babies were diagnosed with moderate to severe HIE. The median gestation at birth was 40 weeks (36-42 weeks) and median birth weight 3,330 g (2,040-4,840 g). 52% were male infants. Incidence of neonatal HIE was 1.2/1,000 live births during normal working hours and 2.6/1,000 live births during out of hours/weekends. This difference was statistically significant (p = 0.01, OR 2.1, 95% CI [1.2-3.8]). There was no difference in the mean gestation, birth weight, gender or grade of HIE if born in hours or out of hours (**Tab. 1**).

CONCLUSIONS

Our data demonstrates a weekend/out of hours' effect in the occurrence of neonatal HIE. This warrants further investigation into relevant maternal factors and obstetric/midwifery/neonatal staffing levels during out of hours/weekends. This information may provide evidence-based guidance for perinatal workforce planning outside normal working hours. A larger study is required to confirm this effect.

ABS 16

WHICH PARTS OF GROWTH SHOULD BE MONITORED FOR NEURODEVELOPMENT OF PRETERM INFANTS

I.G. Song[1], H.R. Yoon[2], Y.M. Yoon[2], J.S. Shin[2], S.H. Shin[2], E.K. Kim[2], H.S. Kim[2]

[1]*Pediatric Department, Kyung Hee University Hospital, Seoul, Korea*

[2]*Pediatric Department, Seoul National University Children's Hospital, Seoul, Korea*

INTRODUCTION

Preterm infants are at risk of growth retardation and impaired development. In this study, we investigated which parts of body growth in pre-/post-discharge era are important for neurodevelopment with assessing z-scores at three points and growth velocity between each period.

METHODS

This was a retrospective cohort study including preterm infants who were born at less than 32 weeks of gestation or 1,500 g between January 2006 and December 2015 at Seoul National University Children's Hospital. We excluded small or large for gestational age, congenital anomalies and subjects who were diagnosed moderate to severe cerebral palsy. We calculated z-score of weight (WZ), length and head circumference (HZ) at birth, postmenstrual age (PMA) 35 weeks, corrected age (CA) 4 and 18 months, and weight growth velocity between birth to PMA 35 weeks and CA 4 months, and 35 weeks to 4 months. Also, we evaluated changes of z-score from PMA 35 weeks to CA 4 and 18 months. Linear regression with adjustment was performed to examine the relationship between growth and Bayley Scales of Infant Development III (BSID) scores.

RESULTS

A total of 115 premature infants were enrolled and 36 infants were excluded. Among 79 subjects, mean BSID cognitive composite scores were 99.1 ± 13.7 and motor composite scores were 96.4 ± 11.9. Cognitive composite scores were correlated with WZ at PMA 35 weeks (β = 6.68, p = 0.037) and weight growth velocity between birth to PMA 35 weeks (β = 1.42, p = 0.032). Changes of HZ between PMA 35 weeks and 4 months (β = 3.75, p < 0.001), and 8 months (β = 4.78, p < 0.001) were correlated with cognitive composite scores, and these were also highly correlated with motor composite scores both PMA 35 weeks to 4 months (β = 2.70, p = 0.001) and 8 months (β = 3.16, p = 0.002). Length at PMA 35 weeks and after discharge was not correlated with development scores.

CONCLUSIONS

Our study indicated that different growth indicators should be monitored for neurodevelopment according to period. That is, bodyweight growth during admission and growth of head circumference after discharge could be correlated with development of cognition and motor function. Further researches about interventions to improve pre- and post-discharge growth and make protocols

to assess growth and development in connection with each other are needed.

ABS 17

TARGETED METHYLATION TESTING OF A 154 PATIENT'S COHORT WITH CLINICAL FEATURES OF IMPRINTING DISORDERS: EVIDENCE OF MULTILOCUS METHYLATION DEFECTS

A.Touati[1], S. Nouri[2], F. Chioukh[3], M. Haddaji Mastouri[1], N. Ben Salah[1], S. Trabelsi[1], S. Hammami[4], S. Mougou[1], M. Gribaa[1], N. Guedich[4], H. Seboui[2], A. Nouri[4], K. Monastiri[3], A. Saad[1], D. H'mida-Ben Brahim[1]

[1]Laboratory of Human Cytogenetics, Molecular Genetics and Reproductive Biology, Farhat Hached University Hospital, Sousse, Tunisia

[2]Department of Neonatology, Farhat Hached University Hospital, Sousse, Tunisia

[3]Department of Neonatology, Fattouma Bourghiba University Hospital, Monastir, Tunisia

[4]Department of Pediatrics, Fattouma Bourghiba University Hospital, Monastir

INTRODUCTION

Imprinting disorders are a group of congenital diseases affecting growth, development and metabolism. Their underlying molecular defects include mutation, epimutation, copy number variation and chromosomal alterations, and can be further complicated by somatic mosaicism and multi-locus methylation defects.

METHODS

In order to investigate multilocus methylation defects (MLMD) in a series of 154 patients referred for Beckwith-Wiedemann (BWS), Silver-Russell (SRS) and Prader-Willi (PWS) syndromes, we studied the methylation status of 5 maternally (6q24, 7q32, 7p12, 11p15.5 and15q11-13) and 3 paternally (11p15.5, 14q32and15q11-13) imprinted loci.

RESULTS

Eight out of 19 BWS patients harbored maternal ICR2 hypomethylation; 1 BWS patient had paternal 11p15.5 uniparental disomy, and 1 BWS patient harbored paternal 11p15.5 duplication. Among the 20 suspected SRS patients, the diagnosis was confirmed in only one patient, who showed maternal 11p15.5 duplications. Among the 115 suspected PWS patients, 7 showed maternal 15q11-13 uniparental disomy, and 5 had paternal 15q11q13 deletion. MLMD concerns only 2 patients out of 154. The first patient referred for BWS carried both maternal ICR2 hypomethylation and 7q32 hypomethylation. He presented a BWS phenotype with macrosomia, macroglossia, facial dysmorphisms, hypothyroidism and no obvious SRS clinical features. The second patient, referred for BWS with macrosomia and macroglossia, surprisingly showed 7p12 and 6q24 hypomethylation.

CONCLUSIONS

Several trans-acting factors involved in the imprinting cycle, have been postulated to cause MLMD and indeed DNA mutations in these factors have been reported. Thus, we suggest investigating mutations in genes implicated in maintenance and establishment such as ZFP57, NLRP2, NLRP7 and CTCF.

ABS 18

STEINERT MYOTONIC DYSTROPHY (DM1): WHAT ABOUT CARDIAC INVOLVEMENT?

H. Hadj Abdallah[1], Y. Halleb[1], N. Ben Salah[1], F.Z. Chioukh[2], K. Ben Ameur[2], F. Kallel[3], L. Ben Slamia[4], S. Hidar[7], M. Bellallah[8], S. Nouri[8], S. Ben Amor[5], A. Hsin[5], M. Grira[5], H. Ajmi[6], S. Zardi[1], S. Abroug[6], N. Mahdhaoui[8], H. Sboui[8], S. Ben Ammou[5], K. Mestiri[2], A. Saad[1], D. H'mida[1]

[1]Department of Cytogenetics, Molecular Genetics and Reproductive Biology, Farhat Hached Hospital, Sousse, Tunisia

[2]Department of Neonatology, Neonate and Maternity Center, Monastir, Tunisia

[3]Private Pediatrician, Sousse, Tunisia

[4]Private Neurologist, Sousse Tunisia

[5]Department of Neurology, Sahloul Hospital, Sousse, Tunisia

[6]Department of Pediatrics, Sahloul Hospital, Sousse, Tunisia

[7]Department of Gynecology and Obstetrics, Farhat Hachad Hospital, Sousse, Tunisia

[8]Department of Neonatology, Farhat Hachad Hospital, Sousse, Tunisia

INTRODUCTION

Steinert's disease or myotonic dystrophy type 1 (DM1) is an autosomal dominant disease mostly of maternal origin, due to an expansion of CTG triplet more than 50 copies in the 3'UTR region of the DMPK gene (Dystrophy Myotonic Protein Kinase). It is a multisystemic disease characterized by myotonic muscular dystrophy that may involve the cardiac system. The cardiac features include rhythm or conduction disorders that can lead to dilated cardiomyopathy. This cardiac involvement can endanger the vital prognosis. It is the principal cause of early mortality in DM1 patients.

METHODS

Herein we report a cohort of 15 patients suspected of DM1 referred to the department of Cytogenetics, Molecular Genetics and Reproductive Biology at the hospital of Farhat Hached in Sousse between the years 2010 and 2017. Our patients have undergone a PCR analysis in search of pathological expansion of more than 50 CTG triplets at the DMPK gene.

RESULTS

A pathological expansion of more than 50 repeats of CTG triplets characteristic of Steinert myotonia has been found in 15 patients. Two patients presented with cardiac conditions: a second degree atrioventricular block and grade II mitral insufficiency. Cardiac involvement is reported in the literature at a rate varying between 50% and 80%. The small proportion of cardiac involvement in our cohort (2 out of 15 patients) could be attributed to the relatively late onset of cardiac symptoms. Generally, cardiac symptoms are seen between 10 and 30 years like the two reported patients, while most of our patients are newborns. This cardiac involvement makes one of the rare cases where pre-symptomatic diagnosis is mandatory for children and minor relatives of DM1 patients. This pre-symptomatic diagnosis is indicated from the age of 10 years to detect precociously a cardiac involvement.

CONCLUSIONS

Early diagnosis and long-term cardiologic monitoring impact the prognosis of DM1. This underscores the importance of coordination between geneticists and cardiologists to ensure adequate patient care and genetic counseling for parents.

ABS 19

ATYPICAL BRAIN DEVELOPMENT ASSOCIATED WITH PRENATAL METHADONE EXPOSURE

V. Monnelly[1], D. Anblagan[2], A. Quigley[3], E. Cooper[4], H. Mactier[5], S. Semple[6], M. Bastin[2], J. Boardman[1,2]

[1]MRC Centre for Reproductive Health, University of Edinburgh, UK

[2]Centre for Clinical Brain Sciences, University of Edinburgh, UK

[3]Department of radiology, Royal Hospital for Sick Children, Edinburgh, UK

[4]Obstetric Department, Royal Infirmary of Edinburgh, UK

[5]Neonatal Department, Princess Royal Maternity, Glasgow, UK

[6]Clinical Research Imaging Centre, University of Edinburgh, UK

INTRODUCTION

Globally, 17.4 million people aged between 15-64 use opiates, of whom approximately 12 million inject drugs intravenously. 5.4% of pregnant women in the US report illicit drug use during their pregnancy. Maternal and perinatal outcomes for pregnant opioid users can be improved by maintenance methadone, but there are uncertainties about the safety of exogenous opioids on the developing brain. There are also concerns regarding neurodevelopmental outcomes of children who were exposed prenatally to methadone. We tested the hypothesis that brain development is altered at birth among infants prenatally exposed to methadone.

METHODS

20 term methadone-exposed infants (mean gestational age [GA] 38 ± 5, mean birth weight 2,721 ± 350 g) and 20 non-exposed term controls (mean GA 39 ± 1 weeks, mean birth weight 3,349 ± 452 g) underwent diffusion MRI scanning without sedation at a mean corrected age of 39 ± 2 and 41 ± 1 weeks, respectively. An optimised Tract-based Spatial Statistics (TBSS) pipeline was used to perform voxel-wise statistical comparison of fractional anisotropy (FA) data. FA is a robust marker of white matter development, associated with later neurodevelopmental outcome, and TBSS is sensitive to group wise differences using sample sizes of 20 per group. The study was funded by Theirworld (www.theirworld.org) and ethical approval was granted. All parents gave written, informed consent.

RESULTS

After adjustment for GA at MRI, methadone-exposed neonates had decreased FA within the centrum semiovale, inferior longitudinal fasciculi (ILF), and both internal and external capsules ($p < 0.05$: **Fig. 1A**). Median FA across the white matter skeleton was 12% lower in methadone-exposed neonates. Head circumference (HC) z-scores were lower in the methadone-exposed group (mean -0.52 vs 1.15, $p < 0.001$). After adjustment for HC, differences in FA remained in the anterior and posterior limbs of the internal capsule and ILF (**Fig. 1B**).

19 of 20 methadone-prescribed mothers smoked tobacco and 12 out of 20 used heroin during pregnancy. Mean methadone dose at delivery was 69 mg (range 8-160 mg).

CONCLUSIONS

Prenatal methadone exposure is associated with reduced microstructural integrity of major white matter tracts at birth, independent of head growth. Further research is required to determine optimal management of opioid addiction during pregnancy for the mother and child. This should include

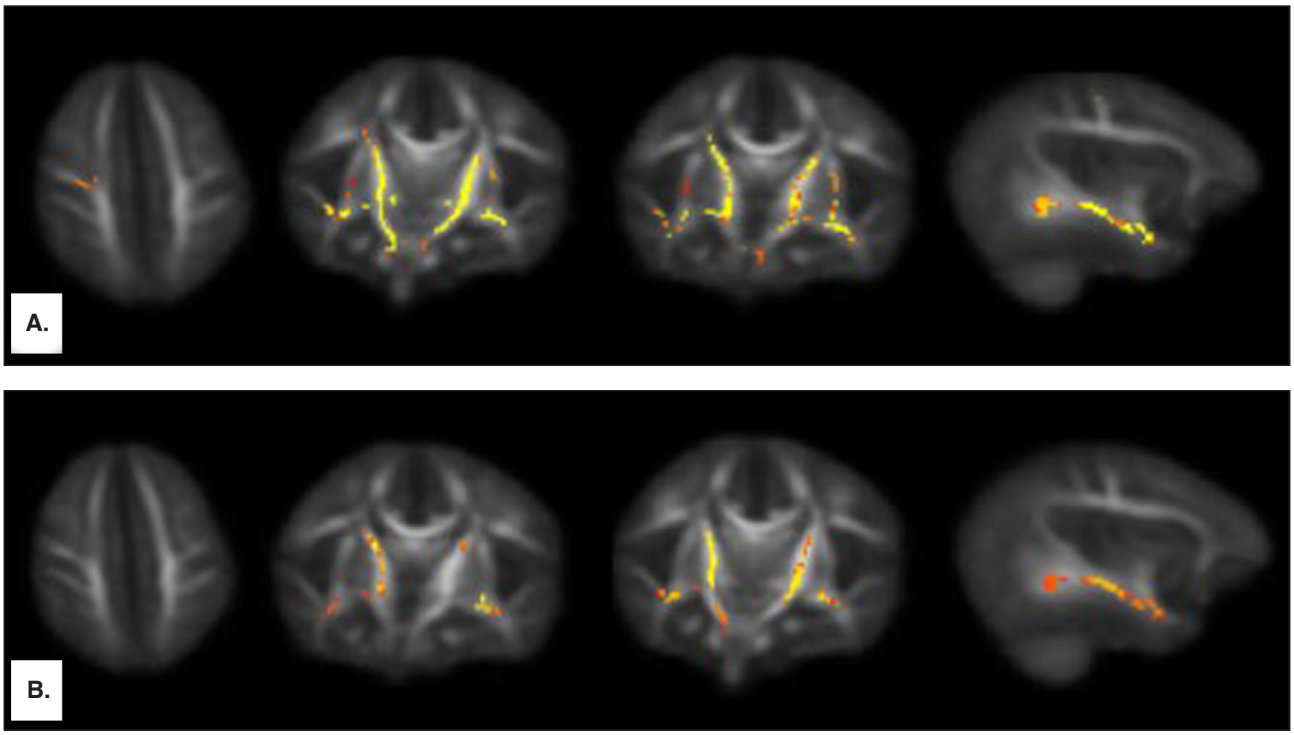

Figure 1 (ABS 19). Mean fractional anisotropy (FA) skeleton shown in white. Voxels with significantly lower FA in the methadone-exposed neonates are shown in warm colour scale.

consideration of alternative opioid substitutes, and evaluation of brain development and long-term neurocognitive outcome.

ABS 20

CHARACTERISATION OF THE NEONATAL CORPUS CALLOSUM (CC) USING MAGNETIC RESONANCE IMAGING (MRI) AND CRANIAL ULTRASOUND (US)

M. Mills[1], V. Pelling[1], L. Harris[1], J. Smith[1], H. Rabe[2], R. Fernandez[2]

[1]Radiological Sciences, Brighton & Sussex University Hospitals NHS Trust, Brighton, UK

[2]Department of Neonatology, Brighton & Sussex University Hospitals NHS Trust, Brighton, UK

INTRODUCTION

Developmental abnormalities of the corpus callosum (CC) are linked to neuro-developmental disorders. Neonatal neuroimaging may allow earlier diagnosis and intervention. Magnetic resonance imaging (MRI) is often considered the most sensitive imaging modality to white matter changes. The majority of studies, which correlate measurements of the CC with neurological outcomes, have used MRI. However, MRI is lengthy, expensive and may require patient sedation. Conversely, cranial ultrasound (US) can repeatedly be performed at the bedside and is inexpensive. If measurements obtained from cranial US correspond well to their MR counterparts they may be used for the same diagnostic purposes. We therefore aimed to assess the level of correspondence between MRI and US.

METHODS

This study aimed to characterise the structure of the neonatal CC visualised in MRI and with a phased and linear array US probes (PUS and LUS), using established methodologies. Images of term neonates with a diagnosis of hypoxic ischaemic encephalopathy were analysed, for which 2D T1 and T2 weighted MRI and cranial US images existed. Both LUS and PUS measurements were compared with those obtained in MRI by correlation analysis. Additionally Bland-Altman analysis was performed to investigate for bias between measurements and the ability to replace MRI with US methods. Image viewing and measurements were performed using Phillips IntelliSpace PACS 4.4. Data are presented as median and IQR and analysis was performed using SPSS® v23; $p < 0.001$ was considered statistically significant.

Table 1 (ABS 20). Displayed are median, interquartile range (IQR) and correlation coefficients (Spearman's Rho, ρ) between MRI and two US modalities.

	Measurement Median, IQR and Correlation Strengths				
	MRI (IQR), mm	PUS (IQR), mm	LUS (IQR), mm	MRI-PUS, ρ	MRI-LUS, ρ
Long axis	43.75 (4.93)	45.00 (3.25)	44.30 (1.60)	**0.72**	**0.87**
Body width	2.30 (1.20)	2.20 (0.70)	2.40 (0.90)	0.42	0.44
Genu width	4.45 (2.55)	4.10 (1.45)	4.80 (2.00)	**0.69**	**0.64**
Splenium width	4.65 (1.15)	5.60 (2.45)	5.40 (1.90)	0.49	**0.71**
Area 1	0.04 (0.04)	0.06 (0.08)	0.07 (0.05)	0.52	0.47
Area 2	0.23 (0.21)	0.19 (0.18)	0.25 (0.12)	**0.65**	**0.79**
Area 3	0.29 (0.11)	0.25 (0.08)	0.25 (0.06)	0.30	0.35
Area 4	0.20 (0.06)	0.15 (0.04)	0.19 (0.05)	0.47	0.06
Area 5	0.16 (0.06)	0.15 (0.06)	0.16 (0.05)	0.36	0.25
Area 6	0.16 (0.07)	0.14 (0.06)	0.13 (0.06)	0.25	0.39
Area 7	0.44 (0.13)	0.47 (0.21)	0.47 (0.16)	**0.68**	**0.65**
Total area	1.48 (0.53)	1.42 (0.44)	1.57 (0.56)	**0.59**	**0.67**
Coronal width	1.95 (0.40)	2.00 (0.40)	2.10 (0.50)	0.57	**0.75**

MRI: magnetic resonance imaging; PUS: phased array ultrasound probe; LUS linear array ultrasound probe.
Significant correlations are highlighted in bold.

RESULTS

Images from 32 term neonates with a birth weight of 3,484 g (IQR 762 g) were analysed. 53% were male. All measured correlations were positive; however there were poor correlation strengths for segmental area measurements in contrast to linear measurements of the CC (long axis length, genu width, body width, splenium width and coronal width) and the total area of the CC. Among those: total length, genu width, total surface area as well as areas 2 and 7 were the most strongly correlated across modalities. Stronger correlations to MRI measurements were observed for LUS than PUS (**Tab. 1**). This was further supported by Bland-Altman analysis.

CONCLUSIONS

US correlates strongly with some MRI measurements of the CC, making them possibly interchangeable. Bedside US providing reliable structural information of the CC may be useful in establishing the risk of neurological impairment without MRI studies. LUS use may be preferable to this end. Currently these measurements do not appear to be used clinically; however current literature on CC associated conditions warrants further ultrasound research.

ABS 21

COGNITIVE TRAJECTORIES FROM INFANCY TO EARLY ADULTHOOD FOLLOWING BIRTH BEFORE 26 WEEKS OF GESTATION

L. Linsell[1], S. Johnson[2], D. Wolke[3], H. O'Reilly[4], J. Morris[5], J. Kurinczuk[1], N. Marlow[4]

[1]National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK
[2]Department of Health Sciences, University of Leicester, Leicester, UK
[3]Department of Psychology, Warwick Medical School, Coventry, UK
[4]Institute of Women's Health, University College London, London, UK
[5]Queen Mary University of London, Barts and The London School of Medicine and Dentistry, London, UK

INTRODUCTION

The most common neurologic impairment in children born extremely preterm is in cognitive function but little is known about their course of cognitive development into adulthood. The aim of this study was to determine the trajectory of cognitive test scores from infancy to adulthood compared to term-born individuals.

METHODS

We conducted a longitudinal analysis of cognitive trajectories in a prospective, population-based cohort of 315 infants born 25 completed weeks at gestation or less and 160 term-born classroom controls followed-up to 19 years. Participants were invited for up to 4 standardized, blinded cognitive assessments.

RESULTS

The mean cognitive scores of extremely preterm individuals over the period were on average 25.2 points below their term-born peers (95% CI: -27.8 to -22.6) and significantly lower at every assessment. Cognitive test scores were stable in both groups.

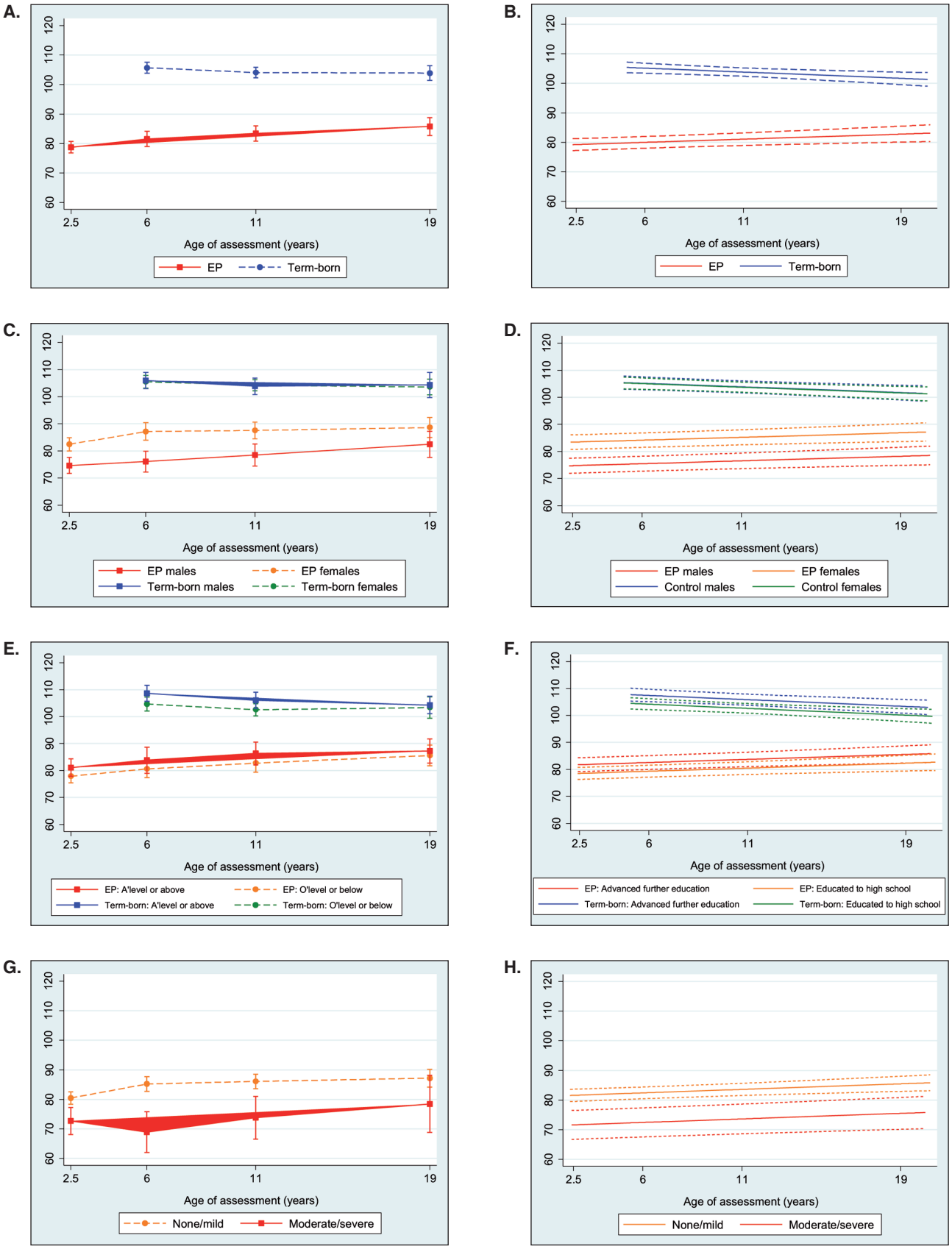

Figure 1 (ABS 21). Observed and predicted cognitive test scores. **A.** Extremely preterms (EP) and term-born controls (observed). **B.** EP and term-born controls (predicted). **C.** EP and term-born controls by sex (observed). **D.** EP and term-born controls by sex (predicted). **E.** EP and term-born controls by maternal education (observed). **F.** EP and term-born controls by maternal education (predicted). **G.** EP by neonatal brain injury (observed). **H.** EP by neonatal brain injury (predicted). Continues on the next page.

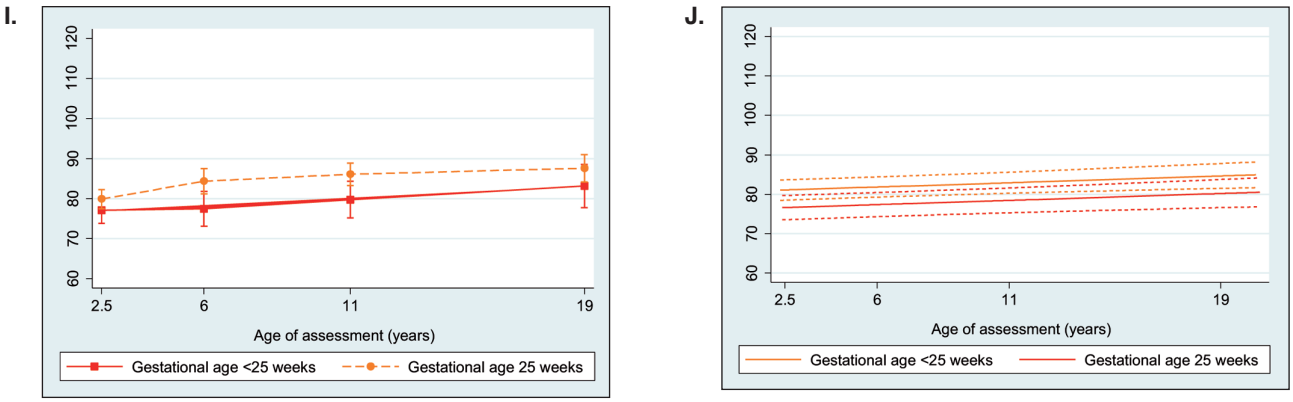

Figure 1 (ABS 21). I. EP by gestational age (observed). **J.** EP by gestational age (predicted). Continues from the previous page.

Cognitive scores in term males and females did not differ significantly, but the scores of extremely preterm males were 8.8 points below those of extremely preterm females (95% CI: -13.6 to -4.0). Higher maternal education elevated scores in both groups by 3.2 points (95% CI: 0.8 to 5.7). Within the extremely preterm group, moderate to severe neonatal brain injury (mean difference: -10.9, 95% CI: -15.5 to -6.3) and gestational age less than 25 weeks (mean difference: -4.4, 95% CI: -8.4 to -0.4) also had an adverse impact on cognitive function. Cognitive test scores are presented in **Fig. 1**.

CONCLUSIONS

There is no evidence that impaired cognitive function in extremely preterm individuals materially recovers or deteriorates from infancy through to 19 years. Cognitive test scores in infancy and early childhood reflect early adult outcomes.

ABS 22

INHIBITORY CONTROL AT 20 MONTHS PREDICTS VP/VLBW AND TERM ADULTS' ATTENTION, IQ, AND WEALTH AT AGE 26 YEARS

J. Jaekel[1,2], N. Baumann[2], P. Bartmann[3], D. Wolke[2]

[1]*Department of Child and Family Studies, University of Tennessee Knoxville, Knoxville, TN, USA*

[2]*Department of Psychology, University of Warwick, Coventry, UK*

[3]*Neonatology, University Hospital Bonn, Bonn, Germany*

INTRODUCTION

Young children born preterm have difficulties inhibiting unwanted responses. Early inhibitory control predicts later attention regulation and academic achievement across the whole gestational age range. Potential life-course effects of impaired inhibitory control on very preterm (< 32 weeks gestation, VP) and/or very low birth weight (< 1,500 g, VLBW) adults' outcomes have never been investigated. The aim was to test (1) whether inhibitory control at age 20 months predicts VP/VLBW and healthy term comparison adults' attention regulation, IQ, and wealth at 26 years, and (2) whether VP/VLBW children's lower inhibitory control moderates or mediates their risk for adverse adult outcomes.

METHODS

Participants were 169 VP/VLBW and 197 healthy term born comparison individuals who were studied from birth to adulthood as part of the prospective geographically defined Bavarian Longitudinal Study (BLS). Inhibitory control was assessed at age 20 months with a standardized behavior observation protocol. At age 26 years, attention regulation was observed and rated by psychologists with the Tester's Rating of Adult Behavior (TRAB), full scale IQ was assessed with the Wechsler Adult Intelligence Scale (WAIS) and wealth via a comprehensive composite score.

RESULTS

Compared with healthy term born individuals, VP/VLBW had lower inhibitory control at age 20 months ($p < 0.001$), and lower attention regulation ($p < 0.001$), IQ ($p < 0.001$), and wealth scores at 26 years ($p < 0.001$). Early inhibitory control predicted both VP/VLBW and term adults' attention regulation ($\beta = 0.13$, $p = 0.010$), IQ ($\beta = 0.22$, $p < 0.001$), and wealth scores ($\beta = 0.09$, $p = 0.046$) at 26 years, after controlling for child sex and family socioeconomic status (SES) at birth. Negative effects of VP/VLBW birth on adult outcomes were mediated by early inhibitory control (Sobel attention = -2.40, $p = 0.016$, Sobel IQ = -3.72, $p < 0.001$, Sobel wealth = -2.09, $p = 0.037$, respectively; see **Fig. 1**). There

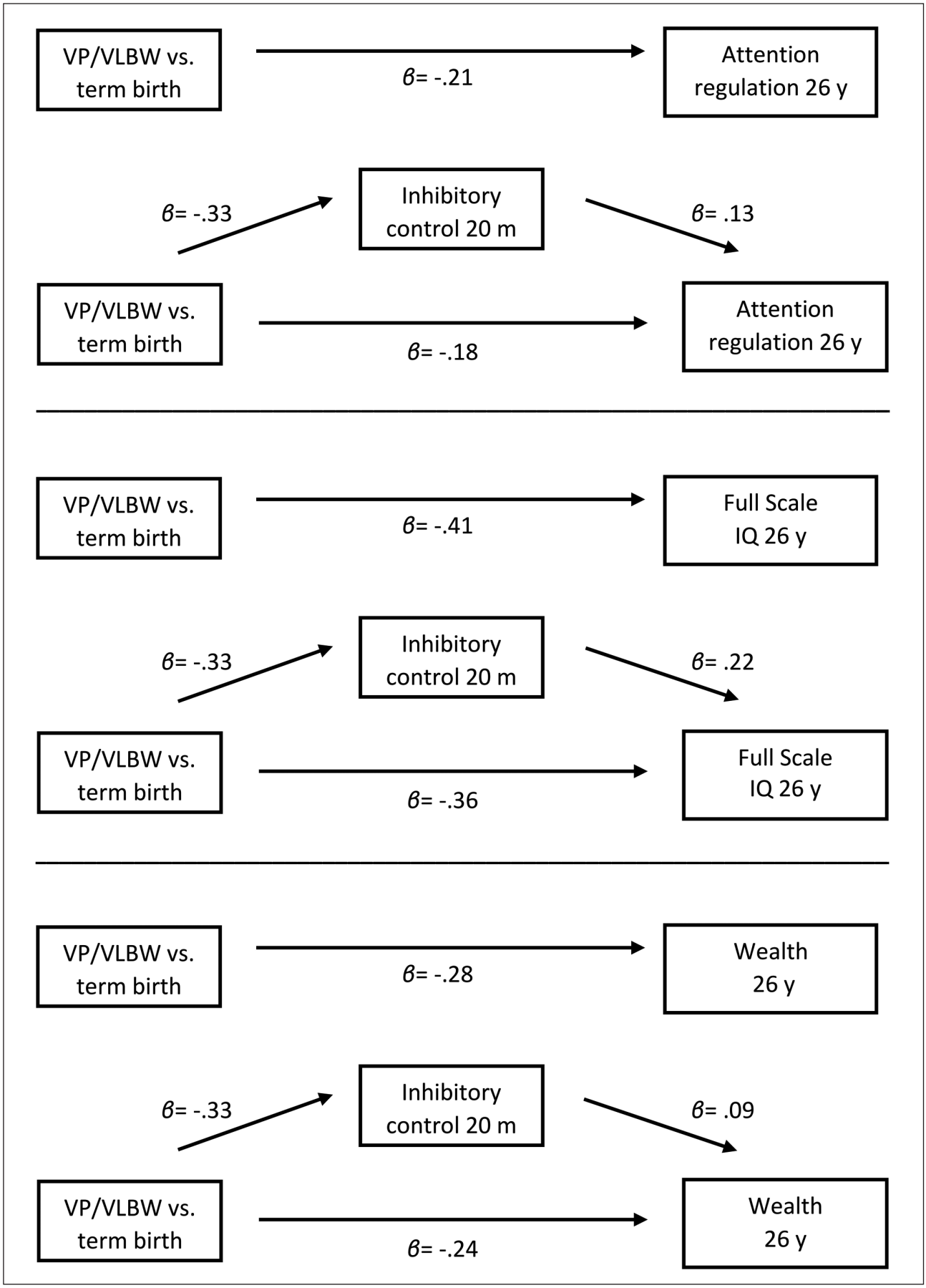

Figure 1 (ABS 22). Mediation of VP/VLBW birth effects via early inhibitory control on adult attention regulation, IQ, and wealth (n = 366).

was no interaction effect of VP/VLBW birth with inhibitory control on adult outcomes.

CONCLUSIONS

Life-long adverse effects of VP/VLBW birth on adult outcomes are mediated by children's early abilities to inhibit unwanted responses. These findings provide important new information about the neurodevelopmental origins linking VP/VLBW birth with life-course underachievement and suggest potential new avenues to intervention.

ABS 23

HEAD MIDLINE POSITION FOR THE PREVENTION OF GERMINAL MATRIX-INTRAVENTRICULAR HEMORRHAGE IN PRETERM INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

O. Romantsik[1], M.G. Calevo[2], M. Bruschettini[1,3]

[1]Department of Paediatrics, Lund University, Skåne University Hospital, Lund, Sweden

[2]Epidemiology, Biostatistics and Committees Unit, Istituto Giannina Gaslini, Genoa, Italy

[3]Research & Development, Section for HTA Analysis, Skåne University Hospital, Lund, Sweden

INTRODUCTION

Head position may affect cerebral hemodynamics and thus be involved indirectly in development of germinal matrix-intraventricular hemorrhage (GM-IVH). It has been suggested that cerebral venous pressure is reduced and hydrostatic brain drainage improved if the patient is in supine midline position (MP). MP might be achieved in the supine and, with the use of physical aids, lateral position as well. MP should be kept at least when the incidence of GM-IVH is greatest, that is, in the first two to three days of life. We aimed to assess whether head MP compared with any other head position is more effective in prevention or extension of GM-IVH in infants born at ≤ 32 weeks' gestational age.

METHODS

We searched the *Cochrane* Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials (RCTs) and quasi-RCTs. We included trials comparing placing very preterm infants in a head MP compared with placing them in a prone or lateral decubitus position, or undertaking a strategy of regular position change, or having no pre-specified position. We used the standard methods of the *Cochrane* Neonatal Review Group. For each of the included trials, two authors independently extracted data and assessed the risk of bias. The primary outcomes considered in this review are GM-IVH, severe IVH and neonatal death. The protocol of this review is published in the *Cochrane* Library.

RESULTS

Two randomized controlled trials, for a total of 110 infants, met the inclusion criteria of this review. Both trials compared supine MP with the bed at 0° to supine head rotated 90° with the bed at 0°. We found no significant differences in the rates of GM-IVH (typical RR 1.14, 95% CI 0.55 to 2.35; 2 studies, 110 infants; $I^2 = 0\%$), severe IVH (typical RR 1.57, 95% CI 0.28 to 8.98; 2 studies, 110 infants; $I^2 = 0\%$), and neonatal mortality (typical RR 0.52, 95% CI 0.16 to 1.65; 2 studies, 110 infants; $I^2 = 28\%$). Among secondary outcomes, we found no significant differences in terms of cystic periventricular leukomalacia, retinopathy of prematurity and severe retinopathy of prematurity. The quality of the evidence supporting these findings is limited due to the imprecision of the estimates. No ongoing studies were identified.

CONCLUSIONS

Supine MP compared with supine with the head rotated 90° seems not to reduce IVH and neonatal mortality in very preterm infants. Limited evidence is available on other clinically relevant outcomes. Given the imprecision of the estimate, the results of this systematic review are consistent with either a benefit or a detrimental effect of supine MP compared to lateral position, and do not provide a definitive answer to the review question.

ABS 24

MOTOR FUNCTION AT EARLY SCHOOL AGE IN EXTREMELY PRETERM BORN CHILDREN WITHOUT MAJOR IMPAIRMENTS IN RELATION TO PERINATAL FACTORS: NATIONAL POPULATION-BASED STUDY (EXPRESS)

J. Bolk[1,2], A. Farooqi[3], M. Hafström[4], U. Åden[1], F. Serenius[5]

[1]Department of Women's and Children's Health, Karolinska Intitutet, Stockholm, Sweden

[2]Sachs'Children and Youth Hospital, Stockholm, Sweden

[3]Department of Clinical Science, Umeå University, Umeå, Sweden

[4]Department of Pediatrics, Institute of Clinical Sciences, The Queen Silvia Children's Hospital, University of Gothenburg, Gothenburg, Sweden

[5]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

INTRODUCTION

Children born extremely preterm are at risk for both cerebral palsy (CP) and more subtle motor impairments. Studies on the risk factors contributing to subtle motor impairments are scarce, and it is not known whether the motor impairments are caused by the prematurity itself or by perinatal risk factors. Our aim was to study the influence of perinatal factors on the development of motor problems in the absence of cerebral palsy, in children born extremely preterm.

METHODS

Children born at gestational age 22-26 weeks, 2004-2007 in Sweden, without CP, visual impairment, autism or cognitive impairment, were assessed at 6.5 years with the Movement-Assessment Battery for Children-2 (M-ABC) within the EXPRESS study (Extremely preterm infants in Sweden study). Definitive motor problems were defined as ≤ 5th percentile, borderline motor function as 6th-15th percentile and normal motor function as > 15th percentile, compared to term born controls. Kruskal-Wallis test, chi-square for trend, and multivariable regression analysis were used as appropriate.

RESULTS

Out of 275 children fulfilling the inclusion criteria, 229 children completed the M-ABC. The children with definitive (n = 85) and borderline (n = 35) motor problems had a lower gestational age ($p < 0.001$), lower birth weight ($p < 0.001$), more days on mechanical ventilation ($p < 0.001$), and had more often been treated with postnatal steroids ($p < 0.001$) compared to the children with normal motor function. The children with definitive motor problems also more often had bronchopulmonary dysplasia (BPD) ($p = 0.03$), severe retinopathy of prematurity ($p = 0.001$) and had more often been treated for patent ductus arteriosus ($p = 0.01$) than children with normal motor function. In the regression model, M-ABC scores were negatively associated to lower gestational age and male sex but not to any other perinatal factors, however, the adjusted R^2 was only 14.5% indicating a small effect size.

CONCLUSIONS

In this group of extremely preterm born children without major impairments, several perinatal factors differed between children with normal motor function and motor problems, however, when put in a regression model only gestational age and male sex remained significant. We conclude that the subtle motor problems seem to be caused by the prematurity itself and not caused by any specific perinatal factor.

ABS 25

COGNITIVE FUNCTIONING IN ADOLESCENTS BORN MODERATELY PRETERM AT 32-26 WEEKS' GESTATION: A SWEDISH REGIONAL POPULATION BASED CASE CONTROL STUDY

M. Adamsson[1], B. Hägglöf[2], M. Bäckman[1], A. Farooqi[1]

[1]Units of Pediatrics, Institute of Clinical Sciences, University of Umeå, Umeå, Sweden
[2]Child and Adolescent Psychiatry, Institute of Clinical Sciences, University of Umeå, Umeå, Sweden

INTRODUCTION

Children born moderately preterm constitute a very large group of preterm children and NICU graduates, yet the extent of adverse outcomes including cognitive functioning in their school years remains grossly under-researched. We assessed cognitive functioning in 12-14 year old adolescents born moderately preterm children (MPT; 32-36 weeks' gestation) at three different hospitals in the northern region of Sweden that represent three different level-of care units and thus are representative of the centers that provide care to these infants in all of Sweden.

METHODS

243 consecutive MPT children born between 2000 and 2003 at 3 hospitals in the northern Swedish region were compared with 225 term-born controls, matched for gender, birth hospital and birth date (± 4 weeks). Subjects were tested by trained psychologists with Wechsler Intelligence Scale for Children (WISC-IV), a children's IQ-test consisting of 10 subtest, within four different cognitive areas: language skills (Verbal Comprehension, VC), visual-spatial skills (Perceptual organization, PO), Working Memory and Processing Speed. Cognitive aspects of executive functioning (EF) were specifically explored using EF-sensitive subscales of the WISC-IV. Relation of perinatal and social risk factors with cognitive impairment was examined. Performed analyses included multivariate linear and logistic regression.

RESULTS

MPT children had significantly lower mean full scale IQ scores (FSIQ) than controls, (Mean difference

-4.7 points, 95% CI, -7.43 to -2.1, p = 001). Borderline intelligence or cognitive impairment (FSIQ scores -2 SD) was present in 22.4% of MPT adolescents and 13.6% of the controls (p < 0.001). The corresponding values of the serious cognitive impairment (FSIQ < -2 SD) was 9.8% vs 3.3%, p < 0.001), respectively. Multivariate analyses of variance of the 4 cognitive domains (VO, PO, working memory and processing speed) revealed significant main effects of group status (MPT vs Controls), sex and social risk composite score, for which all effect sizes were medium (6%-10%).

CONCLUSIONS

Cognitive difficulties affect functioning of more than one-fourth of moderately preterm children. Our findings suggest that identification and monitoring of these problems and their precursors is needed at younger age for timely interventions.

ABS 26

EARLY RISK FACTORS FOR ADVERSE NEUROMOTOR DEVELOPMENT IN TERM INFANTS AFTER MODERATE HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

A. Matic

Neonatology Department, Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia

Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) is one of the main causes of adverse neuromotor development in term infants. Prognosis for infants with mild and severe HIE is rather well established: mild HIE usually leaves no motor sequelae, while severe HIE has death or major neuromotor disability as a consequence. In contrast, in moderate HIE early prognosis of long-term neuromotor outcome is difficult to specify. The aim of our study was to find some risk factors, which could help in early prognosis of neuromotor outcome in term infants after moderate HIE.

METHODS

We retrospectively collected data of all term infants with moderate (Sarnat stage 2) HIE who were born during the period 01.01.2010-31.12.2014 and treated in our tertiary newborn intensive care unit. After two years' follow-up, their neurodevelopment outcome was estimated; those who were lost at follow-up were excluded from the further study. According to motor functions assessment at the age of two years, we divided the whole study sample into two groups: children with adverse neuromotor development in the form of cerebral palsy or abnormal neuromotor function, and children with normal neuromotor development. We compared the two groups according to some early risk factors for impaired neurodevelopment.

RESULTS

Out of 48 term infants with moderate HIE, 5 had no regular follow-up. Of the remaining 43 infants, 15 (34.88%) had major neurodevelopmental disability and 28 (65.1%) had normal neurodevelopment. There was no difference between the groups according to primiparity, section delivery, ablation of placenta, gestation, birth weight, male gender, Apgar score in 1st and 5th minute, intubation at delivery, mechanical ventilation, early brain ultrasound, the use of therapeutic hypothermia. In adverse neuromotor development group, seizures (p = 0.036), repeated seizures (p = 0.004), ictal EEG recording (p = 0.003) and anticonvulsive therapy at discharge (p = 0.019) were significantly more often present. In this group epilepsy was diagnosed in 7 children, microcephaly in 4, vision impairment had one child and percutaneous endoscopic gastrostomy for impaired swallowing was applied in 2 children.

CONCLUSIONS

In our study sample, in term infants with moderate HIE, presence of seizures, multiple seizures, ictal EEG recording and need for anticonvulsive therapy at discharge were significant risk factors for adverse neuromotor development during first two years of life.

ABS 27

THERAPEUTIC HYPOTHERMIA IN BABIES WITH HYPOXIC-ISCHAEMIC ENCEPHALOPATHY: EVIDENCE AND CLINICAL PRACTICE

K. Ghazal, A. Panickar, S. Garg

Neonatal Unit, James Cook University Hospital, Middlesbrough, UK

INTRODUCTION

Neonatal hypoxic-ischemic encephalopathy (HIE) is associated with significant long term neurological deficits in term and near-term neonates. Therapeutic hypothermia is the standard of care for moderate to severe HIE as endorsed by the National Institute for Health and Clinical Excellence in 2010. There is no evidence to support the use of therapeutic hypothermia in babies with mild HIE.

METHODS
Our aim was to assess the practice of therapeutic hypothermia of babies with moderate to severe HIE in a busy tertiary neonatal unit in England and highlight areas which need improvement, to deliver the evidence based care. This study involved retrospective review of medical notes and national database (BadgeNet) of babies admitted to the Neonatal Intensive Care Unit over a period of 6 years (2010 to 2015).
RESULTS
The total cases admitted for active cooling during this period was 54. All but one patient were more than 36 weeks gestation. Active therapeutic hypothermia was started at 80% of babies. In a significant number of cases, it took more than 6 hours to achieve the target temperature. In almost 2/3 of patients, there is an incidence of overcooling. In almost all babies, discussion with parents occurred prior to active cooling and none of the patients has been treated with mannitol or steroids during cooling.
CONCLUSIONS
Therapeutic hypothermia is a well-established treatment modality for HIE although the evidence of benefit is only for selected group of patients. The current evidence also suggests that the active cooling needs to be managed as per the protocol to achieve maximum benefit and avoid complications. There needs to be appropriate documentation of reasons to start therapeutic hypothermia but also of reasons for not starting cooling in borderline cases.

ABS 28

EFFECT OF DEHYDROEPIANDROSTERONE AND ITS SULFATE ESTER ON NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY – PRELIMINARY DATA

A. Posod, M. Lachinger, B. Vejnoska, E. Huber, M. Urbanek, U. Kiechl-Kohlendorfer, E. Griesmaier

Pediatrics II (Neonatology), Medical University of Innsbruck, Innsbruck, Austria

INTRODUCTION
Every year, up to 6 in 1,000 newborns are inflicted by neonatal brain injury, mostly of hypoxic-ischemic origin. Advances in perinatal care have improved survival rates of affected infants, but long-term morbidity is substantial. To date, causal therapies are not available. We have previously shown that substances targeting the sigma-1 receptor are neuroprotective in neonatal excitotoxic and hyperoxic injury models. The aim of the present study was to evaluate the effect of endogenous sigma-1 receptor agonists, dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), in *in vitro* and *in vivo* models of neonatal hypoxic-ischemic brain injury.
METHODS
In vitro, oligodendroglial (OLN-93) and neuronal (HT22) cell lines were subjected to oxygen-glucose deprivation (OGD) for 1-3 hours depending on cell type. DHEAS was applied in increasing dosages (0.1 μM, 1 μM, 10 μM vs. vehicle) prior to (pre-), during (co-) or during and after (co- + post-treatment) OGD. Control cells were kept under standard conditions. Cell viability was assessed after a 24-hour recovery period. *In vivo*, seven day-old (P7) CD-1 mice underwent unilateral common carotid artery ligation and were exposed to 8% oxygen/nitrogen for 20 minutes. 2 hours after hypoxia animals received a single intraperitoneal injection of 0.1 μg/g, 1 μg/g, 10 μg/g bodyweight DHEAS or vehicle. Injury extent was assessed by means of a neuropathological scoring system 24 hours after insult (P8).
RESULTS
In vitro, cell viability of OLN-93 cells exposed to OGD was not affected by DHEAS pre-, co- or co- + post-treatment or DHEAS co- or co- + post-treatment in any dosage, but was significantly increased by pre-treatment with DHEAS 10 μM (mean ± SD, pretreatment DHEAS 10 μM 69 ± 3% vs. vehicle 59 ± 9%, p = 0.032, Kruskal-Wallis with post hoc Mann-Whitney U and Bonferroni correction). In HT22 cells, cell viability following OGD was not affected by DHEAS pre-, co- or co- + post-treatment or DHEAS co-treatment in any dosage, but was significantly decreased by pre- and co- + post-treatment with DHEAS 0.1 μM (pretreatment DHEAS 0.1 μM 49 ± 3% vs. vehicle 76 ± 10%, p = 0.016; co- + post-treatment DHEAS 0.1 μM 38 ± 8% vs. vehicle 58 ± 8%, p = 0.02). *In vivo*, P7 and P8 body weight, P8 brain weight and brain weight/body weight did not differ between groups. Also neuropathological injury extent was not affected by DHEAS treatment.
CONCLUSIONS
In vitro, DHEAS seems to exert differential effects on cell viability following OGD, depending on dosage, treatment regimen and cell type. *In vivo*, no effect on neuropathological hypoxic-ischemic injury extent was observed. Whether DHEAS should be considered neuroprotective or potentially

injurious is currently unclear. Prior to a clinical use, further studies elucidating underlying mechanisms of action are urgently need.

ABS 29

LONG-TERM EFFECTS OF NEONATAL COMPLICATIONS ON BRAIN GROWTH AT 10 YEARS OF AGE IN CHILDREN BORN EXTREMELY PRETERM

N. Padilla[1], C. Jimenez-Espinoza[1], H. Kvanta[1], U. Adén[1,2]

[1]*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

[2]*Department of Neonatology, Karolinska University Hospital, Stockholm, Sweden*

INTRODUCTION

We have demonstrated reduced brain volumes at term-age in extremely preterm (EPT) infants (born 10 days, compared with the other EPT born infants [1]. The long-term impact of these neonatal complications on brain growth during childhood is poorly described. We aim to investigate brain volumetric differences in grey matter, white matter,

Table 1 (ABS 29). Intracranial volume (ICV) in the 2 groups of preterm infants, according to gestational age.

Absolute tissue volume (cm³)	Preterm group I (N)	Preterm group II (N)	Group I vs II t (p-value) [a]	Group I vs II F (p-value) [b]
Gestational age	**≤ 25 weeks (25)**	**≥ 26 weeks (22)**		
Cortical grey matter	735.56	737.74	-0.14 (0.88)	0.02 (0.88)
White matter	438.25	442.27	-0.45 (0.65)	0.20 (0.65)
Cerebrospinal fluid	189.57	192.08	-0.64 (0.52)	0.42 (0.52)
ICV	1,363.39	1,372.10	-0.33 (0.74)	0.11 (0.74)
CPAR	1,173.81	1,180.02	-0.27 (0.78)	0.73 (0.78)
IVH	**no IVH (28)**	**IVH I-II (14)**		
Cortical grey matter	748.48	722.50	1.58 (0.12)	0.10 (0.75
White matter	446.83	431.32	1.58 (0.12)	0.13 (0.71)
Cerebrospinal fluid	195.21	183.60	2,81 (0.07)	2.71 (0.10)
ICV	1,390.52	1,337.44	1.85 (0.07)	0.31 (0.57)
CPAR	1,195.31	1,153.83	1.64 (0.10)	0.12 (0.72)
PDA	**no PDA (13)**	**PDA (31)**		
Cortical grey matter	736.12	740.00	-0.23 (0.81)	0.002 (0.96)
White matter	444.58	440.58	0.40 (0.69)	0.52 (0.47)
Cerebrospinal fluid	190.97	191.00	-0.006 (0.99	0.12 (0.72)
ICV	1,371.67	1,371.59	0.003 (0.99)	0.02 (0.87)
CPAR	1,180.70	1,180.59	0.004 (0.99)	0.06 (0.80)
PDA	**no PDA (13)**	**PDA ligation (15)**		
Cortical grey matter	736.12	730.66	0.28 (0.77)	0.01 (0.91)
White matter	444.58	437.28	0.67 (0.50)	0.44 (0.51)
Cerebrospinal fluid	190.97	186.38	0.89 (0.38)	0.25 (0.61)
ICV	1,371.67	1,354.33	0.51 (0.61)	0.54 (0.81)
CPAR	1,180.70	1,167.95	0.43 (0.66)	0.03 (0.85)
PDA	**PDA ligation (15)**	**PDA Ibuprofen (16)**		
Cortical grey matter	730.66	748.76	-0.95 (0.34)	0.84 (0.48)
White matter	437.28	443.67	-0.54 (0.59)	0.18 (0.90)
Cerebrospinal fluid	186.38	195.33	-2.01 (0.05)	1.59 (0.21)
ICV	1,354.33	1,387.77	-1.00 (0.32)	0.004 (0.95)
CPAR	1,167.95	1,192.44	-0.82 (0.41)	0.003 (0.95)
MV	**MV < 10 days (25)**	**MV > 10 days (17)**		
Cortical grey matter	746.84	725.94	0.096 (0.92)	1.59 (0.21)
White matter	443.89	437.92	-0.34 (0.73)	0.42 (0.51)
Cerebrospinal fluid	193.67	187.25	0.82 (0.42)	0.81 (0.37)
Intracranial volume	1,384.40	1,351.12	-1.19 (0.23)	1.15 (0.28)
Cerebral parenchyma	1,190.73	1,163.87	-1.10 (0.27)	1.16 (0.28)

IVH: intraventricular hemorrhage; PDA: Patent Ductus Arteriosus; MV: Mechanical Ventilation; ICV: intracranial volume = all brain tissues; CPAR: cerebral parechyma = all brain tissues excluding cerebrospinal fluid.
[a] Analyses without covariates; [b] analyses with covariates.

and cerebrospinal fluid between EPT children at 10 years of age who were the most immature and/or had neonatal complications (PDA, IVH I-II, Mechanical Ventilation: MV) with those who had not.

METHODS

Forty-seven EPT children (mean gestational age 25.6 weeks [SD 0.91]) underwent structural magnetic resonance imaging at 10 years of age (mean 9.9 [0.83]). Automatic segmentation of T1-weighted images using age-specific templates in SPM8 was done. We segmented grey matter, white matter, and cerebrospinal fluid (CSF). Intracranial volume was calculated (ICV = all brain tissues). Owing to the fact that variations in CSF volumes could affect the ICV in the EPT children, we also calculated the cerebral parenchyma (CPAR = all brain tissues excluding cerebrospinal fluid). Student's t-test and General Lineal Model Analyses were used for comparisons between groups. Analyses were performed with and without covariates (gestational age and/or gender as appropriate).

RESULTS

Of the 47 children scanned at 10 years of age, 31 (66.6%) EPT children had PDA, 15 (53.6%) had surgical ligation; 14 (33.3%) had IVH I-II; 16 (69.6%) had MV > 10 days, and 25 (53.2%) were the most immature (< 25 weeks of gestation). Even though these children tended to have smaller brain volumes than those without those complications, the differences did not achieve statistical significance (**Tab. 1**). The results were not altered when analyses were adjusted for covariates.

CONCLUSIONS

Contrary to the neonatal findings, immaturity, PDA, IVH I-II and MV > 10 days were not associated with altered global growth at 10 years of age, indicating that there is a catch-up brain growth during childhood in EPT children with a complicated neonatal course. Nevertheless, this does not rule out the presence of differences in brain organization, which requires other methods to be demonstrated.

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ABS 30

SECRETONEURIN SERUM CONCENTRATIONS CORRELATE WITH ABNORMAL NEURO-DEVELOPMENTAL OUTCOME AT THE AGE OF 24 MONTHS IN TERM NEONATES WITH ASPHYXIA

K. Wechselberger[1], A. Schmid[1], M. Höck[1], A. Posod[1], M. Urbanek[1], R. Fischer-Colbrie[2], V. Neubauer[1], U. Kiechl-Kohlendorfer[1], E. Griesmaier[1]

[1]Department of Paediatrics II, Neonatology, Innsbruck Medical University, Innsbruck, Austria

[2]Department of Pharmacology, Innsbruck Medical University, Innsbruck, Austria

INTRODUCTION

Secretoneurin (SN) is a neuropeptide, which is found in several endocrine, neuroendocrine and neuronal cells. Its expression is upregulated following cellular hypoxia. In adult patients suffering from hypoxic brain injury following cardiopulmonary resuscitation SN proved its potential as a prognostic biomarker for poor neurological outcome [1]. We previously reported that SN serum concentrations are elevated in asphyxiated newborns suffering from hypoxic ischaemic encephalopathy [2]. We now aimed to evaluate whether SN could serve as a prognostic biomarker in asphyxiated neonates.

METHODS

From November 2013 until July 2015, we included 132 healthy term newborns and seven term newborns with hypoxic ischaemic encephalopathy. SN serum concentrations were evaluated by means of a radioimmunoassay. Infants were categorized into two groups (SN elevated yes/no), which were defined by an increase of SN concentrations by two SD above average of the reference population. Neurodevelopmental outcome was evaluated at the age of 24 months using the Bayley Scales of Infant Development II/III. Adverse outcome was defined as a score of below 85 on either the PDI and/or the MDI (II) or in the language, motor and/or cognitive scale (III). One term newborn (14%) with hypoxic ischaemic encephalopathy was lost to follow-up.

RESULTS

The mean SN serum concentration was 149.18 ± 85.12 fmol/ml in the healthy control group. In the group of term newborns with hypoxic ischaemic encephalopathy four newborns had normal performance and two children showed abnormal performance in neurodevelopmental testing. These two children with abnormal neurodevelopment showed the highest SN serum concentrations (334.25, 621.46 fmol/ml, respectively). There was a strong correlation between SN serum concentrations and neurodevelopmental outcome ($p = 0.033$; partial eta squared = 0.719). The association between elevated SN levels and abnormal neurodevelopmental outcome at the age

of 24 months was nearly significant (chi-squared test: p = 0.067).

CONCLUSIONS

In this pilot study, SN serum concentrations in umbilical cord blood correlated with abnormal neurodevelopmental outcome in asphyxiated neonates. SN seems to be a prognostic biomarker for neurodevelopmental outcome in term newborns with hypoxic ischaemic encephalopathy. Further evaluation of SN in a larger cohort should follow.

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ABS 31

SCREENING C677T POLYMORPHISM IN METHYLENETETRAHYDROFOLATE REDUCTASE GENE IN TAIWAN POPULATION

C.Y. Chuang[1], C.C. Hung[2], Y.N. Su[1,2], P.N. Tsao[3]

[1]Dianthus Maternal Fetal Medicine Clinic, Taipei, Taiwan

[2]Sofiva Genomics Co., Ltd, Taipei, Taiwan

[3]National Taiwan University Children's Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

INTRODUCTION

Single nucleotide polymorphism (SNP) is commonly seen at the position 677 in the methylenetetrahydrofolate reductase (MTHFR) gene. This SNP affect the stability of the MTHFR enzyme structure, and consequently influence the metabolism of folic acid, causing folic acid deficiency. The lack of folic acid may increase the risk of pregnancy complications and neural tube defects in the fetus.

METHODS

From 2013 to 2015, a total 6,090 pregnant women were tested in Taiwan. Genomic DNA was isolated and genotyped using fluorescence resonance energy transfer (FRET) hybridization probes and real-time PCR detection system for the MTHFR C677T polymorphism.

RESULTS

The maternal age ranged from 20 to 39 years in 96.08% of the women. 74.75% (4,552) lived in northern Taiwan, 2.07% (126) lived in central Taiwan, 23.09% (1,406) lived in southern Taiwan, and the remaining 6 cases (0.09%) were non-informative. Genotype frequencies were found to be 54.10% CC (3,295 cases), 38.56% CT (2,348 cases), and 7.34% TT (447 cases) in our populations.

CONCLUSIONS

Homozygosity for the T allele at nucleotide 677 of the MTHFR gene is associated with a 2-3 fold increased risk of having a child with neural tube defects (NTDs). The incidence of NTDs is approximately 2-3 per 1,000 births worldwide. Folic acid has been shown to be effective in preventing NTDs, therefore, a higher dose of folic acid supplementation in pregnancy is recommended.

ABS 32

GENETIC CONTRIBUTIONS TO THE DEVELOPMENT OF INTRAVENTRICULAR HEMORRHAGE IN PRETERM NEWBORNS

D. Szpecht[1], J. Gadzinowski[1], A. Seremak-Mrozikiewicz[2,3], G. Kurzawińska[2], K. Drews[2], M. Szymankiewicz[1]

[1]Chair and Department of Neonatology, Poznan University of Medical Sciences, Poznan, Poland

[2]Department of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poznan, Poland

[3]Department of Pharmacology and Phytochemistry, Institute of Natural Fibers and Plants, Poznan, Poland

INTRODUCTION

Intraventricular hemorrhage (IVH) is a condition, which mainly affects infants born before 32 weeks of pregnancy. Contemporarily, it is thought that genetic factors may play a significant role in the development of IVH. In the pathogenesis of IVH in preterm infants, an important role is played by: a) changes in venous and arterial cerebral flows; b) inflammation that may increase the fragility of the germinal matrix microvasculature; c) the coagulation disturbances that increased risk of thrombosis in the germinal matrix region.

METHODS

100 infants born from singleton pregnancy, before 32^{+0} weeks of gestation, exposed to antenatal steroids therapy, and without congenital abnormalities were included into study. The following polymorphisms were analyzed: 1) involved in inflammation pathway (interleukin-1β (Il-1β) 3953C>T, interleukin-6 (Il-6) -174G>C and -596G>A, tumor necrosis factor

(TNF) -308G>A and 86 bp variable number tandem repeat polymorphism of interleukin-1 receptor antagonist (Il-1RN 86 bp VNTR); 2). related to regulation of blood flow (synthase nitric oxide [eNOS] 894G>T and -786T>C and endothelin-1 [EDN1] 5665G>T); 3) involved in coagulation pathway (factor V [FV] gene 1691G>A, factor II [FII] gene 20210G>A; methylenetetrahydrofolate reductase [MTHFR] 677C>T and 1298A>C).

RESULTS

In our study population 45 (45%) infants developed IVH, including 15 (33.33%) with stage 1, 19 (42.22%) with stage 2, 8 (17.77%) with stage 3 and 3 (6.66%) with stage 4. We found that infants born before 28^{+6} weeks of gestation with genotype GT eNOS 894G>T have 3.4-fold higher risk of developing of IVH (OR 3.431 [1.049-11.22]; p = 0.004). Analysis showed a prevalence 4.5 times higher of IVH stage 2 to 4 in infants with the genotype CC MTHFR 1298A>C (OR 4.511 [1.147-17.75]; p = 0.026). Our investigation did not confirm any significant prevalence of IVH development in other studied mutations/polymorphisms.

CONCLUSIONS

IVH is a significant problem for preterm infants. In addition to little progress in preventing IVH in preterm babies, substantial research focused on understanding the etiology, mechanism and risk factors for IVH is imperative. In the era of personalized medicine, identification of genetic risk factors creates opportunities to generate preventative strategies. Further studies should be performed to confirm the role of genetic factors in etiology and pathogenesis of IVH.

ABS 33

MRI-DIAGNOSED WHITE MATTER LESIONS IN THE BRAIN OF VLBW BABIES: RISK FACTOR ANALYSIS

A. Parodi[1], S. Raffa[1], M. Malova[1], A. Sannia[1], M. Severino[2], G. Morana[2], D. Tortora[2], M.G. Calevo[3], A. Rossi[2], L.A. Ramenghi[1]

[1]Neonatal Intensive Care Unit, Istituto Giannina Gaslini, Genoa, Italy

[2]Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy

[3]Epidemiology, Biostatistics and Committees Unit, Istituto Giannina Gaslini, Genoa, Italy

INTRODUCTION

In the last decades, perinatal care and the survival rates of very low birth weight infants (VLBW) have improved significantly. Following this trend, the incidence of major brain lesions, like cystic periventricular leukomalacia (c-PVL), has been constantly decreasing. On the other hand, milder forms of white matter damage, like punctate white matter lesions (PWML), are frequently seen in preterm infants undergoing MRI at term equivalent age. The aim of this study was to analyze prevalence of different types of the white matter injury (WMI) as seen on term-equivalent age MRI, and investigate related clinical risk factors.

METHODS

All VLBW infants admitted at birth to our NICU between January 2012 and October 2016 and consecutively scanned at term equivalent age as a part of follow-up program were retrospectively identified and included in the study. Prenatal, perinatal and post-natal clinical data were collected from NICU electronic database and clinical records. MRI scans were performed at 1.5 T system and included T1, T2, diffusion and susceptibility weighted (SWI) sequences. Images were reviewed in order to evaluate prevalence of c-PVL and prevalence, number (less or more than six) and type of PWML (hemorrhagic or non-hemorrhagic according to SWI appearance). Univariate and multivariate analysis of risk factors for all types of WMI was performed.

RESULTS

Study population included 321 newborn. Nine of them (3%) presented c-PVL and 61 (19%) PWML. Inside the last group, in 26 cases (43%) 6 or more PWML were present, while in 15 cases (25%) PWML were seen on SWI indicating haemorrhagic nature of the lesions. Placental abruption (OR = 4.67) and presence of GMH-IVH (OR = 3.94) emerged among the risk factors for c-PVL, while incomplete antenatal steroid treatment (OR 2.71) and intubation (OR = 10.1) resulted significant for PWML ≥ 6. Oxygen treatment for more than 7 days (OR = 0.19) and cesarean section (OR = 0.22) presented OR < 1. The only risk factor associated with SWI + PWML was the presence of GMH-IVH (OR = 8.67).

CONCLUSIONS

Our study confirms an important reduction in c-PVL prevalence in modern NICUs. Respiratory distress emerges as an important risk factor in the development of PWML. Accordingly, incomplete antenatal steroid treatment for pulmonary maturation seems to influence the development of those lesions, while intubation increases the odds of having more than 6 PWML ten-fold. Further studies could help to corroborate our findings.

ABS 34

A NEW EVALUATION INDEX FOR LEFT-RIGHT UNEQUAL VENTRICULOMEGALY IN VERY LOW BIRTH WEIGHT INFANTS: ASSOCIATION WITH WALKING DISABILITIES AT 1.6 YEARS OF CORRECTED AGE

T. Ikuta[1,2], M. Mizobuchi[3], Y. Katayama[4], S. Yoshimoto[2], T. Ioroi[5], M. Yamane[6], T. Morisawa[7], A. Takatera[8], M. Ueda[9], A. Shibata[10], K. Maeyama[1], K. Fujioka[1], N. Nishimura[1], K. Iijima[1], I. Morioka[1]

[1]*Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan*

[2]*Department of Neonatology, Kobe Children's Hospital, Kobe, Japan*

[3]*Department of Developmental Pediatrics, Shizuoka Children's Hospital, Shizuoka, Japan*

[4]*Department of Pediatrics, Takatsuki General Hospital, Takatsuki, Japan*

[5]*Department of Pediatrics, Himeji Red Cross General Hospital, Himeji, Japan*

[6]*Department of Pediatrics, Saiseikai Hyogo General Hospital, Kobe, Japan*

[7]*Department of Pediatrics, Kakogawa Central City Hospital, Kakogawa, Japan*

[8]*Department of Pediatrics, Chibune General Hospital, Osaka, Japan*

[9]*Department of Pediatrics, Toyooka Hospital, Toyooka, Japan*

[10]*Department of Pediatrics, Hyogo College of Medicine, Nishinomiya, Japan*

INTRODUCTION

In very low birth weight infants (VLBWI), a left-right unequal ventriculomegaly is often evident on brain magnetic resonance imaging (MRI) at term-equivalent ages, a finding that is interpreted as white matter injury. Although this ventriculomegaly would associate with neurological prognoses such as motor impairment, an evaluation method for a left-right unequal ventriculomegaly is not established. To propose the lateral ventricle index (LVI) as an updated index for evaluating ventriculomegaly based on our previous report (Pediatr Int, 2014), and to study the relationship between LVI and walking at a corrected age of 1.6 years.

METHODS

A retrospective, multi-center, Japanese cohort study was conducted with the approval of the ethics committee at Kobe University Graduate School of Medicine. A total of 294 VLBWI born between 2009 and 2011 were assessed. Brain T2-weighted MRI was performed at term-equivalent ages (36 to 43 weeks of corrected gestational age), and the right-front atrium width (a), left-front atrium width (b), right-back atrium width (c), and left-back atrium width (d) of the ventricles, cerebral occipitofrontal diameter (e), and cerebral lateral diameter (f) were measured on horizontal slices at the level of Monro foramen. LVI was calculated using the following formula: LVI = [3 * (a + b) + c + d] * 100 / (e + f) (**Fig. 1**). VLBWI were divided into 2 groups according to the establishment of walking without

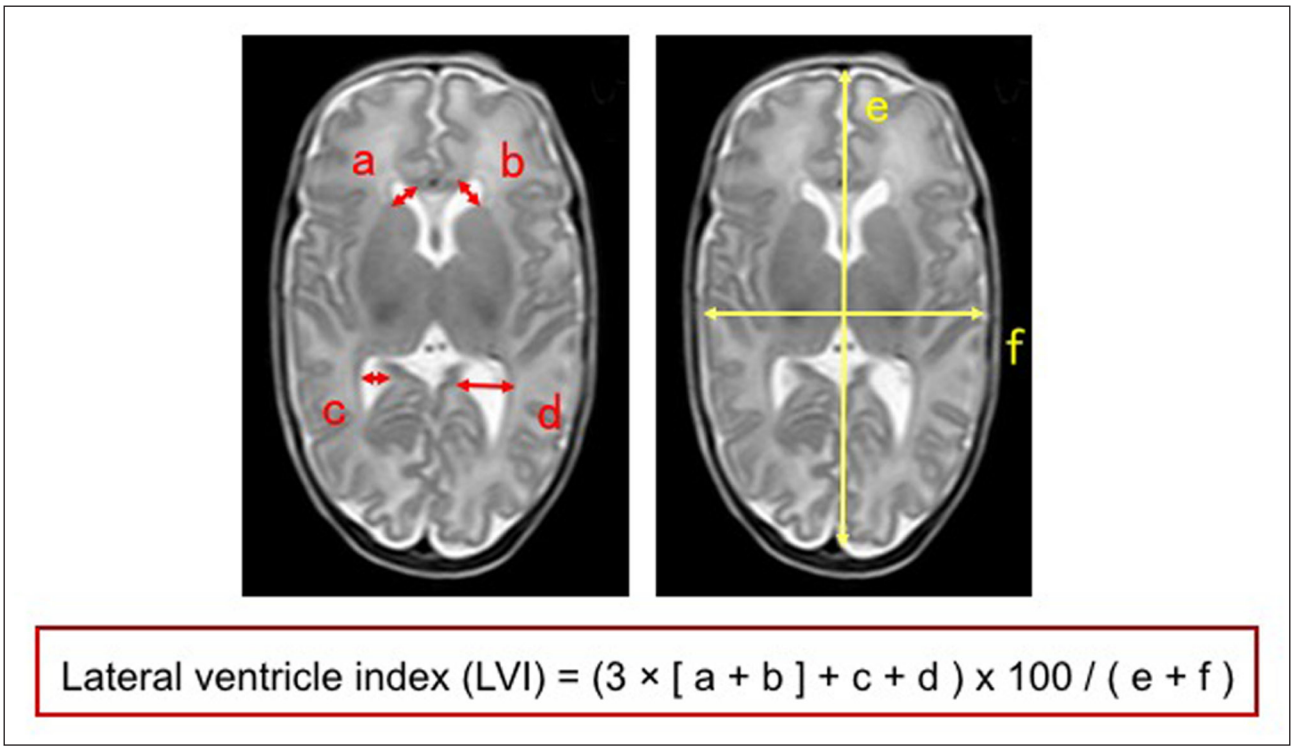

Figure 1 (ABS 34). Lateral ventricle index (LVI).

support at 1.6 years of corrected age and the clinical factors associated with walking disabilities were determined.

RESULTS

Of 294 VLBWI, 39 (13%) did not walk at 1.6 years of corrected age (non-walking group). The median LVI in the non-walking group was significantly higher than in the walking group (18.2 vs. 15.8, respectively, p = 0.02). The LVI cut-off value of 21.5 associated with non-walking was determined using receiver operating characteristic curve analysis. A multiple logistic regression analysis was performed to predict non-walking at 1.6 years of corrected age by using non-walking at 1.6 years of corrected age as a dependent variable and LVI > 21.5, gestational age, birth weight, intraventricular hemorrhage (IVH, III or IV grade), and cystic periventricular leukomalacia (cPVL) as independent variables. LVI > 21.5, IVH, and cPVL were found to be independent predictors with an odds ratio of 2.56 (95% confidence interval [CI], 1.0-6.4; p = 0.045), 10.2 (95% CI, 2.1-50.9; p < 0.01), and 85.2 (95% CI, 9.7-745.2; p < 0.01), respectively.

CONCLUSIONS

We propose that the LVI is a new index for evaluating left-right unequal ventriculomegaly in VLBWI. An LVI > 21.5 on brain MRI at term-equivalent ages may be a clinical factor that predicts walking disability at 1.6 years of corrected age, along with IVH and cPVL.

ABS 35

EPIGENETIC DIFFERENCES IN CORD BLOOD OF NEWBORNS EXPOSED TO ANTIDEPRESSANT MEDICATION DURING PREGNANCY – A STUDY IN THE AARHUS BIRTH COHORT

A.-C. Viuff[1], G.C. Sharp[2,3], L.H. Pedersen[1,4], N.H. Staunstrup[5], K.J. Kyng[6], D. Rai[3], C.L. Relton[2,3], T.B. Henriksen[1,6]

[1]Department of Clinical Medicine, Health, Aarhus University Hospital, Aarhus, Denmark

[2]MRC Integrative Epidemiology Unit, Bristol University, Bristol, UK

[3]School of Social and Community Medicine, Bristol University, Bristol, UK

[4]Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus, Denmark

[5]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark

[6]Department of Paediatrics, Aarhus University Hospital, Aarhus, Denmark

INTRODUCTION

Depression is common during pregnancy and increasing numbers of women are being prescribed antidepressant medications during pregnancy – especially selective serotonin reuptake inhibitors (SSRIs). There is emerging evidence suggesting that maternal use of SSRIs may be associated with an increased risk of congenital defects and adverse neurodevelopmental outcomes. One suggestion is that prenatal exposure to maternal depression or SSRIs might influence offspring health through a mechanism involving DNA methylation. The aim of this study was to investigate the association between SSRI exposure during pregnancy and methylation changes in the cord blood of the newborn.

METHODS

We measured DNA methylation at over 850,000 CpG sites in cord blood from 176 newborns in the Aarhus Birth Cohort, selected according to maternal depression or SSRI use status. We carried out epigenome-wide association studies to compare DNA methylation between three groups: (1) SSRI use in pregnancy (n = 88); (2) non-medicated depression in pregnancy (n = 44); (3) unexposed = no depression or SSRI use in pregnancy (n = 44). We performed a single-site regression analysis and a regional analysis adjusting the results for the following covariates: maternal smoking, parity, maternal age at delivery, the use of other types of medication and socio-economic status (SES), batch effects, and estimated cell composition.

RESULTS

We found 99 unique differentially methylated regions (DMRs) when comparing the three exposure groups. 18 DMRs were specific to the SSRI exposed compared to the unexposed, and 53 DMRs were specific to the depressed, non-medicated group vs. the unexposed. 27 DMRs were specific to the SSRI exposed compared to the non-medicated, depressed group. 1 DMR was found in both the SSRI exposed group and the depressed, non-medicated group.

CONCLUSIONS

Prenatal exposure to untreated depression was associated with more differences in newborn DNA methylation than prenatal exposure to SSRIs. Further research is warranted to confirm these findings and investigate causality.

ABS 36

AUTISM SPECTRUM DISORDER IN EX-PRETERMS IS PRECEDED BY ALTERED NEONATAL BRAIN VOLUMES IN MULTIMODAL

ASSOCIATION AREAS AND ALTERED PATTERNS OF BRAIN ASYMMETRY

N. Padilla[1], E. Eklöf[1], G. Mårtensson[1], S. Bölte[1,2], H. Lagercrantz[1,3], U. Åden[1,3]

[1]*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

[2]*Division of Child and Adolescent Psychiatry, Stockholm County Council, Karolinska Institutet, Stockholm, Sweden*

[3]*Department of Neonatology, Karolinska University Hospital, Stockholm, Sweden*

INTRODUCTION

It has been demonstrated in children that autism spectrum disorder (ASD) disrupts the systems organization of the brain reflected in anomalous patterns of cerebral volumes and asymmetry. In this regard, anomalous patterns of asymmetries may indicate altered regional specialization as well as impaired information processing. We aimed to study whether brain volumes and patterns of asymmetry in the primary sensory cortex (PSC), unimodal association cortex (UAC), and higher order association cortex at term-equivalent age (TEA), differ between extremely preterm (EPT) children with and without positive screening for ASD at 6.5 years.

METHODS

We included 33 EPT infants < 27 weeks of gestational age (positive-ASD = 11, with scores above cut off on the Social Responsiveness Scale and negative-ASD = 22). We used atlas-based segmentation [1]. Volumes were calculated by summing the voxels in each region. Regions were grouped processing type, primary sensory cortex, unimodal association cortex, and higher order association cortices by summing their components. Asymmetry was calculated by using the symmetry index (SI) = 2 (left volume – right volume) / (left volume + right volume) * 100. Group comparisons were performed by using a multivariate analysis, with total grey matter volume and full-scale IQ cut-off (70) as covariates.

RESULTS

Compared with the negative-ASD group the positive-ASD group had significantly smaller volumes in the left-higher order association cortex (p = 0.01), specifically involving the anterior cingulate cortex (p = 0.009), the insula (p = 0.003), and the superior orbito-frontal cortex (p = 0.03) (**Fig. 1**). A non-significant trend was found in the left-UAC (p = 0.06) involving the fusiform gyrus (p = 0.03). The symmetry index was significantly different between groups in the rolandic operculum (p = 0.02 left-asymmetry), and the supplementary motor area (p = 0.04 right-asymmetry). We found a non-significant trend in the superior orbito-frontal cortex (p = 0.07 left-asymmetry).

CONCLUSIONS

Volumetric abnormalities in the higher order association cortex and different patterns of asymmetry were identified in the neonatal period in EPT infants that later developed ASD symptoms. This may reflect alterations in multi-sensory integration and abnormal brain growth trajectories reported in older ASD subjects.

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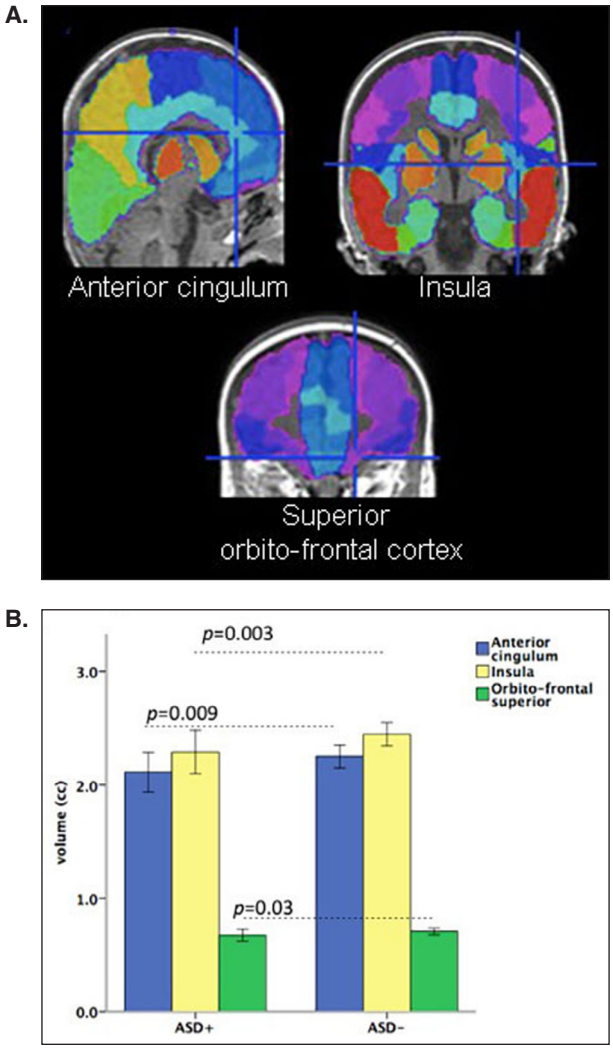


Figure 1 (ABS 36). A. Anatomical atlas overlaid on the T1-weighted image of a single subject showing brain regions with significant volumetric difference between groups. **B.** Bar chart showing significant differences between groups.
ASD+: children tested ASD positive, ASD-: children tested ASD negative. Left = right.

ABS 37

COGNITIVE OUTCOME IN ADULTS BORN WITH VERY LOW BIRTH WEIGHT OR SMALL FOR GESTATIONAL AGE

S. Weider[1], A.M.W. Lærum[2], K.A.I. Evensen[2], S. Lydersen[3], A.M. Brubakk[2], M.S. Indredavik[3,4]

[1]*Department of Psychology, Faculty of Social and Educational Sciences, Norwegian University of Science and Technology, Trondheim, Norway*

[2]*Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway*

[3]*Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway*

[4]*Department of Children and Youth, Mental Health Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway*

INTRODUCTION

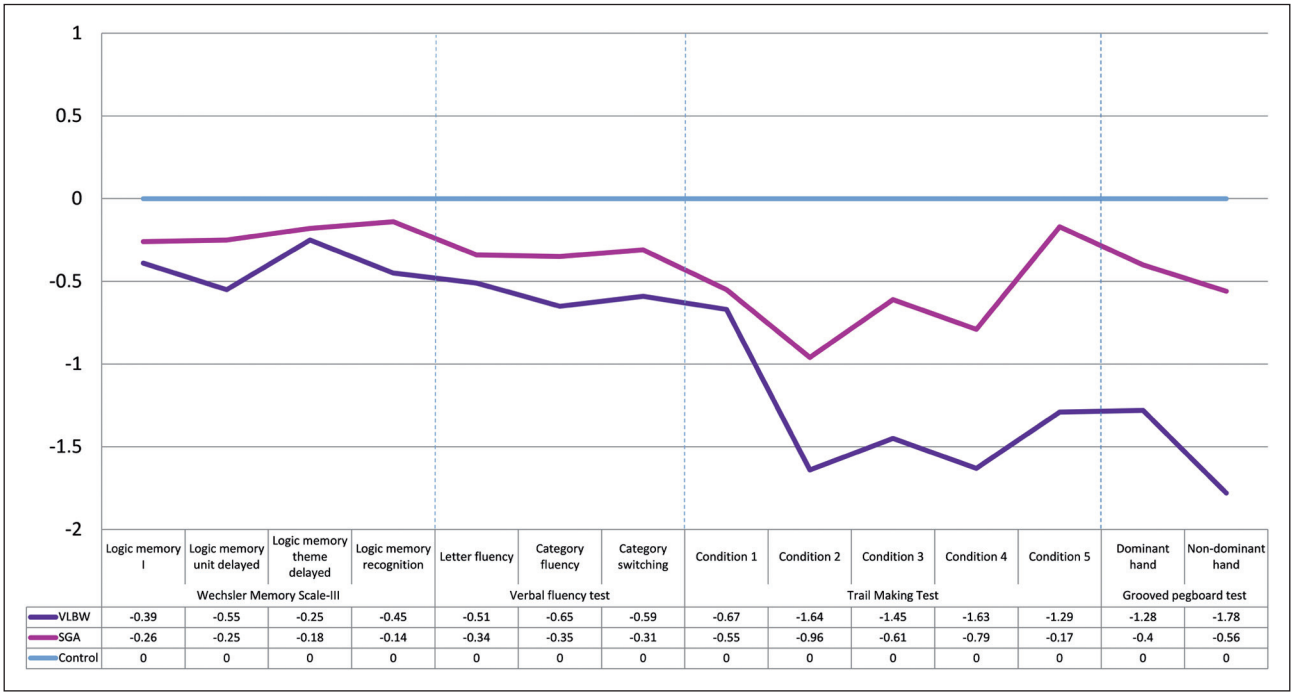
Cognitive sequelae in childhood have consistently been reported in individuals born preterm with very low birth weight (VLBW). There are also reports of similar difficulties in children born small for gestational age (SGA) at term. However, it is not clear whether these difficulties persist into adulthood. Furthermore, few studies have investigated cognitive function beyond IQ, and there is a need to investigate the broader cognitive profiles related to being born with VLBW or SGA. Our aim was to investigate cognitive outcome in adults born preterm at VLBW or term born SGA compared to a group of term born controls assessed with a broad battery of cognitive and neuropsychological tests.

METHODS

The present study is a follow-up at age 26 of 46 individuals born preterm with VLBW (≤ 1,500 g), 63 individuals born SGA at term and 81 term born controls, all born in 1986-1988. The groups were assessed with a battery of cognitive and neuropsychological tests including the Wechsler Abbreviated Scale of Intelligence (WASI), the Logical Memory Test from the Wechsler Memory Scale-III (WMS-III), the Verbal Fluency Test and the Trail Making Test (TMT) 1-5 from Delis-Kaplan Executive system (D-KEFS), and the Grooved Pegboard test (GP).

RESULTS

Full-scale IQ (FIQ) was significantly lower for both the VLBW group (97.9 ± 19.0) and the SGA group (108.0 ± 10.6) compared with the control group (113.2 ± 11.3) ($p < 0.01$). Similar differences were also seen on Performance IQ ($p < 0.01$), but only the VLBW group performed below the control group on measures of Verbal IQ. On the other cognitive tests (**Fig. 1**), the VLBW group performed lower than the controls on one measure from the Logical Memory Test and on all conditions of the Verbal Fluency Test (letter fluency, category fluency and switching). In addition, the VLBW group scored



	Logic memory I	Logic memory unit delayed	Logic memory theme delayed	Logic memory recognition	Letter fluency	Category fluency	Category switching	Condition 1	Condition 2	Condition 3	Condition 4	Condition 5	Dominant hand	Non-dominant hand
	Wechsler Memory Scale-III				Verbal fluency test			Trail Making Test					Grooved pegboard test	
VLBW	-0.39	-0.55	-0.25	-0.45	-0.51	-0.65	-0.59	-0.67	-1.64	-1.45	-1.63	-1.29	-1.28	-1.78
SGA	-0.26	-0.25	-0.18	-0.14	-0.34	-0.35	-0.31	-0.55	-0.96	-0.61	-0.79	-0.17	-0.4	-0.56
Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 1 (ABS 37). At 26 years of age, both VLBW and term SGA adults had lower cognitive and neuropsychological results than term born controls.

below the controls on all conditions of the TMT 1-5 with a performance ≥ 1.5 SD lower than the control group on conditions 2-4. The SGA group also scored below the controls on the TMT 1-4. Both the VLBW group and the SGA group performed poorer than the control group on the GP with both dominant and non-dominant hand ($p < 0.01$).

CONCLUSIONS

At 26 years of age, both VLBW and term SGA adults had lower IQ scores, psychomotor speed and motor function than controls. In addition, VLBW adults had poorer verbal memory and verbal fluency. These findings clearly indicate that cognitive difficulties previously reported in individuals born preterm with VLBW or SGA at term continue into adulthood.

ABS 38

PERFORMANCE OF THE GERMAN VERSION OF THE PARCA-R QUESTIONNAIRE AS A COGNITIVE SCREENING TOOL IN VERY PRETERM INFANTS AT 2 YEARS OF CORRECTED AGE

G. Natalucci[1,2], N. Bechtel[3], C. Borradori-Tolsa[4], M. Bickle-Graz[5], M. Adams[1], S. Grunt[6] for the Swiss Neonatal Network & Follow-Up Group

[1]*Department of Neonatology, University of Zurich and Zurich University Hospital, Zurich, Switzerland*

[2]*Child Development Centre, University Children's Hospital Zurich, Zurich, Switzerland*

[3]*Division of Neuropediatrics and Developmental Medicine, University Children's Hospital Basel, Basel, Switzerland*

[4]*Department of Paediatrics, Geneva University Hospital, Geneva, Switzerland*

[5]*Department Woman-Mother-Child, University Hospital Lausanne, Lausanne, Switzerland*

[6]*Division of Neuropediatrics, Development and Rehabilitation, University Children's Hospital, Berne, Switzerland*

INTRODUCTION

As very preterm infants (VPT) are at increased risk of neurodevelopmental impairment, post-discharge follow-up is recommended for early identification and intervention in this population. Standardized neuropsychological testing require many resources, it is thus difficult to reach clinical follow-up rates that allow adequate health coverage or representative outcome data analysis. Alternative instruments to screen infants' neurodevelopment are needed. This study aimed to validate a German version of the revised Parent Report of Children's Abilities (PARCA-R) questionnaire and test its clinical effectiveness as a screening tool for mental delay.

METHODS

Multicentre cross-sectional study. German speaking parents of infants born with gestational age < 32 weeks in three Swiss centers, were asked to complete the PARCA-R questionnaire, designed to measure their offspring's cognitive level, within three weeks before the scheduled follow-up assessment at the corrected age of two years. The infant's mental development was assessed with the Mental Development Index (MDI) of the Bayley Scales of Infant Development 2nd edition (BSID-II). Spearman correlation between the MDI and the Parent Report Composite (PRC) of the PARCA-R was tested. The area under the receiver operating characteristic (ROC) curve was used to identify optimal PRC cut-offs for the prediction of mental delay, defined as MDI < 70.

RESULTS

A sample of 154 consecutive VPT infants (42% female, mean [SD] gestational age 29.0 [2.0] weeks, and birth weight 1,170 [355] grams) was assessed, using both the PARCA-R and the BSID-II at a mean age of 23.1 (1.8) months. The mean PRC score (70.5 [31.1]) was significantly correlated with the MDI (92.2 [17.3]; $r = 0.54$; $p < 0.0001$). Using the Youden index, the optimal PCR cut-off for identifying children with mental delay was 41. Resulting predictive values (95%-CI) were: sensitivity 75% (48; 93), specificity 84% (77; 90), positive predictive value 35% (25; 47), negative predictive value 97% (93; 99), and an area under the ROC curve of 0.840 (0.729-0.952). With this cut-off, 3% of the children with PRC scores < 41 had a false-negative screen.

CONCLUSIONS

In this sample of VPT children, the German version of the PARCA-R has good validity with the results of the BSID-II, and PCR scores < 41 provide optimal discriminatory power for the identification of mental delay at two years of corrected age. This practical and cost-efficient parental questionnaire may be an alternative as first-line cognitive screening in this high-risk population, when direct testing is not possible.

ABS 39

NEURODEVELOPMENT IN 7-YEAR OLD CHILDREN BORN WITH MARGINALLY LOW BIRTH WEIGHT

J. Starnberg, M. Norman, B. Westrup, M. Domellöf, S.K. Berglund

Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden
Division of Pediatrics, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
Division of Neonatology, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

INTRODUCTION
Being born with low birth weight (LBW, < 2,500 g) has been associated with neurocognitive deficits later in life. However, the magnitude of such deficits in marginally LBW (MLBW, 2,000-2,500 g) children is not well known. The aim of this study was to explore neurodevelopmental functions in school aged children born with MLBW.
METHODS
This was originally a randomized controlled trial investigating the effects of early iron supplementation given to 285 MLBW children. Since there were no effects of iron supplements on cognitive assessments, we have explored the combined MLBW group and compared their results to 95 enrolled controls with normal birth weight (NBW, 2,501-4,500 g) in an observational design. At 7 years, a paediatric psychologist assessed the children using WISC IV (Wechsler Intelligence Test for Children), Beery VMI (Visual-Motor Integration) and TEA-Ch (Test of Everyday Attention in Children).
RESULTS
MLBW children, compared to NBW controls, had lower verbal comprehension IQ (104 vs 107, p = 0.0184), lower VMI-scores (96.5 vs 100, p = 0.031) and poorer results at TEA-Ch, (total mean score 8.49 vs 9.73, p = 0.001). These differences remained significant also when adjusting for sex, maternal age at birth, maternal birth country, and parental education. There was no difference between the groups in prevalence of IQ below 85. However, the MLBW children had a higher proportion of children below -1 SD for VMI (14.0% vs 4.5%, p = 0.045) and for the TEA-Ch subtests assessing selective attention (targets found, 15.6% vs 3.2%, p = 0.008 and time per target, 51.7% vs 30.2%, p = 0.003) (**Tab. 1**).
CONCLUSIONS
MLBW children had lower verbal comprehension IQ and performed poorer at VMI and TEA-Ch, than NBW children. Our findings suggest that otherwise healthy children born with MLBW have an increased risk of cognitive difficulties up to school age. We believe this subgroup of LBW children should be given enhanced attention in follow-up programs.

ABS 40

EARLY NEONATAL EEG MARKERS FOR DYSLEXIA RISK: A PILOT STUDY

Table 1 (ABS 39). Group differences for WISC IV, Beery VMI and TEA-Ch between normal birth weight children (NBW; 2,501-4,500 g) and marginally low birth weight children (MLBW; 2,000-2,500 g) at 7 years of age. Included analyses stratified for being born term or preterm.

	Controls	MLBW	MLBW preterm	MLBW term
WISC	**n = 69-70**	**n = 197-200**	**n = 107-110**	**n = 90**
Verbal comprehension IQ	107.2 (10.2)	104.1 (9.3)[a,b]	104.4 (9.4)[b]	103.6 (9.1)[a,b]
Perceptual reasoning IQ	106.8 (11.2)	105.0 (11.6)	106.3 (11.5)	103.5 (11.6)
Working memory IQ	88.8 (10.2)	87.4 (12.6)	87.1 (12.5)	87.7 (12.7)
Processing speed IQ	98.1 (12.6)	97.7 (13.9)	96.1 (13.2)	99.6 (14.6)
Full scale IQ	102.3 (10.2)	100.0 (11.1)	100.3 (11.2)	99.7 (11.0)
Beery VMI	**n = 67**	**n = 200**	**n = 109**	**n = 91**
Standardized score	100.0 (11.2)	96.5 (11.8)[a,b]	98.2 (12.4)	94.4 (10.8)[a,b]
TEA-Ch test	**n = 57-63**	**n = 158-180**	**n = 85-98**	**n = 73-83**
Sky search, targets found (scale points)	11.8 (3.0)	10.4 (3.6)[a,b]	10.8 (3.5)	9.89 (3.6)[a,b]
Sky search, time per target (scale points)	8.16 (3.3)	6.87 (3.4)[a,b]	6.49 (3.1)[a,b]	7.32 (3.6)
Sky search, attention score (scale points)	8.94 (3.4)	7.60 (4.1)[a]	7.21 (2.9)[a,b]	8.06 (5.2)
Score! (scale points)	10.2 (3.3)	9.12 (3.7)	8.99 (3.6)[a]	9.27 (3.9)
Mean TEA-Ch (scale points)	9.73 (2.2)	8.49 (2.8)[a,b]	8.37 (2.5)[a,b]	8.63 (3.1)[a]

Data are mean (SD).
[a]p-value < 0.05, for differences between marginally low birth weight children and controls using independent student's t-test; [b]p-value < 0.05 adjusted for sex, maternal age, mothers are born in Scandinavia, maternal education level, fathers level of education, using analyses of covariance (ANCOVA).

S. Martini[1], P. Cyr[1], L. Brightman[2], L. Amunts[2], G. Belteki[3], T. Austin[1], V. Leong[2]

[1]*Evelyn Perinatal Imaging Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

[2]*Department of Psychology, University of Cambridge, Cambridge, UK*

[3]*The Rosie Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

INTRODUCTION

Dyslexia is a neurodevelopmental disability in learning to read that has a strong heritable component, affecting up to 10% of the population. Early identification of high-risk individuals could facilitate earlier diagnosis and provision of intervention support for affected children. Although the neurobiological mechanisms underlying dyslexia are still unclear, one hypothesis suggests an impairment of neural mechanisms for phonological (speech sound) processing, arising from inaccurate neuronal oscillatory phase-locking to the temporal structure of speech (e.g. syllables and stress patterns). This pilot study aimed to compare phase-locking acuity to rhythmic speech in newborns with familial risk of dyslexia compared to controls, in order to identify possible early markers for dyslexia risk.

METHODS

Thirty-two healthy term newborns, of which 12 had a familial risk of dyslexia (defined as the presence of ≥ 1 parent and/or sibling with dyslexia) and 20 controls (no familial history of dyslexia) were included in the study. At ≤ 7 days of life (median 3 days, interquartile range 1-5), the infants underwent an EEG recording including 20 minutes of resting state and 20 minutes of passive listening to spoken nursery rhymes. EEG was acquired using BrainVision software, and analysed in Matlab. To assess acuity of speech processing, the Phase-Locking Value (PLV) was computed between infants' oscillatory response and the speech amplitude envelope.

RESULTS

Preliminary findings indicate a group difference between high-risk and control infants' oscillatory phase-locking acuity. This difference was most pronounced over the right temporal cortex. Our neural results indicated that, over right temporal cortical regions (electrodes T4 + F8), high-risk neonates showed significantly poorer neural oscillatory processing of low-frequency (1-3 Hz) speech sounds than low-risk neonates ($F[1,27] = 5.3$, $p < 0.05$). **Fig. 1** shows phase-locking accuracy over right temporal cortex (T4 electrode) for different speech frequencies for low-risk (blue) and high-risk infants (red).

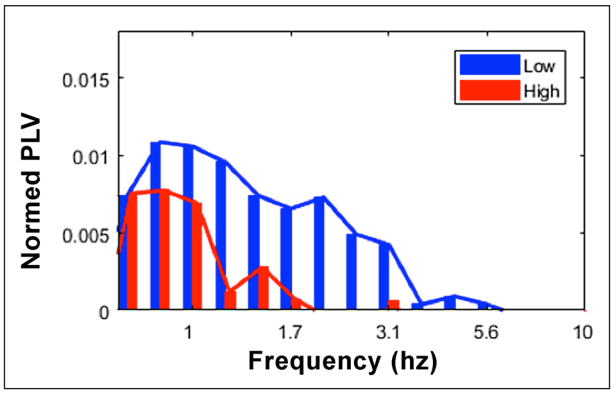


Figure 1 (ABS 40). Phase-Locking Value (PLV) accuracy over right temporal cortex (T4 electrode) for different speech frequencies for low-risk (blue) and high-risk infants (red).

CONCLUSIONS

Our preliminary results suggest that the evaluation of neuronal oscillatory phase-locking acuity in neonates within the first week of life might represent a potential neonatal biomarker for dyslexia risk. However, larger longitudinal studies are needed to assess the long-term predictive value of early phase-locking indices on children's language and reading development.

ABS 41

MATERNAL SWIMMING DURING PREGNANCY PROTECTS THE NEONATAL RAT BRAIN FROM HYPOXIC-ISCHEMIC INJURY

E.F. Sanches[1], Y. van de Looij[2], A. Silva[2], J. Romero[2], S.V. Sizonenko[1]

[1]*Division of Child Growth and Development, Department of Pediatrics, University of Geneva, Geneva, Switzerland*

[2]*Centre for Biomedical Imaging (CIBM), Federal Institute of Technology, Lausanne, Switzerland*

INTRODUCTION

Neonatal brain hypoxia-ischemia (HI) is a major cause of neurological impairments especially in preterm neonates [1]. Physical exercise during pregnancy promotes mother and foetus health during pregnancy but also later in life. Thus it could interfere on HI cascade protecting fetus brain for the HI induced challenge [2]. The aim of this work was to assess the early (P4) and long term (P60) effects of swimming (SW) during pregnancy in the very

immature brain HI rat model [3] using multimodal approach of advanced magnetic imaging (1H-MR spectroscopy and diffusion imaging) with protein expression and behavioural testing.

METHODS

Female pregnant Wistar rats were submitted to a swimming protocol (or control situation) lasting from the gestational day 0 (DG0) to DG21 (20 min/day; in a circular tank filled with 32°C water). At P3, newborn pups were divided in 4 groups (SESH: sedentary-sham, SEHI: sedentary-HI, SWSH: swimming-sham and SWHI: swimming-HI). HI was performed on the P3 pups: the right common carotid artery was occluded and followed by systemic hypoxia (6% O_2 for 30 min at 37°C) [3]. 24 hours after HI (P4) pups were scanned for cerebral metabolic profiling using 1H-MRS analysis (n = 8-21/group). From P45 to P60 behavioural testing was performed (Morris water maze, elevated plus maze and open field; n = 8-16/group). At P60, ex-vivo diffusion tensor (DTI) and (NODDI) imaging in a 9.4T scanner was performed (n = 4-6/group). Cortex and hippocampus were collected (at P4 and P60) for the protein expression levels of cleaved caspase3, GFAP, BDNF, TRK-B and MBP assessment (n = 6-8/group).

RESULTS

1H-MRS showed brain metabolism alterations (decrease in alanine, creatine and lactate) in the SEHI group, restored by the swimming in the mild HI cases of SWHI animals. At P4, the SEHI rat pups showed increased GFAP and ccasp3 expression in ipsilateral hemisphere; both proteins were not over-expressed the SWHI group. The SWHI group, although it showed a decrease in the BDNF expression, as the SEHI, presented increased expression of TRK-B receptor. From P45, the behavioral analysis showed no effect on anxiety-related, nor in general locomotor activity on elevated plus maze nor open field; however, the cognitive impairment observed in the SEHI group on water maze was reverted in the SWHI group. DTI/NODDI showed altered parameters on white matter fibre tracts in the SEHI group in the corpus callosum and external capsule, that was restored in the SWHI. At P60, an increase in BDNF levels was observed in the contralateral hemisphere.

CONCLUSIONS

Swimming during pregnancy counteracted some effects of neonatal HI in progeny trough different pathways: maintaining brain metabolism, decreasing apoptotic cell death and astrogliosis as well maintaining the levels of neurotrophins. Physical exercise could be used as a preventive treatment for both insults (prematurity and hypoxia-ischemia) representing a high cost-effectivity therapy.

ACKNOWLEDGEMENT

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ABS 42

PERSISTENT MATHEMATICS LEARNING DIFFICULTIES FROM CHILDHOOD TO ADOLESCENCE IN VERY PRETERM CHILDREN IN MAINSTREAM SCHOOL

S. Clayton[1], L. Cragg[2], C. Gilmore[3], N. Marlow[4], V. Simms[5], R. Spong[1], S. Johnson[1]

[1]Department of Health Sciences, University of Leicester, Leicester, UK

[2]School of Psychology, University of Nottingham, Nottingham, UK

[3]Mathematics Education Centre, Loughborough University, Loughborough, UK

[4]Institute for Women's Health, University College London, London, UK

[5]School of Psychology, Ulster University, Coleraine, UK

INTRODUCTION

Primary school aged children born very preterm (VP; < 32 weeks) have significantly lower mathematics achievement than their term-born peers. The move from primary to secondary education imposes greater cognitive demands and the mathematical ideas and procedures to be learned become increasingly complex. The development of mathematical processes from childhood to adolescence has not been explored in a contemporary cohort of VP children. In the present study we assessed the mathematical skills and learning difficulties of VP children (born 2001-2003) in primary school and again in secondary school.

METHODS

83 VP children born < 32^{+0} weeks gestation (mean gestational age = 28.6 weeks; SD = 1.9) in mainstream school and 49 term-born classmates matched for age

and sex completed a battery of standardised tests of mathematics achievement and nonverbal IQ at primary school (Mean age = 9.6 years) and again at secondary school (Mean age = 13.6 years). Children were assessed individually by a psychologist. Mathematics achievement was assessed using the Wechsler Individual Achievement Test-II (WIAT-II) Numerical Operations and Mathematical Reasoning subtests and non-verbal IQ with the Raven's Coloured Progressive Matrices (CPM, primary) and Raven's Standard Progressive Matrices Plus (SPM+, secondary).

RESULTS

VP children had significantly lower IQ scores in comparison to their term-born peers at primary school (mean difference -9.55; 95% CI -15.38, -3.72) and secondary school (-6.61; -12.90, -0.33). Likewise, VP children demonstrated significantly poorer mathematics achievement than term-born controls at both time points (primary: -14.79; -21.67, -7.90; secondary: -15.04; -22.30, -7.78). Group differences in mathematics achievement persisted after controlling for IQ. There were no significant differences in socioeconomic status between groups. Group differences in IQ and mathematics were stable over time (**Fig. 1**). Rates of mathematics learning difficulties (scores < -1 SD) were significantly higher in VP children than term-born controls at primary school (VP: 38.6%; Control: 14.3%) and secondary school (VP: 48.2%; Control: 18.4%).

CONCLUSIONS

VP children in mainstream school are at an increased risk for persistent mathematics difficulties and do not catch up with their term-born peers. Relative to controls, the size of these deficits remains stable over time and mathematics difficulties are not accounted for by low IQ. Research is needed to elucidate the cognitive mechanisms underpinning these difficulties to develop interventions to support VP children's attainment at school.

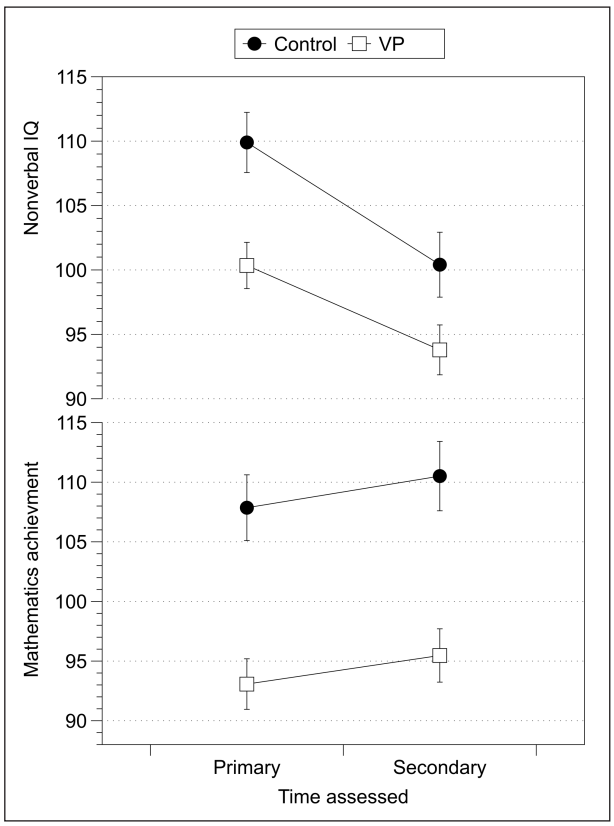

Figure 1 (ABS 42). Mean standard scores for nonverbal IQ and mathematics achievement of VP and term-born control children assessed in primary school and again in secondary school. Error bars represent standard error. Note: differences in test items are likely to account for the overall change in test scores from primary to secondary school, however the relative difference between groups remains constant over time.

ABS 43

PRENATAL METHADONE EXPOSURE AND NEURODEVELOPMENTAL AND NEURO-IMAGING OUTCOMES: A SYSTEMATIC REVIEW

V. Monnelly[1], R. Hamilton[2], F. Chappell[3], H. Mactier[4], J. Boardman[1,3]

[1]*MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK*

[2]*Department of Clinical Physics and Bioengineering Royal Hospital for Children, Glasgow, UK*

[3]*Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK*

[4]*Princess Royal Maternity, Glasgow, UK*

INTRODUCTION

A key component of the management of opioid addiction during pregnancy is prescribed substitute opioid. Methadone has been used in this context for more than four decades with well documented benefits for maternal lifestyle and improved perinatal outcomes. There are, however, increasing uncertainties about the effect of exogenous opioids on the developing brain and later childhood outcomes. We report a systematic review of the evidence regarding the neurodevelopmental, visual and neuroimaging outcomes of children prenatally exposed to methadone.

METHODS

We searched MEDLINE, EMBASE and PsycINFO; search terms "methadone" and "prenatal" or "prenatal exposure" or "prenatal drug exposure" or "*in utero*" (PROSPERO registration number

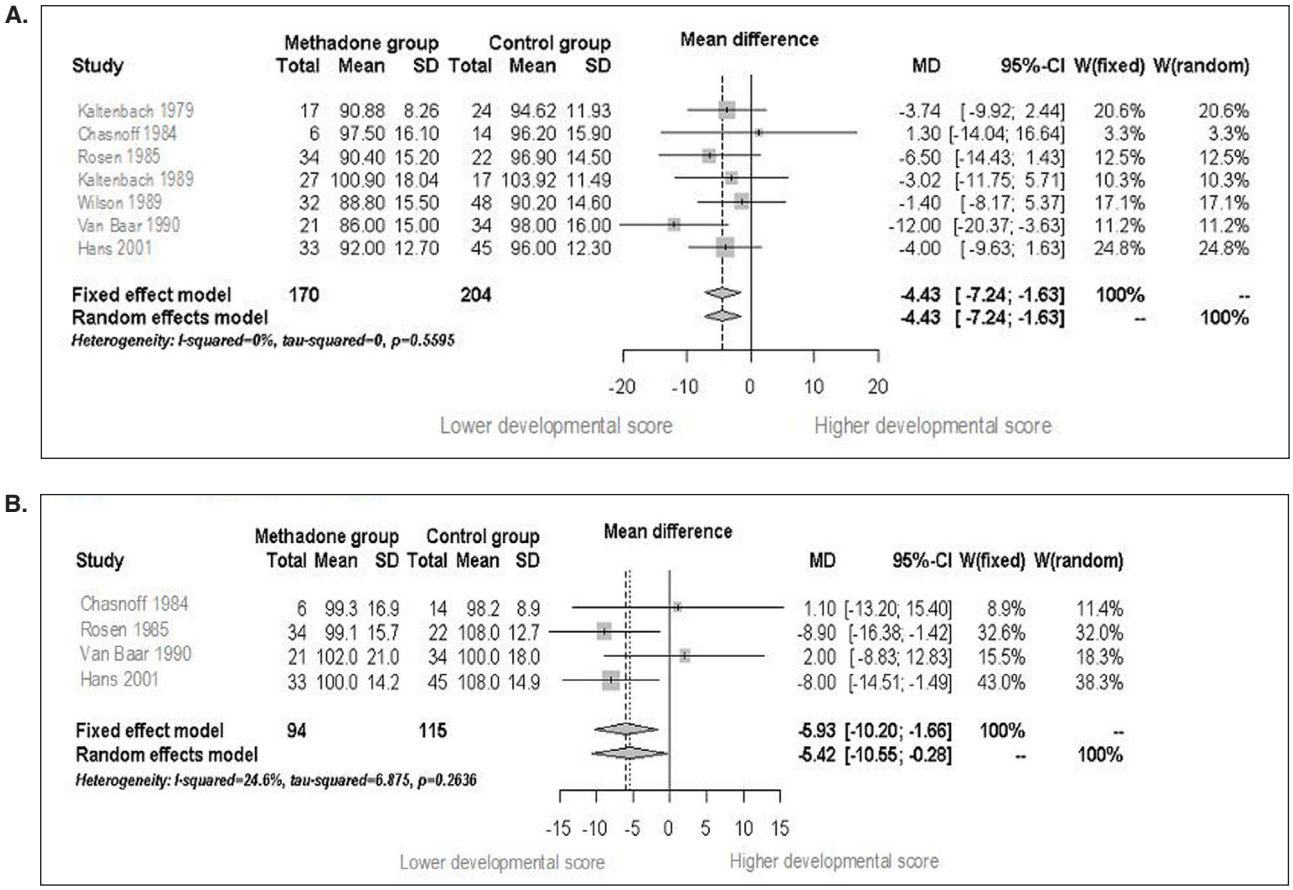

Figure 1 (ABS 43). Forest plots of developmental outcome in children with prenatal methadone exposure compared to control children. **A.** Cognitive outcome (MDI) at 18-24 months. **B.** Motor outcome (PDI) at 18-24 months.

CRD42017063987). Studies including mothers treated with alternative opioid substitutes during pregnancy were excluded. Outcomes were assessed in three domains: neurodevelopment; vision; neuroimaging. Data from studies reporting neurodevelopmental outcome at 18-24 months using a standardised assessment tool were pooled in statistical meta-analysis using R 3.2.2 (https://cran.r-project.org/). Effect sizes were expressed as weighted mean differences (WMD) with 95% confidence intervals. Quality and bias were assessed using a modified GRADE scheme.

RESULTS

1,021 papers were screened, 114 full-text articles assessed and 43 were eligible for inclusion. No randomised controlled trials included infant outcomes in any of the three domains. Quality of included studies was poor to intermediate, usually due to poor methods reporting, attrition and confounding. 29 studies reported neurodevelopment. 9 case control studies used the Bayley Scales of Infant Development, 7 of which were amenable to meta-analysis. Mental Development Index (MDI) WMD was -4.3 (95% CI -7.24 to -1.63) (**Fig. 1A**). Psychomotor Developmental Index (PDI) WMD was -5.42 (95% CI -10.55 to -0.28) (**Fig. 1B**). 11 studies reported visual outcomes: atypical visual evoked potentials were reported in 4/5 studies measuring this outcome, and increased prevalence of strabismus and nystagmus was a consistent finding. 2 studies reported neonatal neuroimaging; one used cranial ultrasound, the other used MRI.

CONCLUSIONS

Neurodevelopment, cognition and visual development appear to be altered in association with prenatal methadone exposure. Current evidence is of insufficient quality to be reassured about the safety of prenatal methadone exposure. Future research into optimal management of pregnant women who use opioids should evaluate fetal/neonatal brain development and long term neurocognitive outcome.

ABS 44

NEURODEVELOPMENT FOLLOW-UP FOR HIGH-RISK BABIES IN LIVERPOOL: A QUALITATIVE STUDY. FOUNDATION STUDY "FOLLOW-UP

FOR NEURODEVELOPMENTALLY AT RISK INFANTS OF NEONATAL CARE"

A. Komoriyama, F. Paize, C. Dewhurst, M. Gladstone

Department of Women and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

INTRODUCTION

Infants born prematurely or who have had neurological complications such as hypoxemic ischaemic encephalopathy are at an increased risk of neurodevelopmental delay and disability. Identifying infants with early signs of neurodevelopmental disorders is crucial for these children to achieve their full developmental potential. Currently, there is variable guidance on follow-up and referral process for these children and little information on the needs of patients, families and healthcare professionals in relation to their current practices and experiences of follow-up.

METHODS

We undertook a qualitative study using in-depth interviews with thirty parents of children who were born at risk (prematurely or with hypoxic ischaemic encephalopathy) within the Merseyside region. Parents of high-risk children from 0-3 years were recruited from neonatal and community follow-up clinics. We also undertook 11 in-depth interviews with multidisciplinary professionals (doctors, nurses, allied health professionals) who have been involved in follow-up of at risk infants. Interviews were undertaken using a topic guide, which iteratively developed over time. The interviews were recorded, transcribed and analysed using a thematic analysis and framework approach.

RESULTS

Five themes were identified: (1) information, (2) health (3) development and disability, (4) parent-professional relationship and (5) capacity of the health care system. Some parents had received a diagnosis for their child, and this experience had hugely affected their views of the follow-up clinics. Most parents wanted to be prepared for a diagnosis and appreciated a realistic and honest approach by the professionals. Most parents perceived that neonatologist's focus was on the short-term management, and they were reluctant to discuss the long-term developmental outcome of a child with parents to avoid ruining the enjoyment of having a baby. Long-term parental emotional support was often neglected and many parents wanted to be offered a counselling service. Having no standard referral process created variable care pathways, which frustrated both parents and professionals.

CONCLUSIONS

Most parents viewed follow-up beneficial however, the quantity, content and quality of information given at the time of discharge and during follow-up can be variable and uncertain. The way the information of child's progress was communicated made parents anxious and uncertain about the future. Furthermore, professionals need to have more awareness on parental mental health and give more emotional support throughout the follow-up care.

ABS 45

COLD-INDUCIBLE RBM3 PROMOTES NEUROGENESIS AFTER BRAIN HYPOXIC-ISCHEMIA/REPERFUSION INJURY

X. Zhu[1], C. Brégère[2], J. Yan[1], U. Fisch[2,3], J. Kapfhammer[2], R. Guzman[2,4], S. Wellmann[1]

[1]*Neonatology Department, University Children's Hospital of Basel, Basel, Switzerland*

[2]*Biomedicine Department, University of Basel, Basel, Switzerland*

[3]*Neurology Department, University Hospital of Basel, Basel, Switzerland*

[4]*Neurosurgery Department, University Hospital of Basel, Basel, Switzerland*

INTRODUCTION

Moderate cerebral hypothermia (32°C) ameliorates hypoxic-ischemia/reperfusion (HI/R) injury in newborn infants with hypoxic-ischemic encephalopathy (HIE). It is also highly protective in adult rodent models for ischemic stroke, and is being tested in clinical trials of stroke treatment. Previously, the cold-inducible RNA-binding motif protein 3 (RBM3) has been shown to co-express in nestin-positive neural stem/progenitor cells (NSPCs) and doublecortin (Dcx)-positive neuroblasts in rodent brain, but it is unclear whether RBM3 can regulate NSPC proliferation and promote neurogenesis after HI/R injury.

METHODS

C57BL/6J RBM3 wild-type (WT) and knock-out (KO) mice were used in this study. For *in vitro* experiment, NSPCs were isolated from P0 mice and cultured either in the form of suspending neurospheres or adherent monolayers. Cultured NSPCs were challenged with oxygen glucose deprivation (OGD) to mimic hypoxic-ischemia, and labeled with BrdU before 24 h reoxygenation (R) at

either normothermia or hypothermia. Neurosphere numbers and the percentage of BrdU+ cells were counted. For *in vivo* experiments, right-hemispheric HI/R injury was elicited in adult RBM3 WT or KO mice by temporary occlusion of the right common carotid artery and exposure to 8% hypoxia for 30 min at 37°C. Then the occlusion was removed, and the animals were injected with BrdU before 24 h reperfusion. The infarction size was assessed by cresyl violet staining. The numbers of BrdU+/Dcx+ cells were counted.

RESULTS

Without OGD/R stress, no difference is observed in size and number of neurospheres, nor in BrdU+ cell percentage between RBM3 WT and KO NSPCs. After OGD/R stress, the absence of RBM3 in NSPCs leads to a significant proliferation deficiency with less neurospheres and less BrdU+ cells. Moderate hypothermia promotes RBM3 expression and preserves NSPC proliferation from OGD/R damage but failed to rescue in RBM3 KO cells. In HI/R model, the infarction is generally mild as analyzed by cresyl violet staining. There is little difference of infarction volume between RBM3 WT and KO mice. Upon HI/R injury, the number of newborn neuroblasts (BrdU+/Dcx+) in ipsilateral subventricular zone (SVZ) is significantly larger than in contralateral SVZ in RBM3 WT mice, indicating HI/R injury induces neurogenesis in WT mice. In contrast, in RBM3 KO mice the induction of neurogenesis is absent.

CONCLUSIONS

We demonstrate that the absence of RBM3 reduces the protective effect of hypothermia against OGD/R damage in NSPCs *in vitro* and inhibits the induction of neurogenesis after HI/R *in vivo*. Thus, our data suggest that RBM3 is necessary for SVZ neurogenesis upon HI/R injury.

ABS 46

REACHING SKILLS OF INFANTS BORN VERY PRETERM PREDICT NEURODEVELOPMENT AT 3 YEARS

Y. Fredriksson Kaul[1], K. Rosander[2], H. Grönqvist[1], K. Strand Brodd[1,3], L. Hellström-Westas[1], C. von Hofsten[2]

[1]*Department of Women's and Children's Health, Uppsala University, Uppsala University Hospital, Uppsala, Sweden*

[2]*Department of Psychology, Uppsala University, Uppsala, Sweden*

[3]*Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden*

INTRODUCTION

Infant reaching ability constitutes an important part of neurodevelopmental progress beyond motor function. Reaching for moving objects relies not only on motor function but also on cognitive functions such as prediction and estimation. We have previously shown that very preterm infants are equally successful as full-term infants in catching a moving object at 8 months but their reaching strategies are less efficient. The aim of the present study was to investigate if reaching strategies at 8 months are associated with gestational age (GA) and neurodevelopment at 3 years corrected age in very preterm infants (GA < 32 weeks).

METHODS

Thirty-six very preterm infants, 13 extremely preterm (GA < 28 w) and 23 very preterm (GA 28-31 w), underwent a reaching task at 8 months corrected age. A camera system captured the movements of the hands and the object, and parameters reflecting movement planning and visuomotor control (aiming, movement speed, number of movement units used to plan and execute the reach, as well as shortest possible path of the hand relative the actual path taken by the hand towards the object) were calculated. Success and strategy parameters (how often the infant tried to reach, if it used both hands in coordination and how often it was successful) were noted. At 3 years corrected age, cognition and language skills were tested with the Bayley Scales of Infant and Toddler Development (BSID III).

RESULTS

Tab. 1 shows a summary of the results. For both groups there were associations between reaching for moving objects and cognitive and language skills at 3 years. The more cognitively dependent parameters were in focus for the extremely preterm children, indicating relevance of basic problems on how motion information is used in action planning. For the very preterm children, bimanual strategies and success were of greater importance. Velocity during the reach and number of hits were not associated with outcome.

CONCLUSIONS

Early reaching skills are associated with later neurodevelopment in preterm children, but the associations differ between extremely preterm infants and very preterm infants. This information can offer additional insights to functional developmental trajectories and future intervention programs.

Table 1 (ABS 46). Correlations between reaching parameters at 8 months corrected age and BSID III subscale scores at 3 years of corrected age in 26 children born extremely preterm and very preterm, respectively.

	GA < 28 w, n = 13			GA 28-31 w, n = 23		
	Cognition	Receptive language	Expressive language	Cognition	Receptive language	Expressive language
Planning and control of movement						
Aiming (P)	0.763 [a]	0.633 [a]	0.602 [b]			
Relative length (S)	0.744 [a]	0.644 [b]	0.713 [a]			
Movement units (P)	0.773 [a]	0.591 [b]	0.601 [b]			
Strategy and success						
Number of trials (S)				0.399 [c]	0.544 [a]	0.415 [b]
Number of bimanual hits (S)					0.511 [b]	
Proportion of bimanual coupled reaches (S)				0.649 [a]	0.432 [b]	
Number of bimanual coupled reaches (S)				0.606 [a]	0.432 [b]	

Pearson (P) correlations and Spearman (S) correlations were used according to data characteristics.
[a] $p < 0.01$; [b] $p < 0.05$; [c] $p < 0.06$.

ABS 47

RETINOPATHY OF PREMATURITY AND NEUROCOGNITIVE FUNCTION AT AGE 10 IN CHILDREN BORN EXTREMELY PRETERM

M. Holm[1], T.S. Morken[2], R.M. Joseph[3], M.E. Msall[4], T.M. O´Shea[5], K.C.K. Kuban[6], O. Dammann[7], E.N. Allred[8], A. Leviton[8]

[1]Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), and Department of Pediatrics, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[2]Department of Neuroscience (INM), Faculty of Medicine, Norwegian University of Science and Technology (NTNU), and Department of Ophthalmology, Trondheim University Hospital, Trondheim, Norway

[3]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA

[4]JP Kennedy Research Center on Intellectual and Developmental Disabilities, and Section of Developmental and Behavioral Pediatrics, University of Chicago, Comer Children's Hospitals, Chicago, IL, USA

[5]Division of Neonatology, Department of Pediatrics, University of North Carolina, Chapel Hill, NC, USA

[6]Division of Pediatric Neurology, Department of Pediatrics, Boston University, Boston, MA, USA

[7]Department of Public Health and Community Medicine,Tufts University School of Medicine, Boston, MA, USA, and Perinatal Epidemiology Unit, Hannover Medical School, Hannover, Germany

[8]Neuroepidemiology Unit, Department of Neurology, Boston Children's Hospital, and Harvard Medical School, Boston, MA, USA

INTRODUCTION

Children born extremely preterm are at increased risk of retinopathy of prematurity (ROP) as well as neurocognitive problems in early childhood compared to infants born at term. Here we explore the relationship between severe ROP and neurocognitive outcome at school age in a large cohort of children born extremely preterm.

METHODS

As part of the ELGAN study, 889 10-year-old children born before the 28th week of gestation were evaluated with the Differential Ability Scales-II (DAS-II), the Developmental NEuroPSYchological Assessment-II (NEPSY-II), Oral and Written Language Scales (OWLS), and the Wechsler Individual Achievement Test-III (WIAT-III). Additional analyses were restricted to children with an IQ ≥ 70. We calculated odds ratios and 99% confidence intervals of 2 or more standard deviations (SDs) below the expected mean on each neurocognitive test and prethreshold ROP, adjusting for gestational age, birth weight Z-score <-2, sex and maternal education and government provided health insurance. Prethreshold ROP was defined as disease in zone II, stage 2 with plus disease or stage 3 with or without plus disease.

RESULTS

Children with prethreshold ROP in infancy had lower scores on all neurocognitive subtests when assessed at age 10. In adjusted analyses of the total sample, prethreshold ROP significantly predicted test scores at or below -2 SDs in the DAS-II nonverbal IQ score, Working memory components, and NEPSY-II subtests Inhibition Switching, Arrows and Geometrical Puzzles. ROP was not associated with low scores on the OWLS or the WIAT-III. When children with an IQ score ≥ 70 were analyzed

separately, no differences in test scores were found between those with and without ROP.

CONCLUSIONS

Severe ROP in infancy was associated with low IQ, and problems with executive and visuospatial functioning 10 years later. Among children with an IQ in the normal range, however, ROP was not associated with subnormal test scores on any of the neurocognitive tests.

ABS 48

UNDERSTANDING ADHD AND ASD IN VERY PRETERM CHILDREN FROM A SENSORY PROCESSING PERSPECTIVE: A CONTROLLED NEUROPSYCHOLOGICAL STUDY

T. Bröring[1], K. Oostrom[1,2], M. Königs[2], E. van Dijk-Lokkart[1], H. Lafeber[3], A. Brugman[1], J. Oosterlaan[2,3,4]

[1]Department of Medical Psychology, VU University medical center Amsterdam, Amsterdam, the Netherlands

[2]Department of Pediatrics, Emma Children's Hospital, Academic Medical Center Amsterdam, Amsterdam, the Netherlands

[3]Department of Pediatrics, VU University medical center Amsterdam, Amsterdam, the Netherlands

[4]Clinical Neuropsychology Section, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

INTRODUCTION

Very preterm children are at risk for a wide range of neurodevelopmental problems, including behavioral impairments and sensory processing difficulties, which are associated with white matter brain abnormalities due to hypoxia-ischemia and infections, exacerbated by noxious effects of the neonatal intensive care unit (NICU) environment. This study investigates ADHD and ASD symptoms and sensory processing in terms of somatosensory registration, multisensory integration and modulation in very preterm children and studies whether sensory processing mediates the relationship between prematurity and ADHD and ASD symptoms.

METHODS

57 very preterm children, aged 8-10, and 56 gender and age-matched full-term children were included. ADHD and ASD symptoms were measured using parent and teacher behavioral questionnaires. Sensory processing was assessed using somatosensory registration tasks, a neurocognitive multisensory integration task and a parent-reported questionnaire on sensory modulation. Group differences were investigated using t-tests and Mann-Whitney U tests. Mediation analyses tested whether sensory processing difficulties mediate the relation between prematurity and aggregated ADHD and ASD symptom levels (using principal component analysis).

RESULTS

Parents and teachers reported more symptoms of ADHD and ASD in very preterm children than in matched full-term children. Very preterm children performed worse on sensory registration and modulation than full-term children, but not on multisensory integration. Moreover, sensory modulation mediated the relationship between prematurity and ADHD symptoms as well as ASD symptoms.

CONCLUSIONS

Indeed, sensory processing difficulties may play a key role in understanding symptoms of ADHD/ASD in very preterm children.

ABS 49

SOCIAL-EMOTIONAL DEVELOPMENT IN VERY PRETERM INFANTS DURING EARLY INFANCY

P.H. Gray[1,2], D.M. Edwards[1], M. Pritchard[2,3]

[1]Growth and Development Unit, Mater Mothers' Hospital, Brisbane, Queensland, Australia

[2]Mater Research Institute-University of Queensland, Brisbane, Queensland, Australia

[3]Australian Catholic University, Mater Mothers' Hospital, Brisbane, Queensland, Australia

INTRODUCTION

Mental health disorders among children are of growing importance, with social-emotional development being a measure of mental health problems during early infancy. The aim of the study was to compare the social-emotional development of very preterm infants at 2 years with infants born at term. The association of maternal and neonatal factors and developmental outcome was also determined.

METHODS

Participants were 96 preterm infants (≤ 30 weeks' gestation) and 77 term infants. The mothers completed the Bayley Scales of Infant and Toddler Development – Social Emotional Scale (Bayley-SE), the Depression Anxiety Stress Scale (DASS), the Parenting Stress Index (PSI) and the Child Behaviour Checklist (CBCL) for each child. The infants had a developmental assessment including the Bayley-III.

RESULTS

The mean composite score on the Bayley-SE was significantly lower for the preterm infants (103.2 ±

16.2) compared to the term group (109.6 ± 14.9) with a difference of 7.5 following adjustment for multiple births (p = 0.004). For the preterm infants, there were no perinatal or neonatal variables associated with high Bayley-SE scores. Results on the Bayley-III, the DASS, the PSI and CBCL however were significantly associated with the Bayley-SE. On multiple regressions the strongest independent variables were Bayley-III motor (p = 0.004), CBCL externalising (p < 0.001) and Total PSI (p < 0.001).

CONCLUSIONS

Social-emotional development is significantly impaired in preterm infants at 2 years, with motor performance on the Bayley-III, infant externalising behaviours and maternal parenting stress being significantly associated independent variables.

ABS 50

TOUCHSCREENS FOR COGNITIVE ASSESSMENT OF TODDLERS

D.M. Twomey[1], C. Wrigley[1,2], C. Ahearne[1], R. Murphy[2], M. de Haan[3], N. Marlow[4], D.M. Murray[1]

[1]Department of Paediatrics and Child Health, University College Cork, Ireland

[2]Department of Applied Psychology, University College Cork, Ireland

[3]Centre for Developmental Cognitive Neurosciences, University College London, London, UK

[4]Department of Neonatology, UCL Institute for Women's Health, University College London, London, UK

INTRODUCTION

Early identification of cognitive delay is critical for improving developmental outcomes in children. Existing gold-standard neurodevelopmental assessments rely heavily on children's receptive communication and fine motor skills and a high volume of child-administrator interaction is often required to get them to engage. A computerised cognitive assessment that is relatively independent of these factors would be fundamental to addressing these issues, however,

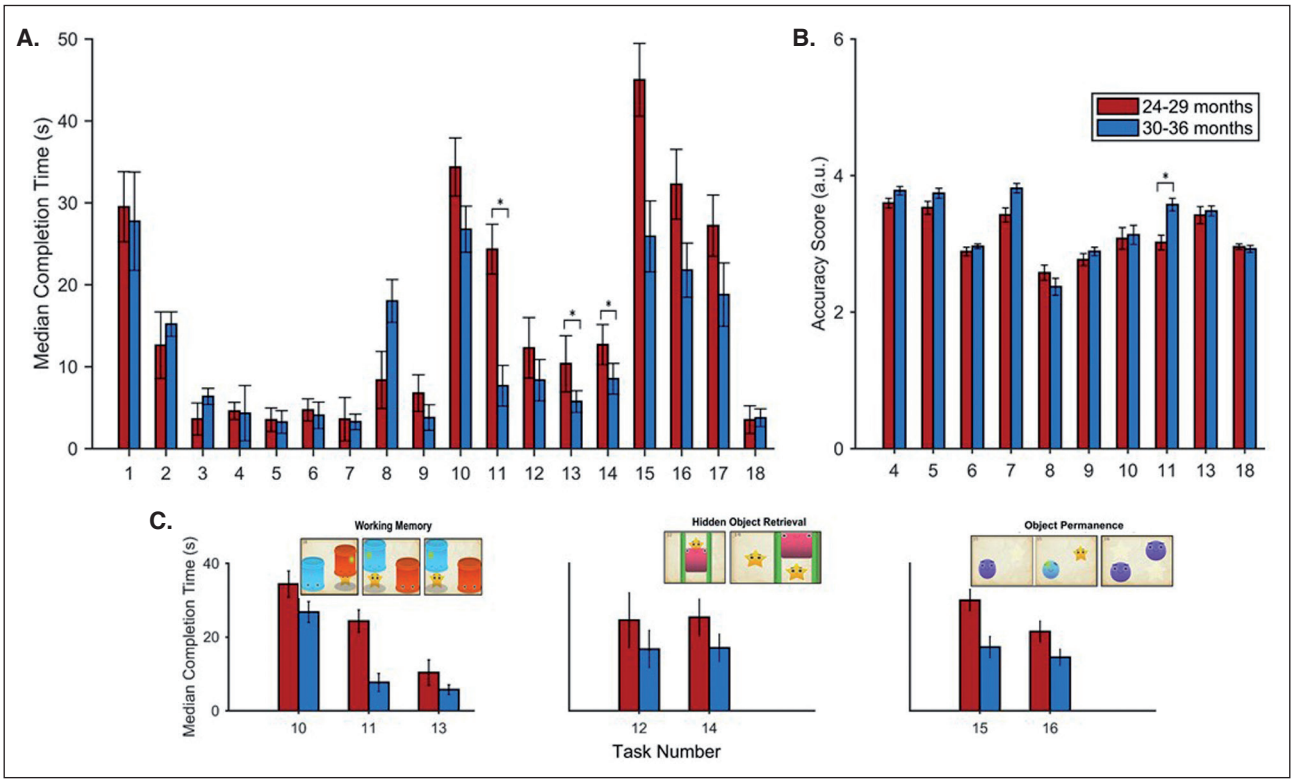

Figure 1 (ABS 50). A. Children aged 30-36 months were able to complete more cognitive tasks than those aged 24-29 months both with and without a visual demonstration. Older children completed two of the three working memory tasks (task 11 and 13) and a hidden object retrieval task (task 14) significantly faster than their younger peers. **B.** Accuracy did not differentiate between the two age groups with the exception of one working memory task (task 11); wherein the older children were more accurate. **C.** Indicative of learning; children became progressively faster at completing the working memory items (tasks 10, 11 and 13) with each exposure and registered similar completion times on the two iterations on the hidden object retrieval (tasks 12 and 14) and object permanence (tasks 15 and 16) tasks despite the fact that demands were two-fold on the second exposure.

none is currently available for use with children under the age of three. With this in mind, we explored the potential of a novel touchscreen assessment tool to measure emerging cognitive capacities in children aged 2-3 years.

METHODS

112 typically developing children with a mean age of 30.1 months (SD = 4.2) interacted with a touchscreen cognitive assessment tool designed to measure selective attention, working memory, hidden object retrieval and an understanding of object permanence. We examined the sensitivity of the assessment to age-related changes in cognition by comparing the number of items completed, the speed of task completion and accuracy in children aged between 24-29 months and 30-36 months old. We also examined whether children demonstrated learning on repeated iterations of the working memory, hidden object retrieval items and object permanence items. Where multiple comparisons were conducted a Bonferroni correction was applied.

RESULTS

Results are presented in **Fig. 1**.

CONCLUSIONS

Children as young as 24 months can complete a cognitive assessment on a touchscreen device, with no verbal instruction and minimal child-administrator interaction. The physical contingency of touchscreen devices allows very young children to learn new skills very quickly. Touchscreen technology is an exciting vehicle for relatively language, motor and administrator independent developmental assessment in very young children.

ABS 51

NEUROPROTECTIVE INTERVENTION AFTER HYPOXIA-ISCHEMIA MAY CHANGE INTRA-CEREBRAL METABOLIC MEASURES IN A NEWBORN PIGLET MODEL

T.C. Andelius[1], N. Bøgh[2], M.V. Pedersen[1], C. Omann[2], V.E. Hjortdal[2], M. Pedersen[3], T.B. Henriksen[1], K.J. Kyng[1]

[1]Department of Paediatrics, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark

[3]Comparative Medicine Lab, Aarhus University Hospital, Aarhus, Denmark

INTRODUCTION

Hypoxic-Ischemic Neonatal Encephalopathy (HIE) is a major contributor to neurological impairment and death in children. Due to the similarity with the human brain, newborn piglets are often used in studies of new treatments for HIE. Cell death after hypoxia ischemia (HI) occurs in stages, each offering different targets for interventions. Therapeutic hypothermia (TH) is the only treatment for HIE. We hope to provide knowledge concerning the metabolic processes occurring in the brain after HI. The aim of this study was to quantify changes in intracerebral metabolism, pressure, flow, and oxygen saturation after HI in controls and TH piglets. We present preliminary data from the first animals.

METHODS

Piglets (< 24 hours old) were anaesthetized, intubated and ventilated. Two probes and one microdialysis catheter were inserted 10 mm into the left parasagittal cortex. Probes measured intracranial pressure (ICP), flow, temperature, and oxygen tension. By microdialysis we measured lactate, glucose, glycerol, and pyruvate. A NIRS-probe was placed on the right side of the head and aEEG electrodes were placed on each side. After 24 hours of stabilisation, HI was induced for 45 minutes. Piglets were randomized to either TH (rectal temperature of 33.5°C) or normothermia and intracerebral measures were taken every hour for 48 consecutive hours. TH was initiated immediately after HI and was continued for the 48 hours.

RESULTS

Preliminary results from two controls and one piglets subjected to HI are presented. The HI piglet was randomized to normothermia. All measures described were successfully recorded. Controls showed unaffected intracerebral measures. In the HI piglet, glycerol increased through the whole observation period, while lactate plateaued after approximately 24 hours. Lactate/pyruvate ratio and ICP showed a parabolic pattern in the HI piglet (**Fig. 1**).

CONCLUSIONS

We present a novel take on an already well-established animal model for HIE. We expect to provide basic knowledge of how interventions may affect intracerebral metabolic measures, pressure and gas-exchange. These measures may also guide optimal timing of potential new treatments.

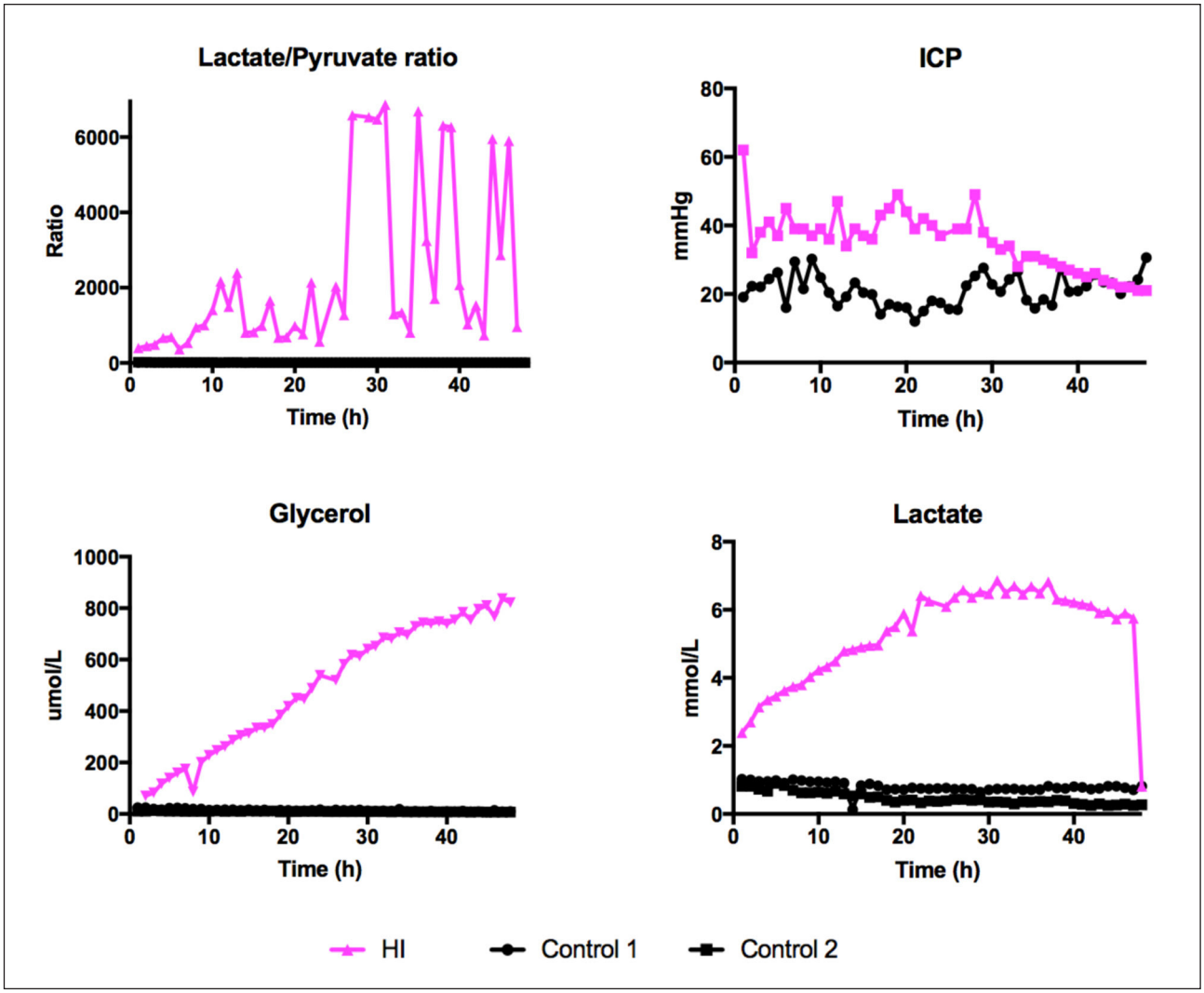

Figure 1 (ABS 51). In the HI piglet, glycerol increased through the whole observation period, while lactate plateaued after approximately 24 hours. Lactate/pyruvate ratio and ICP showed a parabolic pattern in the HI piglet.

ABS 52

TWO-YEAR OUTCOME OF EXTREMELY PRETERM INFANTS < 26 WEEKS OF GESTATION BORN IN SWITZERLAND: IS INTENSITY OF PERINATAL CARE ASSOCIATED WITH INCREASED NEURODEVELOPMENTAL IMPAIRMENT?

G. Natalucci[1,2], T.M. Berger[3], C. Borradori-Tolsa[4], M. Bickle-Graz[5], S. Grunt[6], R. Gerull[7], D. Bassler[1], M. Adams[1] for the Swiss Neonatal Network & Follow-Up Group

[1]*Department of Neonatology, University of Zurich and Zurich University Hospital, Zurich, Switzerland*

[2]*Child Development Centre, University Children's Hospital Zurich, Zurich, Switzerland*

[3]*Swiss Neonatal Network*

[4]*Department of Paediatrics, Geneva University Hospital, Geneva, Switzerland*

[5]*Clinic of Neonatology, Department Woman-Mother-Child, University Hospital Lausanne, Lausanne, Switzerland*

[6]*Division of Neuropaediatrics, Development and Rehabilitation, University Children's Hospital, Berne, Switzerland*

[7]*Division of Neonatology, University of Basel Children's Hospital, Basel, Switzerland*

INTRODUCTION

In Switzerland, neonatal survival of extremely low gestational age neonates (ELGANs) with gestational age < 26 weeks improved following the publication of the 2002 Swiss guidelines for the perinatal care of infants born at the limit of viability, with no increase in the rate of short-term complications. A substantial center-to-center difference in neonatal mortality persisted after the guidelines' publication. This study aimed to compare survival and neurodevelopmental impairment rates at 2 years of

corrected age among ELGANs born alive in the 9 Swiss level III perinatal centers and to investigate the impact of center-specific levels of perinatal interventional activity on these outcomes.
METHODS
Prospective population-based study including all ELGANs without major congenital malformations born alive in Switzerland in 2006-2013 with gestational age 1; equivalent of a developmental test score < 2 SD from the respective norm; hearing loss; uni- or bilateral blindness) and favorable outcome (none of the above). Crude and risk-adjusted standardized outcome ratios (SOR, 95%-CI) based on the center-specific level of perinatal interventional activity were calculated with regression models using 5-fold imputed data.
RESULTS
Among 927 included infants, 564 (61% of cohort) died before discharge and 319 (88% of survivors) were assessed at 2 years corrected age (46% females, mean [SD] gestational age 25.1 [0.5] weeks). Favorable and unfavorable outcomes were observed in 75% and 25% of survivors, respectively. After risk adjustment (for gestational age, birth weight z-score, male sex, multiple birth, out-born rate and socioeconomic status), mortality was significantly higher (1.33, 1.30-1.36) and favorable outcome significantly lower (0.76, 0.74-0.79) in centers with low perinatal interventional activity compared to other centers. In centers with high perinatal interventional activity, mortality was significantly lower (0.84, 0.80-0.90) and favorable outcome significantly higher (1.07, 1.07-1.13) compared to other centers.
CONCLUSIONS
There are significant differences in 2-year outcome of ELGANs between the 9 Swiss level III perinatal centers. The level of perinatal interventional activity for ELGANs is negatively correlated with mortality and positively correlated with favorable outcome.

ABS 53

SELF-REPORTED WIDESPREAD PAIN IN ADULTS BORN EARLY AND LATE PRETERM

K.A.I. Evensen[1,2], M. Tikanmäki[3,4], K. Heinonen[5], H.-M. Matinolli[6,7], M. Sipola-Leppänen[6,7,8], A. Lano[9], D. Wolke[10], M. Vääräsmäki[6,8], J.G. Eriksson[6,11,12], S. Andersson[9], M.-R. Järvelin[7,13], P. Hovi[6], K. Räikkönen[5], E. Kajantie[6,8,9]

[1]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway

[3]Chronic Disease Prevention Unit, National Institute for Health and Welfare, Oulu and Helsinki, Finland

[4]Institute of Health Sciences, University of Oulu, Oulu, Finland

[5]Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland

[6]National Institute for Health and Welfare, Helsinki and Oulu, Finland

[7]Institute of Health Sciences, University of Oulu, Oulu, Finland

[8]PEDEGO Research Unit (Research Unit for Pediatrics, Dermatology, Clinical Genetics, Obstetrics and Gynecology), Medical Research Center Oulu (MRC Oulu), Oulu University Hospital and University of Oulu, Oulu, Finland

[9]Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[10]Department of Psychology, University of Warwick, Warwick, UK

[11]Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[12]Folkhälsan Research Center, Helsinki, Finland

[13]Imperial College, London, UK

INTRODUCTION
As newborns, individuals born preterm are often exposed to pain through multiple invasive procedures in neonatal care. While some studies suggest long-term hypersensitivity to pain, larger epidemiological studies have not been able to demonstrate associations between prematurity and chronic widespread pain in adults, when accounting for confounding factors. As chronic widespread pain constitutes a large burden to both the individual and the society, we aimed to investigate the prevalence of self-reported widespread pain in young adults born early and late preterm compared with a full-term reference group.
METHODS
We studied 1,175 young adults (mean age 24.1 ± 1.4 years) from two birth cohorts: ESTER (Northern Finland 1985-1989) and AYLS (Uusimaa, Finland, 1985-1986). Of the participants, 184 were born early preterm (< 34 weeks), 350 were born late preterm (34 to < 37 weeks), and 641 were term-born. They all completed a pain questionnaire, indicating number of pain sites and pain location. We defined widespread pain as pain in three or more pain sites including both upper and lower parts of the body as well as axial pain. Group differences were examined by logistic regression models, adjusting for sex and cohort (Model 1), potential early life confounders (Model 2), lifestyle covariates like body composition and smoking (Model 3) and depressive symptoms (Model 4).
RESULTS
Widespread pain was reported in 50-56% of all participants. Odds ratio for self-reported widespread

pain was 0.79 (95% CI: 0.60-1.04) in the late preterm group and remained the same when we adjusted for early life confounders, body composition, smoking and depressive symptoms (Model 4: 0.76; 95% CI: 0.57-1.02). The odds for reporting widespread pain were similar in the early preterm group (1.00; 95% CI: 0.72-1.41) as in the full-term reference group. Results were similar when we excluded individuals with neurosensory impairments, severe physical or mental disability (n = 17).

CONCLUSIONS

We did not find evidence of long-term hypersensitivity to pain in adults born early or late preterm. In contrast, adults born late preterm had a tendency of lower risk of widespread pain, also when taking lifestyle factors into account.

ABS 54

BRAIN VOLUMES BY CEREBRAL MRI AND CORRELATIONS WITH PSYCHIATRIC SYMPTOMS IN LOW BIRTHWEIGHT ADULTS

A.M.W. Lærum[1], L.M. Rimol[2], S.K. Reitan[3], A. Brubakk[1], K.A.I. Evensen[1], K.J. Bjuland[4], S. Lydersen[5], J. Skranes[1], M.S. Indredavik[5,6]

[1]*Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway*

[2]*Department of Circulation and Medical Imaging, NTNU, Trondheim, Norway*

[3]*Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway*

[4]*Department of Research, Sørlandet Hospital HF, Arendal, Norway*

[5]*Department Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway*

[6]*Department of Children and Youth, Mental Health Care, St. Olavs Hospital, Trondheim University Hospital*

INTRODUCTION

Low birth weight individuals are at increased risk of brain developmental deviations as well as adult psychiatric problems. Our objective was to examine brain volumes in low birth weight adults compared to term born non-SGA controls. Further, we aimed to examine correlations between specific psychiatric symptoms and relevant brain volumes.

METHODS

This is a longitudinal cohort study of one group born preterm at very low birth weight (VLBW: ≤ 1,500 g) n = 47, one group born at term but Small for Gestational Age (SGA: < 10th percentile) n = 55 and one control group n = 73, born 1986-1988 in Mid-Norway. Participants were assessed with 3T structural MRI, and Freesurfer 5.3.0 for volume analysis. The Achenbach System of Empirically Based Assessment: Adult Self-Report, was used to assess psychiatric symptoms. For analyzing the connection between psychiatric symptoms and

Table 1 (ABS 54). Absolute brain volumes in the three study groups.

Estimated marginal means, ml, mean (95% CI)	VLBW, n = 47	p	SGA, n = 55	p	Control, n = 73
Total intracranial volume	1,602.19 (1,561.40-1,642.98)	0.001	1,636.10 (1,598.68-1,673.51)	0.022	1,693.99 (1,661.43-1,726.54)
Cerebral white matter	463.81 (449.53-478.09)	< 0.001	474.32 (461.22-487.42)	0.003	500.54 (489.14-511.94)
Ventriculi laterales	23.10 (20.80-25.40)	< 0.001	13.19 (11.08-15.30)	0.993	13.18 (11.34-15.01)
Cerebellum white matter	29.39 (28.34-30.44)	< 0.001	31.27 (30.31-32.23)	0.012	32.90 (32.07-33.74)
Cerebellum grey matter	116.26 (113.32-119.19)	0.004	116.60 (113.91-119.29)	0.005	121.78 (119.44-124.12)
Thalamus proper	14.95 (14.54-15.36)	< 0.001	16.19 (15.82-16.57)	0.041	16.72 (16.39-17.04)
Nucleus caudatus	7.27 (7.01-7.53)	0.002	7.54 (7.30 -7.78)	0.120	7.79 (7.58-8.00)
Putamen	10.46 (10.14-10.79)	< 0.001	10.56 (10.26-10.86)	0.001	11.24 (10.99-11.50)
Globus pallidus	2.86 (2.77-2.95)	0.001	2.88 (2.80-2.96)	0.001	3.05 (2.98-3.12)
Hippocampus	8.63 (8.40-8.86)	< 0.001	9.05 (8.83-9.26)	0.086	9.30 (9.11-9.48)
Amygdala	3.09 (2.99-3.19)	< 0.001	3.23 (3.14-3.32)	0.077	3.34 (3.26-3.42)
Nucleus accumbens	1.07 (1.02-1.13)	< 0.001	1.12 (1.07-1.17)	0.001	1.23 (1.18-1.27)
Corpus callosum posterior	0.90 (0.85-0.95)	0.005	0.96 (0.92-1.00)	0.361	0.99 (0.95-1.03)
Corpus callosum mid posterior	0.43 (0.40-0.46)	< 0.001	0.50 (0.47-0.53)	0.404	0.51 (0.49-0.54)
Corpus callosum central	0.46 (0.42-0.49)	0.002	0.52 (0.49-0.55)	0.698	0.52 (0.50-0.55)
Corpus callosum mid anterior	0.48 (0.45-0.52)	0.030	0.54 (0.50-0.57)	0.915	0.54 (0.51-0.57)
Corpus callosum anterior	0.90 (0.85-0.95)	0.012	0.95 (0.90-1.00)	0.232	0.99 (0.95-1.03)

General linear model with birthweight group as fixed factor and age at MRI scan and sex as covariates. P-values vs. controls.

brain volumes partial correlation was performed, controlling for gender and age. P-values ≤ 0.010 were regarded as significant.

RESULTS

Brain volumes are presented in **Tab. 1**. When controlling for intracranial volume, the VLBW group had significantly larger lateral ventricles, less cerebellar white matter and smaller thalamus, hippocampus, amygdala, nucleus accumbens, and mid-posterior corpus callosum. In the VLBW group, none of the correlation coefficients between volumes and psychiatric symptoms were statistically significant. The SGA group had significantly smaller putamen and n. accumbens after controlling for intracranial volume. Attention problems were significantly related to cerebellar grey matter volume: r = 0.393, p = 0.004 and hippocampus: r = 0.370, p = 0.006. Controlling for IQ (in addition to age and gender) did not change the results substantially.

CONCLUSIONS

The preterm VLBW and term born SGA group had smaller brain volumes compared to the control group. In the VLBW group thalamus, amygdala and corpus callosum were among the particularly affected structures, though no correlation to psychiatric symptoms were seen. In the SGA group putamen and n. accumbens were particularly affected. Self-reported psychiatric symptoms were related to cerebellar grey matter and hippocampus volumes in the SGA group.

ABS 55

POSTURE AND MOBILITY INFLUENCE ON ATTENTION ABILITIES IN HEALTHY 7 YEARS OLD CHILDREN

H. Ceyte[1], J. Rosenbaum[1,2], S. Caudron[1], J.-M. Hascoet[1,2]

[1]Université de Lorraine, EA 3450 DevAH «Development, Adaptation and Disability», Faculty of Sport Sciences, Nancy, France

[2]Department of Neonatology, Maternité Régionale, CHRU Nancy, France

INTRODUCTION

Seven years of age is a milestone for basic knowledge learning abilities strongly related to attention skills and executive functions, which allow for appropriate adaptation to primary school. The Attention Network Test for children (ANT) showed that alerting and orienting skills improve up to 6 years of age while inhibition function may improve up to 7 years then remain stable. Recent studies suggested that, contrary to a common thinking, children's mobility at school might induce significant improvements of attention levels and school performance. This preliminary study aimed to determine the influence of posture and mobility on the level of each attention components in 7 years old children.

METHODS

Children in their expected grade without learning difficulty agreed to participate after parental consent. They were equipped with a head-mounted display (Vision-720VR 3D video glasses) in which the ANT was presented. They were asked to identify, as quickly and accurately as possible, the direction of a central fish by pressing the right or the left mouse button whatever the direction of a possible flanking fish (congruent, incongruent, and neutral conditions). Each target was preceded by one of the four cue conditions: center cue (arousal), double cue (alerting), spatial cue (orienting), or no cue. The task was composed of 12 practice trials in seated posture then three experimental blocks of 48 trials performed in one out of 3 randomized postures: seated, standing or free posture.

RESULTS

Four boys and 6 girls, 7 ± 1 year of age, were included; 2 of them were excluded due to the lack of respect of the postural instructions and guessing answers. Friedman tests were carried out on the median response time (medRT) with the 3 postures as a within-subject factor for alerting and orienting skills, and inhibition function. For alerting skills, the standing posture tended to reduce medRT versus the seated posture (Median [Interquartile Range]): 56 [126] vs. 145 [90] msec respectively (Chi^2 [8.2] = 6.25; p = 0.09). For the orienting skills, no postural effect was shown. For the inhibition function, a significant effect of the posture was demonstrated: the free posture medRT (94 [152] msec) was lower than that the seated posture medRT (190 [107] msec) not different from the standing posture (195 [196] msec) (Chi^2 [8.2] = 6.25; $p < 0.05$).

CONCLUSIONS

These preliminary data suggest that child mobility may influence the level of the inhibition function and alerting skill. Previous studies suggested that mobility reflects unintentional attempt to increase arousal level to facilitate information processing. Our findings raise the question of the exact role of the spontaneous mobility often associated with poor attentional performances in vulnerable populations such as preterm born children.

ABS 56

SURGICAL DECISION MANAGEMENT IN CHIARI TYPE 2 MALFORMATION: A SINGLE CENTER EXPERIENCE

S.A. Ozdemir[1], N. Ozdemir[2], A. Karadag[2], E.A. Ozer[3]

[1]*Department of Neonatology, Behcet Uz Children's Hospital, Izmir, Turkey*

[2]*Department of Neurosurgery, Tepecik Training and Research Hospital, Izmir, Turkey*

[3]*Department of Neonatology, School of Medicine, Mugla Sıtkı Koçman University, Izmir, Turkey*

INTRODUCTION

Chiari malformation type II (CM-II) is frequent with meningomyelocele (MMC). We aim to present the accurate timing and indications and to reveal the necessity of the CM-II surgery.

METHODS

This was a prospective and observational study, which involved 25 patients (9 infants operated, 16 infants non-operated). Spinal and cranial MRI examinations were performed on all infants. MMC, CM-II and hydrocephalus of infants were evaluated clinically and radiologically. The operation decision was made for infants who had symptoms of apnea, nourishment, respiratory distress, persistent vomiting and progressive weakness in the upper extremity, and these symptoms were associated with CM-II malformation. The follow-up decision was made independently of the MRIs that did not show these symptoms. Clinical, surgical management and long-term outcomes were compared for both groups.

RESULTS

25 infants were included, 14 of them were male. 9 MMC baby was performed during neonatal period due to symptomatic CM-II, while 16 babies were followed up for CM-II after MMC repair. Mean duration of follow-up for operated infants was 31.0 ± 16.9 and non-operated group was 31.3 ± 9.9. Comparing the lowest border of downward herniated cerebellar tonsil levels for CM-II cases, the presence of cerebellar tonsils below C3 level was present in 77% of the operated cases and only 37% of the cases without operation ($p = 0.05$). Apnea was the most common symptom in the operated cases.

CONCLUSIONS

Cerebellar tonsils were located lower in the cervical spinal canal in the operated infants. In the presence of clinical symptoms due to CM-II, MRI findings may be the second step.

ABS 57

EFFECTS OF NEURAL STEM CELL MEDIA ON HYPOXIC INJURY IN RAT HIPPOCAMPAL SLICE CULTURES

N.M. Lee[1], S.A. Chae[1], H.J. Lee[2]

[1]*Department of Pediatrics, Chung-Ang University Hospital, College of Medicine, Chung-Ang University, Seoul, Korea*

[2]*Biomedical Research Institute, Chung-Ang Universit Hospital, Seoul, Korea*

INTRODUCTION

Neonatal hypoxic-ischemic brain injuries cause serious neurological sequelae, yet currently there is no effective treatment for them. We hypothesized that neurotrophic factors released into the media by stem cells could supply some regenerative ability to hypoxia-damaged organotypic hippocampal slice cultures.

METHODS

We prepared organotypic slice cultures of the hippocampus of 7-day-old Sprague-Dawley rats based on the modified Stoppini method; slices were cultured for 14 days *in vitro* using either Gahwiler's media (G media) and stem cell-conditioned media (S media) as culture media. At 14 days *in vitro*, hippocampal slice cultures were exposed to 3 hours of hypoxic damage, the extent of which was then measured using propidium iodide fluorescence and immunohistochemistry images. We performed dot blotting to estimate neurotrophic/growth factor levels in the G media and S media.

RESULTS

Organotypic hippocampal slices cultured using S media after hypoxic injury were significantly less damaged than those cultured using G media (**Fig. 1**). GLUT1, NGF, GDNF, VEGF, GCSF, and IGF2 levels were higher in S media than G media, whereas FGF1, HIF, and MCP3 levels were not significantly different between media.

CONCLUSIONS

Stem cell-conditioned media had a neuroprotective effect against hypoxic injury. Of the various neurotrophic factors in the S media, NGF, GDNF, and VEGF can contribute to neuroprotection.

ABS 58

A NOVEL CEREBRAL ULTRASOUND SCORING SYSTEM IS ASSOCIATED WITH NEUROLOGICAL OUTCOME IN NEONATES WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

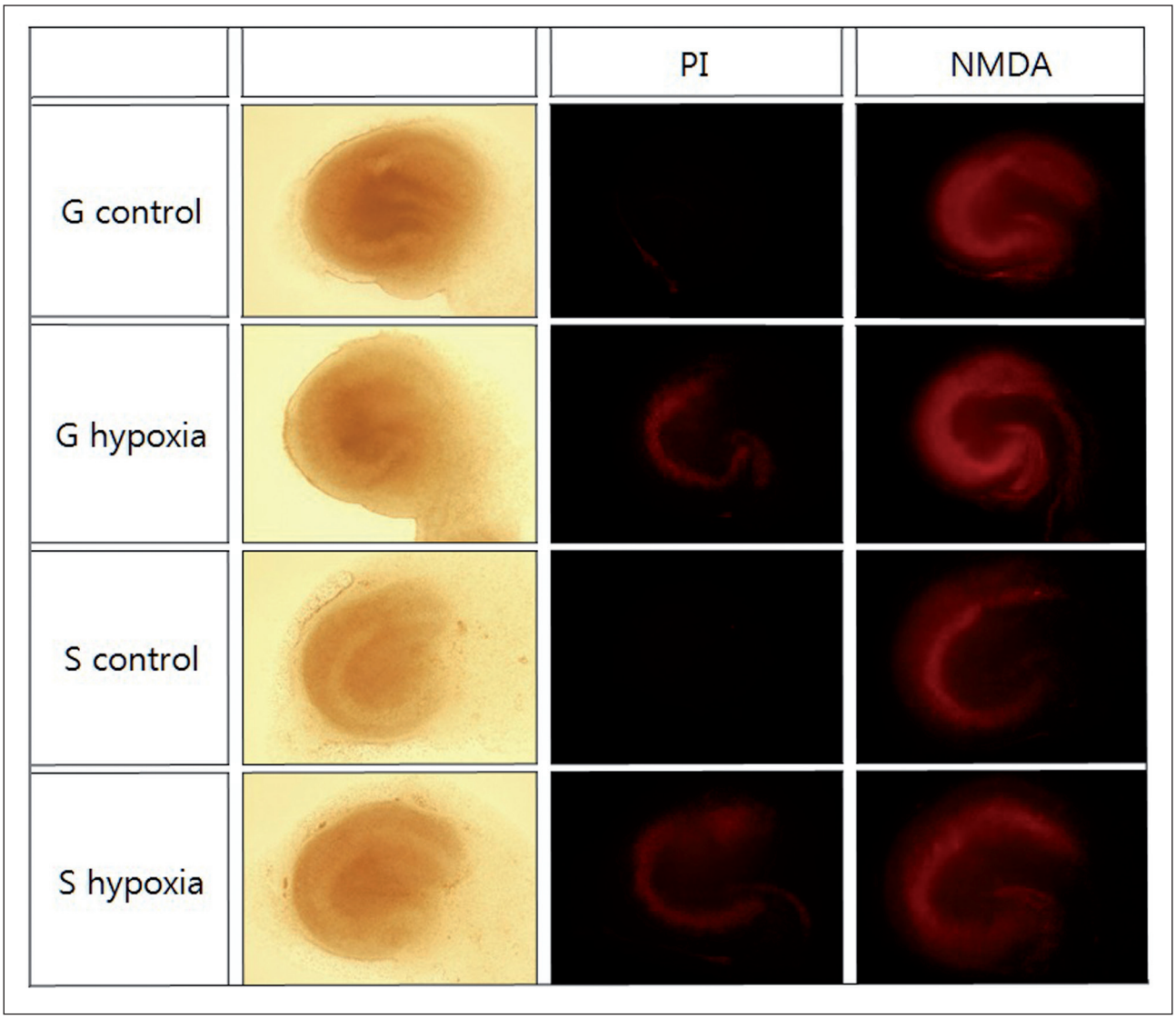

Figure 1 (ABS 57). Organotypic hippocampal slices cultured using S media after hypoxic injury were significantly less damaged than those cultured using G media.

K. Annink[1], F. Groenendaal[1], M. Lequin[2], D. Vijlbrief[1], L. de Vries[1], M. Benders[1], J. Dudink[1]

[1]Department of Neonatology, Wilhelmina Children's hospital, University Medical Center Utrecht, Utrecht, the Netherlands

[2]Department of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is an important cause of morbidity and mortality in neonates and can result in long-term neurological damage. Currently, magnetic resonance imaging (MRI) is considered the gold standard to predict motor and cognitive outcome in infants with HIE. However, there are circumstances when MRI is not feasible or not easily accessible. In these cases, cerebral ultrasound (cUS) can be an alternative technique. At present, there is no validated cUS scoring system available for this population. The aim of this study was to develop an early cUS scoring system to predict outcome in infants with HIE.

METHODS

Infants with HIE that underwent hypothermia in the Wilhelmina Children's Hospital, with at least a cUS on day 1 and day 3-7 postpartum and with available outcome data, were retrospectively included. Adverse outcome was defined as death, cerebral palsy or a score on the BSITD-III-NL < 85 at two years of age. We searched the literature for items to include in this scoring system. The cUS items were related to adverse outcome in univariate logistic regression. Multivariable logistic regression was performed to develop the final cUS scoring system based on the cUS on day

Table 1 (ABS 58). The scoring system. White matter damage is the sum of edema, periventricular and subcortical white matter damage (0-6 points). Grey matter damage includes hyperechogenicity of the thalami, putamen, presence of the PLIC, and four column sign (0-6 points).

	Normal-mildly abnormal (0)	Moderately abnormal (1)	Severely abnormal (2)
Impaired white/grey matter differentiation and/or slit like ventricles			
Hyperechogenicity periventricular white matter			
Hyperechogenicity subcortical white matter			
Hyperechogenicity thalamus			
Hyperechogenicity putamen			

	Absent (0)	Present (1)
Four column sign		
Hypo-echogenicity internal capsule		
Resistive index	RI ≥ 0.55	RI < 0.55

3-7. The resistive index (0-1 point), the sum of deep grey matter damage (0-6 points) and white matter damage (0-6 points) were included in this analysis.

RESULTS

A comparable cohort from the Erasmus Hospital was used to validate the scoring system. In total 83 children were included in the initiation cohort. On day 1 postpartum, only severe periventricular white matter damage was associated with adverse outcome. On day 3-7 postpartum, all items were independently predictive of adverse outcome. The final cUS scoring system contains a sum of the white matter (OR 2.61, 95% CI 1.46-4.69) and deep grey matter damage (OR 2.70, 95% CI 1.68-4.35) (**Tab. 1**). The resistive index was not significant and was excluded. The following formula can be used to predict the probability of adverse outcome in HIE: 1 / (1 + e - (-3.385 + 0.960 * white matter + 0.995 * deep grey matter). In the validation cohort 35 infants were included. The cUS scoring system performed well in the initiation cohort (AUC = 0.904) and in the validation cohort (AUC = 0.889). The sensitivity, specificity, negative and positive predictive values for a cut-off value of ≥ 3 were ≥ 75% in both cohorts.

CONCLUSIONS

This cUS scoring system is associated with an adverse outcome in neonates with HIE and seems to be a promising alternative if MRI is not feasible. Both the sum of white matter damage as the sum of grey matter damage were predictive of adverse outcome and were included in the final scoring system, but the resistive index was not. This scoring system performed well in a validation cohort.

ABS 59

MONITORING THE ENERGY METABOLISM IN PLASMA FROM NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE) DURING THERAPEUTIC HYPOTHERMIA

Á. Sánchez-Illana[1], A. Núñez-Ramiro[1], M. Cernada[1], A. Parra[1], E. Valverde[2], D. Blanco[3], M.T. Moral-Pumarega[4], F. Cabañas[5], H. Boix[6], A. Pavon[7], M. Chaffanel[8], I. Benavente-Fernández[9], I. Tofe[10], B. Loureiro[11], J.R. Fernández-Lorenzo[12], B. Fernández-Colomer[13], J. Kuligowski[1], M. Vento[1,14]; the HYPOTOP Study Group

[1]Neonatal Research Unit, Health Research Institute La Fe, Valencia, Spain

[2]Hospital Universitario La Paz, Madrid, Spain

[3]Hospital Universitario Gregorio Marañón, Madrid, Spain

[4]Hospital Universitario 12 de Octubre, Madrid, Spain

[5]Hospital Universitario Quirónsalud, Madrid, Spain

[6]Hospital Universitario Vall D'Hebron, Barcelona, Spain

[7]Hospital Universitario Virgen del Rocío, Sevilla, Spain

[8]Hospital Materno Infantil Carlos Haya, Málaga, Spain

[9]Hospital Universitario Puerta del Mar, Cádiz, Spain

[10]Hospital Universitario Reina Sofía, Córdoba, Spain

[11]Hospital Universitario Cruces, Vizcaya, Spain

[12]Hospital Álvaro Cunqueiro, Vigo, Spain

[13]Hospital Central de Asturias, Oviedo, Asturias, Spain

[14]Division of Neonatology, University & Polytechnic Hospital La Fe, Valencia, Spain

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) as a result of perinatal asphyxia is a major cause of neurologic disabilities and mortality in the term neonate. Therapeutic hypothermia (TH) is the most effective

treatment for HIE. In this context, new synergistic therapies are being explored. The HYPOTOP trial (Eudract 2011-005696-17) is a randomized, multicenter, double blinded placebo-control clinical trial, aiming at the evaluation of the neuroprotective effect of topiramate (TPM) combined with TH in patients with HIE. This work aims at studying several key metabolites in newborns with HIE undergoing TH in the HYPOTOP cohort and comparing them to levels found in healthy term newborns.

METHODS

The HYPOTOP trial recruited term infants fulfilling the following inclusion criteria: prenatal signs compatible with hypoxia-ischemia, i.e. alterations of cardiac registry, abnormal fetal scalp, pH (10 min after birth, cord pH ≤ 7.0 and BE ≥ -16 mEq L^{-1}); moderate-severe status following a modified Sarnat scale. Determinations were performed by Gas Chromatography-Mass Spectrometry (GC-MS). The method was validated and applied to 194 samples from HYPOTOP patients for the determination of lactate, pyruvate, ketone bodies and several Krebs cycle metabolites at different sampling time points. Also, plasma from 19 healthy term newborns was analyzed.

RESULTS

Regarding the characteristics of the studied populations (i.e. control and HYPOTOP), no significant differences were found for gestational age, gender and birth weight. For all parameters used for the diagnosis of HIE in the delivery room (i.e. Apgar scores, cord pH, BE and lactate), highly significant differences were found. Concerning the GC-MS method, analytical figures of merit were assessed following stringent FDA requirements. The analysis of plasma samples from newborns with HIE revealed a decrease of lactate, pyruvate and β-hydroxybutyrate concentrations, whereas rising malate concentrations were observed (**Fig. 1**). In healthy control newborns significantly lower levels of pyruvate and lactate were found in comparison to age-matched newborns with HIE undergoing TH whereas acetoacetate and β-hydroxybutyrate levels were clearly increased. TPM administration did affect levels of the studied metabolites.

CONCLUSIONS

Access to a validated analytical method and a controlled cohort of newborns with HIE undergoing TH for the first time allowed the in depth-study of the evolution of key metabolites of metabolic junctions in this special study population. The results are compared to published data from studies involving both, animals and humans shedding light into the effect of TH on metabolite levels in newborns with HIE.

ABS 60

PHOSPHOLIPID SYNTHESIS RELATED BIO-MARKERS IN PLASMA FROM NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

J. Kuligowski[1], Á. Sánchez-Illana[1], J.D. Piñeiro-Ramos[1], A. Núñez-Ramiro[1], M. Cernada[1], A. Parra[1], E. Valverde[2], D. Blanco[3], M.T. Moral-Pumarega[4], F. Cabañas[5], H. Boix[6], A. Pavon[7], M. Chaffanel[8], I. Benavente-Fernández[9], I. Tofe[10], B. Loureiro[11], J.R. Fernández-Lorenzo[12], B. Fernández-Colomer[13], M. Vento[1,14]; the HYPOTOP Study Group

[1]*Neonatal Research Unit, Health Research Institute La Fe, Valencia, Spain*

[2]*Hospital Universitario La Paz, Madrid, Spain*

[3]*Hospital Universitario Gregorio Marañón, Madrid, Spain*

[4]*Hospital Universitario 12 de Octubre, Madrid, Spain*

[5]*Hospital Universitario Quirónsalud Madrid, Spain*

[6]*Hospital Universitario Vall D'Hebron, Barcelona, Spain*

[7]*Hospital Universitario Virgen del Rocío, Sevilla, Spain*

[8]*Hospital Materno Infantil Carlos Haya, Málaga, Spain*

[9]*Hospital Universitario Puerta del Mar, Cádiz, Spain*

[10]*Hospital Universitario Reina Sofía, Córdoba, Spain*

[11]*Hospital Universitario Cruces, Vizcaya, Spain*

[12]*Hospital Álvaro Cunqueiro, Vigo, Spain*

[13]*Hospital Central de Asturias, Oviedo, Spain*

[14]*Division of Neonatology, University & Polytechnic Hospital La Fe, Valencia, Spain*

INTRODUCTION

Diagnosis of hypoxic-ischemic encephalopathy (HIE) is based on clinical manifestations using Apgar score and sentinel events combined with lactate and blood gases analysis. The access to new biomarkers that could provide information about both, duration of asphyxia and severity of HIE, would be desirable. Metabolomics studies in animal models have shown the potential of choline, cytidine, uridine and betaine in plasma for tracing back the duration of asphyxia and hence, severity of HIE. This work presents the study of these markers in the HYPOTOP cohort involving newborns with HIE undergoing therapeutic hypothermia (TH).

METHODS

The HYPOTOP cohort includes term newborns with: (1) prenatal signs compatible with hypoxia-ischemia: alterations of cardiac registry, abnormal fetal scalp, pH (10 min after birth, cord pH ≤ 7.0

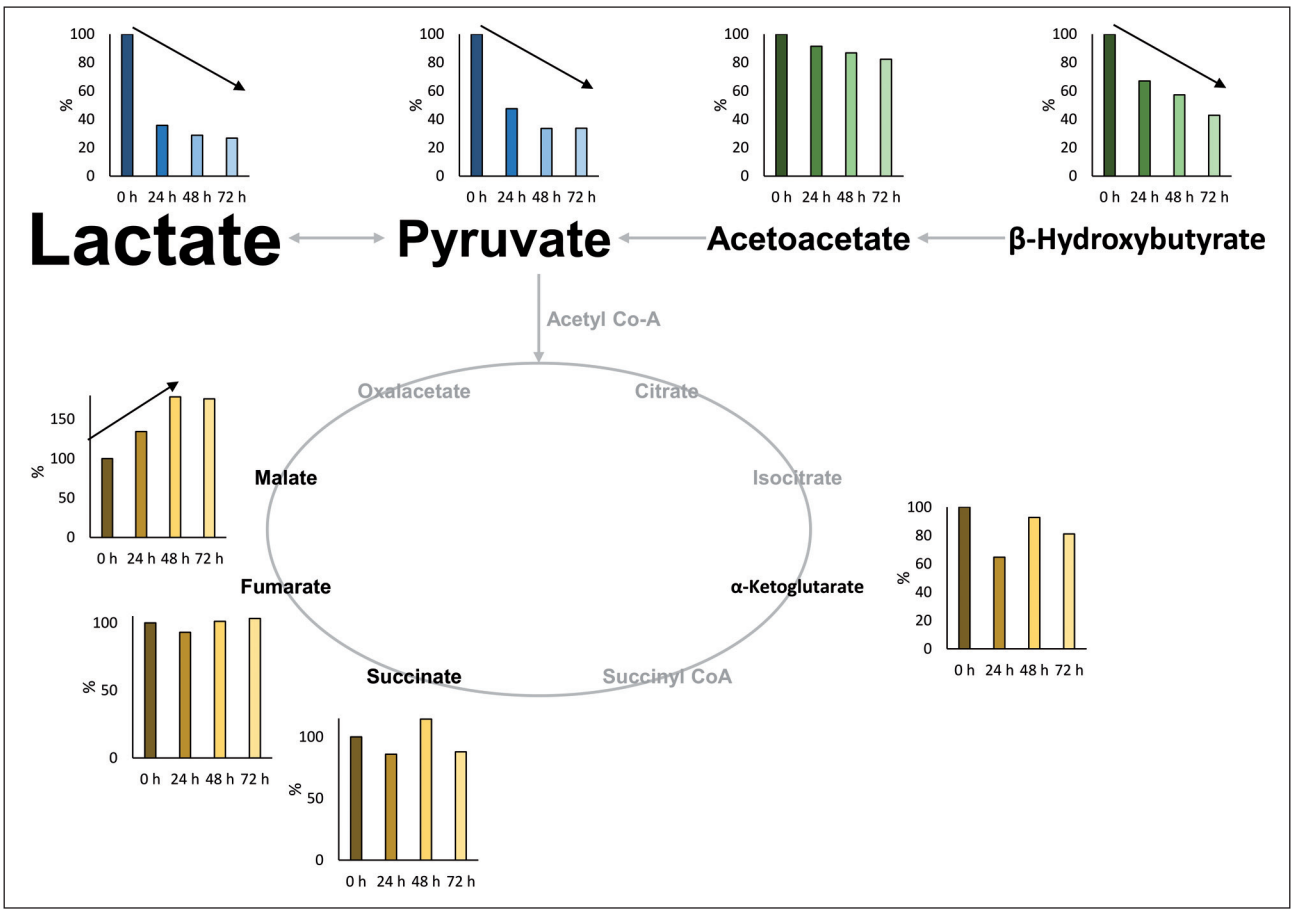

Figure 1 (ABS 59). Relative changes of metabolites as a function of age of newborns with HIE enrolled in the HYPOTOP trial. Median values as a relative measure to median values at t0; letter size proportional to concentration level; arrows indicate tendencies.

and BE ≥ -16 mEq L-1); (2) moderate-severe HIE according to Sarnat scale. Determinations were performed by Liquid Chromatography-tandem Mass Spectrometry (HPLC-MS2). The method was applied to 208 samples from HYPOTOP patients for the determination of choline, cytidine, uridine and betaine in cord plasma and 24, 48, and 72 h plasma after initiation of TH. Also, cord plasma from 21 healthy term newborns was analyzed.

RESULTS

Regarding the characteristics of the studied populations, between the HYPOTOP and control groups, no significant differences were found for gestational age, gender and birth weight. For all parameters used for the diagnosis of HIE in the delivery room (i.e. Apgar scores, cord pH, BE and lactate), highly significant differences were found. Determinations in cord plasma samples from newborns with HIE compared to the control group showed a significant increase for choline, betaine and cytidine and a decrease of uridine (**Fig. 1**). As shown in the figure, with regard to the evolution of the studied markers during TH, all studied biomarkers decreased with time.

CONCLUSIONS

For the first time, changes in choline, betaine, cytidine and uridine previously observed in an animal model of perinatal asphyxia were confirmed in a clinical cohort involving HIE patients. The results are a step forward in the clinical validation of new biomarkers of HIE in concordance with results obtained from a piglet model employing non-targeted metabolomics.

ABS 61

CEREBROSPINAL FLUID LACTATE IN NEWBORN AND PRETERM INFANTS. PILOT DATA

G. Uclés, D. Arjona, R. Borrego, R. Díaz, M.D. Sánchez-Redondo, A. Escobar

Paediatric Department, Hospital Virgen de la Salud, Toledo, Spain

INTRODUCTION

Cerebrospinal fluid (CSF) lactate is an important tool in diagnostic work of many disorders, but there

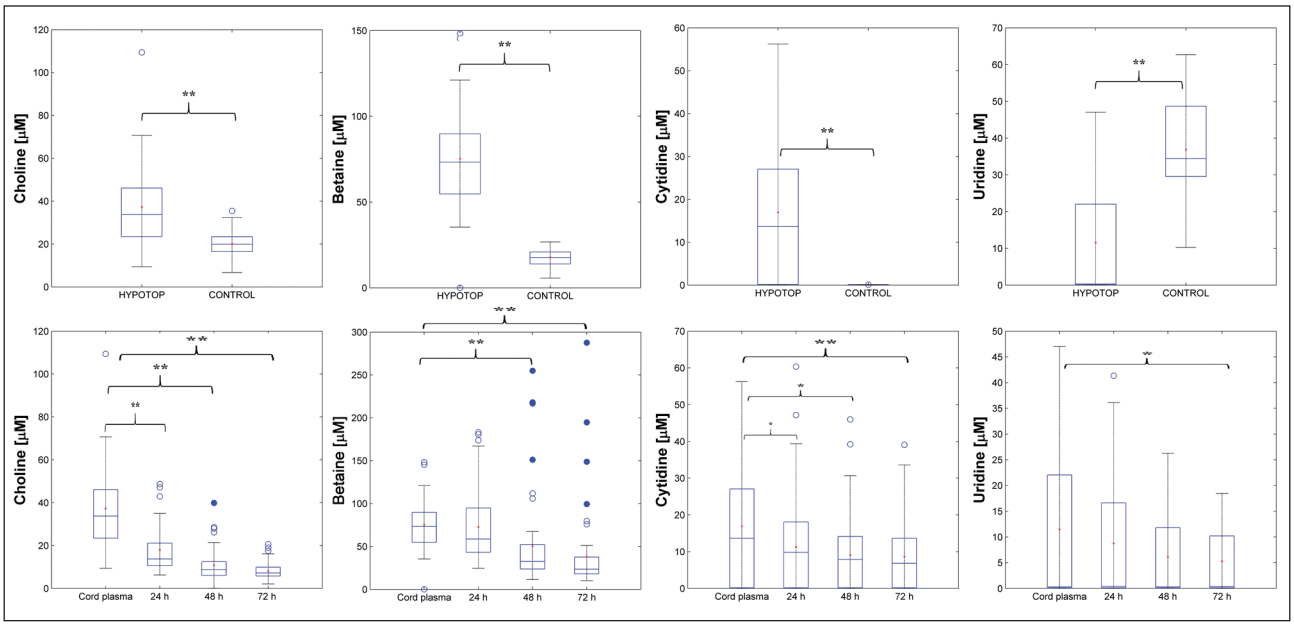

Figure 1 (ABS 60). Boxplots of metabolite concentrations in cord plasma samples from newborns included in the HYPOTOP trial vs. control group (top) and newborns included in the HYPOTOP trial at different times (bottom).
P-values calculated employing the Wilcoxon rank sum test for equal medians: * = $p < 0.05$; ** = $p < 0.01$.

is a lack of reference in term newborns and preterm infants. The aim of this study is to define CSF lactate ranges in this population.

METHODS

Retrospective observational study in a tertiary care hospital. We analysed CSF lactate, glucose, proteins and total cellularity in preterm infants and newborns under 28 days of age. Forty-six patients were included with forty-eight samples.

RESULTS

Of the 22 male and 26 female included, 28 were preterm infants, 11 of them less than 1,000 g. Mean gestational age was 33 weeks (range 23-41), mean birth weight was 2,330 g (range 510-3,800 g). Mean lactate was 14.6 mg/dl (1.57 mmol/l), SD ± 6.2 mg/dl (0.68 mmol), mean glucose 51 ± 18 and mean protein was 139 mg/dl, but with a great variance due to xantocromic fluid. There were no differences between preterm infants and term newborns.

CONCLUSIONS

CSF lactate in term newborns and preterm infants appears to vary slightly from values of older paediatric patients, but reference interval is needed in order to use it as diagnostic tool.

ABS 62

DIFFERENCES BETWEEN INTRAUTERINE AND EXTRAUTERINE GROWTH OF THE CEREBELLUM

A.I. Toma[1,2], I. Cuzino[1], A. Cozinov[1], R.G. Olteanu[1]

[1]*Neonatology, Life Memorial Hospital, Bucharest, Romania*

[2]*University Titu Maiorescu, Faculty of Medicine, Bucharest, Romania*

INTRODUCTION

The extra-uterine development of the brain in premature neonates has been a subject of research, focused mainly on the cerebral hemispheres. The aim of this study was to establish if the dimensions of the cerebellum, measured by ultrasound, are different between the neonates at term and the premature infants at 40 weeks corrected age.

METHODS

The measurements were performed through the mastoid fontanel, in transverse sections at 40 weeks corrected age, in a cohort of 40 premature (32-35 weeks) and 100 term neonates. We measured the transverse cerebellar diameter, the transverse diameter of the vermis and the area of the vermis. The premature infants group was stratified according to several risk factors: gestational age, gender, need for mechanical ventilation, duration of mechanical ventilation, presence of apneic spells. Neonates with congenital cerebral malformations were excluded from the study.

RESULTS

The transverse cerebellar diameter was significantly lower in preterm neonates at term (42 mm ± 5.6 mm) compared to term neonates (49 mm ± 7.5 mm)

($p < 0.01$). The transverse diameter of the vermis was also found to be significantly lower in preterm neonates at 40 weeks corrected age compared to term neonates (10.8 mm ± 2.6 mm versus 11.51 mm ± 1.32 mm) ($p < 0.001$), as well as the area of the vermis (1.02 mm^2 versus 2.30 mm^2). The risk factors found to be associated with decreased cerebellar diameters at term corrected age were low gestational age (< 33 weeks) and male gender. No association was found between decreased cerebellar diameters and need or duration of mechanical ventilation or presence of apneic spells.

CONCLUSIONS

The diameters of the cerebellum and vermis and the area of the vermis seem to be significantly smaller in the preterm neonates at 40 weeks corrected age than in term newborns, the main risk factors for this being gestational age lower than 33 weeks and male gender.

ABS 63

CAN DIFFERENCES IN EARLY FUNCTIONAL CONNECTIVITY IN HEALTHY NEWBORNS EXPOSED TO OLFACTORY STIMULATION HELP US UNDERSTAND CRYING BEHAVIOUR AT 6 WEEKS OF LIFE?

L. Freitas[1,2,3], A. Adam-Darque[1], F. Grouiller[2], J. Sauser[4], F. Lazeyras[2], P. Pollien[4], C.L. Garcia-Rodenas[4], G. Bergonzelli Degonda[4], D. Van De Ville[2,3], P. Hüppi[1], R. Ha-Vinh Leuchter[1]

[1]Division of Development and Growth, Department of Pediatrics, University of Geneva, Geneva, Switzerland

[2]Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland

[3]Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne,Switzerland

[4]Nestlé Research Center, Vers-chez-les-Blanc, Lausanne, Switzerland

INTRODUCTION

Crying in infancy is part of normal neurodevelopment, typically following a curve that peaks at 6 weeks of age. Excessive crying in otherwise healthy infants – also called infant colic (IC) – could indicate a difference in central nervous system functioning. Previous results from

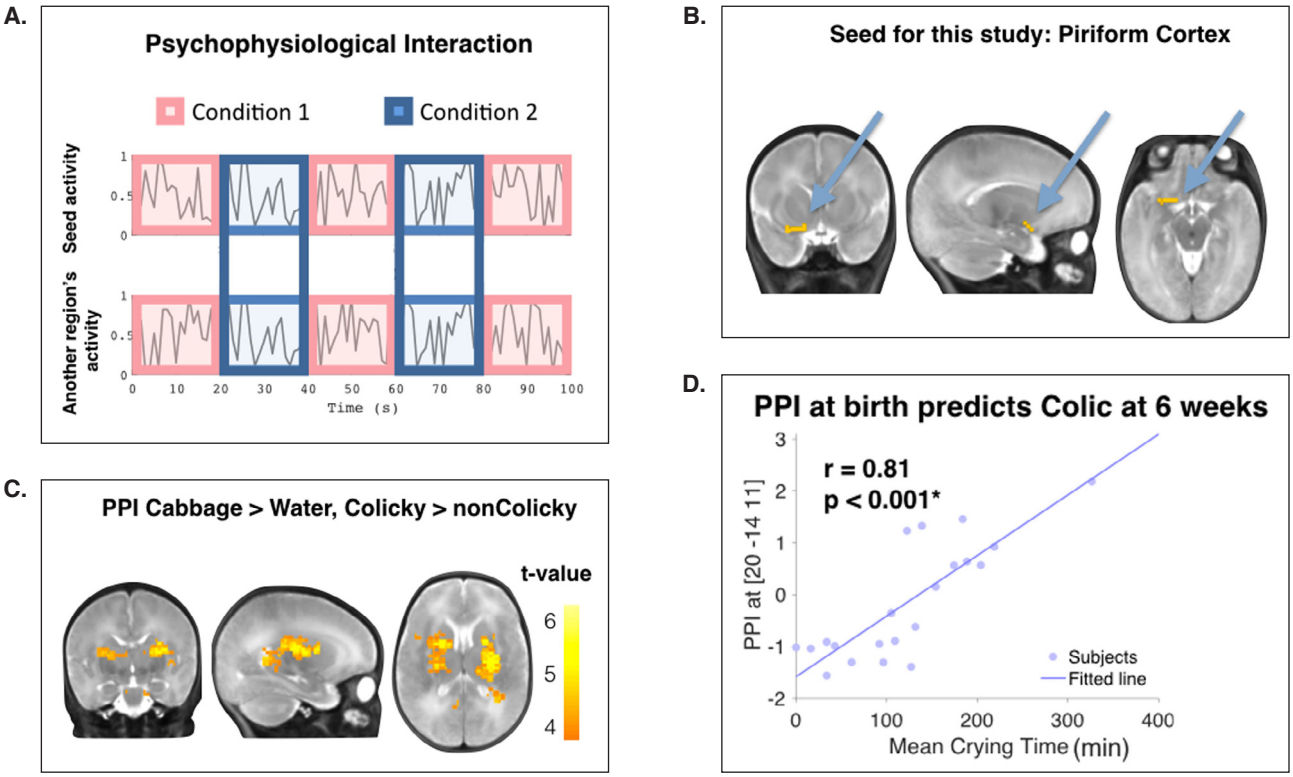

Figure 1 (ABS 63). The Psychophysiological Interaction (PPI) between the left Piriform Cortex and the bilateral Caudate Nucleus (CN) during olfactory stimulation predicts colic at 6 weeks. **A.** How PPI works: it investigates regions whose respective activities become more increasingly similar during one condition as compared to another. **B.** We used the Piriform Cortex (PC, yellow) as a seed for this study. **C.** The bilateral CN's activity becomes more related to that of the PC during Cabbage exposure in babies who cry more at 6 weeks of age. **D.** PPI at the peak voxel correlates significantly with mean crying at 6 weeks.

our group showed that colicky babies present higher cerebral responses to non-painful sensory stimuli shortly after birth. Here, we aimed to further characterise the cerebral response to olfactory stimuli present in healthy newborns who cry excessively at six weeks of age.

METHODS

Functional magnetic resonance imaging (fMRI, 3T) data were acquired from 36 babies (mGA: 39.7 w, SD: 0.97) in the first week of life. 3 odourants: banana-; cabbage-; and eucalyptus-like, were presented in a pseudo-randomised order in 20s blocks. Each odourant was repeated 5 times and alternated with a neutral odour (water). A T2-weighted image was acquired for anatomical reference. We performed a Psychophysiological Interaction (PPI) analysis of 21 infants using the piriform cortex (PC) as a seed. Babies were grouped according to a validated crying diary completed by the parents on weeks 5-6 of age: those who cried > 3 h a day, for > 3 days within 7 consecutive days were considered Colicky (Rome III criteria); and Non Colicky otherwise.

RESULTS

For the Cabbage>Water contrast, we did not find regions that showed a PPI with the seed activity in either of the groups. However, a between-group comparison for the same contrast, revealed a significantly stronger relationship between the piriform cortex and the bilateral caudate nucleus (CN) in the Colicky group (n = 11) than in the NonColicky group (n = 10; cluster 1 centered at [20 -14 11], p = 0.001, FWE corrected; cluster 2 centered at [-19 -16 17], p < 0.001, FWE corrected). Moreover, the PPI strength shortly after birth correlates strongly with the mean crying time at 6 weeks of age (r = 0.81, p < 0.001), suggesting its predictive value for crying behaviour (**Fig. 1**).

CONCLUSIONS

Our analysis reveals different cerebral functioning, already present shortly after birth, in babies who later develop IC. We found a significantly stronger PPI effect between exposure to olfactory stimuli and PC activity on the CN response in this group. This effect was highly predictive of crying behaviour 6 weeks later. This suggests that colicky infants may be more sensitive to non-painful sensory stimuli and thus more likely to cry.

DECLARATION OF INTEREST

Three of the co-authors (P. Pollien, C.L. Garcia-Rodenas and G. Bergonzelli Degonda) are Nestec Ltd. employees, and the study was partly financed by a Nestec Ltd grant. The analysis was performed by an independent laboratory and all other authors declare no conflict of interest.

ABS 64

LESS INVASIVE SURFACTANT ADMINISTRATION (LISA) NOT ONLY IMPROVES MORTALITY AND MORBIDITY BUT ALSO NEURODEVELOPMENTAL OUTCOME OF PRETERM INFANTS

K. Klebermass-Schrehof, A. Grill, M. Hayde, N. Haiden, A. Flunt, R. Fuiko, S. Brandstetter, A. Berger

Department of Pediatrics, Medical University of Vienna, Vienna, Austria

INTRODUCTION

Within current meta-analysis LISA (less invasive surfactant administration) was identified as most effective non-invasive therapy for respiratory distress syndrome, with the lowest association to mortality and chronic lung disease [1, 2]. Hence short-term benefit of this method is already established, but it is still unknown, if this method can also improve long-term outcome of preterm infants. The aim of our study was to analyse neurodevelopmental outcome at two years of age of our preterm cohort treated by LISA at our hospital, compared to outcome data of historical controls not treated according to LISA protocol.

METHODS

Every preterm infant within 23^{+0}-27^{+6} weeks of gestation, born within 01/2009-12/2014 (n = 546) was initially treated by LISA protocol, all infants of the same gestational age born within 01/2003-12/2008 (n = 402) served as a control group. Neurodevelopmental outcome at the corrected age of two years was assessed by Bayley Scales of Infant Development.

RESULTS

Within the LISA-cohort 2009-2014 80.5% of all preterm infants born < 28 weeks of gestation survived, compared to 46.3% of infants within the historical control group 2003-2008 (p = 70) at two years of age, compared to 31.4% of infants within the historical control group (p ≥ 0.001). 19.7% of infants showed moderate or severe impairment (MDI/PDI > 70) within the LISA-cohort, compared to 14.7% of historical controls (p = 0.03) (**Fig. 1**). 46.0% within the LISA-cohort survived without morbidity (= IVH > II, cPVL, NEC, ROP > II, CLD) compared to 22.7% within historical control (p = 0.012).

CONCLUSIONS

Infants treated by LISA-protocol show – at our unit – not only improved short-term outcome, but also significantly improved neurodevelopmental outcome.

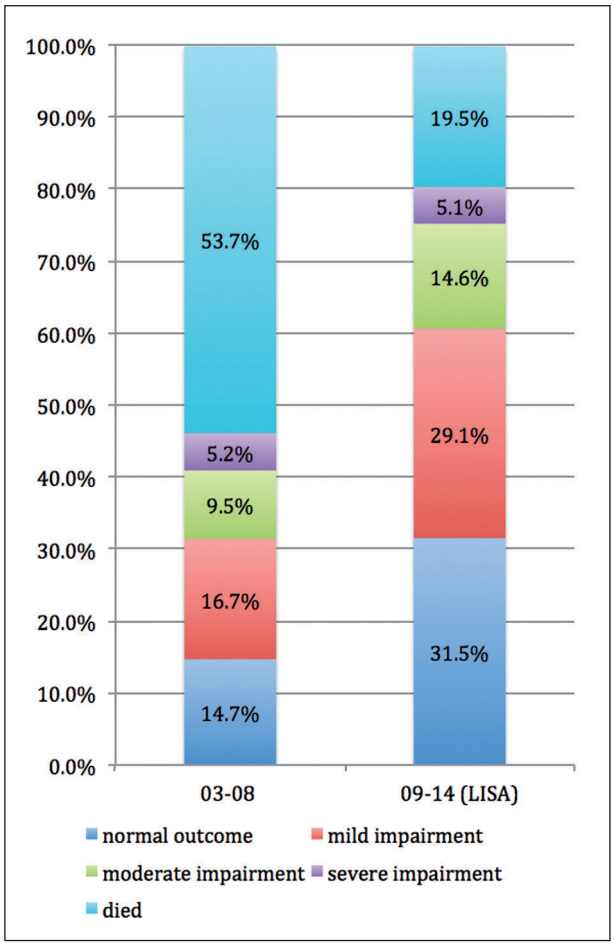

Figure 1 (ABS 64). Outcome of LISA-cohort (2009-2014) vs. historical controls (2003-2008).

Although survival rates were significantly improved, the amount of infants with severely impaired outcome did not increase. Limitation of our study is that we had to compare our data to a historical control group, as it is known, that outcome data continuously improves over time. As big advantage of our study we see that data from a single center could be used and a high number of patients could be analysed.

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ABS 65

REDUCED PREVALENCE OF SEVERE INTRAVENTRICULAR HEMORRHAGE IN VERY PRETERM INFANTS DELIVERED AFTER MATERNAL PREECLAMPSIA

E. Morsing[1], K. Maršál[2], D. Ley[1]

[1]*Department of Pediatrics, Clinical Sciences, Lund University, Lund, Sweden*
[2]*Department of Obstetrics and Gynecology, Clinical Sciences, Lund University, Lund, Sweden*

INTRODUCTION

Very preterm delivery (< 30 gestational weeks) occurring due to severe preeclampsia has been reported to be associated with adverse perinatal and neonatal outcome. However, it is still unclear whether fetal exposure to preeclampsia *per se* during early pregnancy modifies the prevalence of severe neonatal morbidities associated with very preterm birth. The aim of this study was to evaluate neonatal morbidity in fetuses exposed to second trimester maternal preeclampsia (PE) compared to very preterm (PT) fetuses without maternal PE, delivered for other reasons.

METHODS

Between 1998 and 2014 at Lund University Hospital, Sweden, 197 live-born very preterm (PT) infants were delivered at < 30 GW due to maternal PE and admitted to the NICU. They had a mean (SD) birth weight (BW) of 816 (230) g and a mean gestational age (GA) of 26.6 (1.6) weeks. During the corresponding time period, 908 very PT live-born infants (controls) were delivered for other reasons and admitted for neonatal care. The controls had a mean (SD) BW of 929 (287) g and a mean GA of 26.1 (1.7) weeks. Data on survival to discharge and neonatal morbidities; respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), septicemia, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) grade 3-4 and treatment for retinopathy of prematurity was retrieved from hospital charts.

RESULTS

Prevalence of cesarean section (CS) and BW SGA was higher in the PE group (98% and 57%, respectively) compared to the control group (66% and 18%), both $p < 0.001$. Rate of RDS was higher in the PE group (89%) compared to the control group (81%), $p = 0.003$), whereas rates of NEC, septicemia and BPD did not differ between the groups. Prevalence of severe IVH and treatment for ROP was significantly lower in the PE group (2% and 2%) compared to the control group (11% and 7%), $p < 0.001$ and $p = 0.022$ respectively. Survival to discharge was significantly higher in the PE

Group (91%) compared to the control group (85%), p = 0.042. After adjustment for gestational age, asphyxia, CS and antenatal steroid treatment, PE as a cause of very PT delivery remained associated with a reduced prevalence of severe IVH, p < 0.001.

CONCLUSIONS

Fetal exposure to early-onset PE appears to have a profoundly protective effect on development of severe IVH following very PT birth. Knowledge of the underlying mechanisms may supply a basis for treatment strategies leading to prevention of IVH in the very PT infant.

ABS 66

COGNITIVE STABILITY IN CHILDREN WITH CONGENITAL HEART DISEASE

N. Naef[1], C. Schaefer[1], V. Rousson[2], R. Liamlahi[1], S. Polentarutti[1], I. Beck[1], V. Bernet[3,4], H. Dave[5], W. Knirsch[4,6], B. Latal[1,4]

[1]*Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland*

[2]*Division of Biostatistics, Institute of Social and Preventive Medicine, University Hospital of Lausanne, Lausanne, Switzerland*

[3]*Neonatology and Pediatric Intensive Care Unit, University Children's Hospital Zurich, Zurich, Switzerland*

[4]*Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland*

[5]*Congenital Cardiac Surgery, Pediatric Heart Center, University Children's Hospital Zurich, Zurich, Switzerland*

[6]*Pediatric Cardiology, Pediatric Heart Center, University Children's Hospital Zurich, Zurich, Switzerland*

INTRODUCTION

Neurodevelopmental impairments remain a major concern in the growing population of children with severe congenital heart disease (CHD) and there is little data on cognitive stability in these children. The aim of our study was to describe cognitive trajectories in children with CHD and compare them to a population of healthy children.

METHODS

A total of 148 prospectively included children, who underwent cardiovascular surgery using cardiopulmonary bypass at the University Children's Hospital Zurich from May 2004 to July 2009 were prospectively assessed at the age of 1, 4 and 6 years. Population stability of cognitive function was assessed, by comparing average measurements of cognitive and motor functions at 1, 4 and 6 years. Individual stability was assessed using Spearman correlation. A subsample of healthy children from the Zurich generational study was taken as comparison, they were assessed at the age of 1, 4 and 7 years.

RESULTS

Overall cognitive function significantly improved over time (p = 0.01). Individual stability between 1 and 6 years in cognition was comparable to the stability in healthy children between 1 and 7 years (CHD cognition: rho = 0.20, p = 0.016; healthy children cognition: rho = 0.28, p = 0.001) (**Fig. 1**). Socioeconomic status correlated with a positive individual IQ trajectory (rho = 0.34, p < 0.001) with a stronger influence at older compared to younger age (interaction with age: p < 0.001). The correlation between motor and cognitive functions was higher in CHD children compared to healthy children at the age of 1 but similar at the ages of 6, resp. 7 years (1 year: CHD: rho = 0.47, p < 0.001, healthy children: rho = 0.24, p = 0.002; 6/7 years: CHD: rho = 0.30, p < 0.001, healthy children: rho = 0.35, p < 0.001).

CONCLUSIONS

Children with CHD after bypass surgery show a catch-up in cognitive function between 1 and 6 years with socioeconomic status becoming a stronger determinant of cognition with older age. Cognitive stability in CHD children is similar to that of healthy children, however, overall not very strong. Repeated follow-up of these children is therefore crucial, particular also extending until adolescents to determine long-term outcome and predictors of outcome.

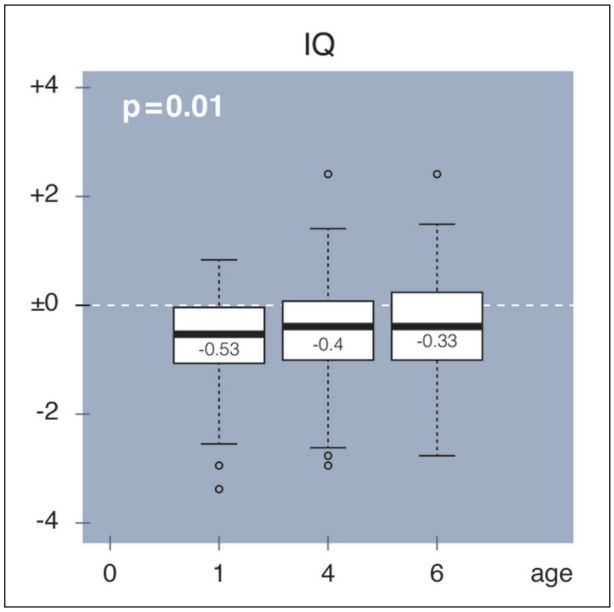


Figure 1 (ABS 66). IQ trajectory between 1 and 6 years.

ABS 67

PERIPHERAL T CELL DEPLETION BY FINGOLIMOD IS ASSOCIATED WITH EXACERBATED HYPOXIC-ISCHEMIC BRAIN INJURY IN NEONATAL MICE

I. Bendix, M. Crasmöller, C. Köster, M. Serdar, U. Felderhoff-Müser, J. Herz

Department of Pediatrics I/Neonatology, Experimental Perinatal Neuroscience, University Hospital Essen, University Duisburg-Essen, Essen, Germany

INTRODUCTION

In spite of the increasing knowledge about the pathophysiological role of inflammation in adult and neonatal ischemic brain injury, therapeutic approaches are still limited. Common to both developmental stages is a sustained ischemia-induced inflammatory response, which has largely been linked to lesion growth and neurological impairment. The immunomodulator Fingolimod (FTY720), a sphingosine-1-phosphate receptor modulator, has been shown to reduce ischemic neurodegeneration in adult stroke through its lymphopenic mode of action. Therefore, we analysed the therapeutic potential and immunomodulatory function of FTY720 in a term-equivalent rodent model of hypoxic-ischemic (HI) brain injury.

METHODS

HI was induced in postnatal day 9 C57BL/6 mice through occlusion of the right common carotid artery followed by one hour hypoxia (10% oxygen) after one hour recovery with their dams. Animals received intraperitoneal injections of 1 mg/kg FTY720 (n = 26) or phosphate buffered saline (control, n = 27) immediately after hypoxia. Brain tissue injury and cerebral immune cell infiltration were assessed at 7 days post HI using histology, western blot and flow cytometry, respectively. An additional set of naive mice was used to determine peripheral circulating lymphocyte counts via flow cytometry at 1, 3 and 7 days post FTY720 injection (n = 7-10).

RESULTS

FTY720 exacerbated HI-induced brain injury, as demonstrated by significantly increased neuropathological injury scores and significantly reduced expression of the neuronal/axonal marker microtubule associated protein-1. FTY720-induced sustained peripheral lymphopenia, particularly affecting T cells, resulted in significantly reduced cerebral infiltration of CD4 and CD8 T cells which was accompanied by an increased infiltration of innate immune cells (e.g. natural killer cells).

CONCLUSIONS

These results suggest that in contrast to adult stroke T cells in general or specific T cell subtypes have a protective function after HI in neonates. Therefore, differences between adult and neonatal neuroinflammatory responses may have a substantial impact on neurological outcome and therapeutic concepts cannot be translated unequivocally.

ABS 68

DIFFERENTIATING THE PRETERM PHENOTYPE: DISTINCT PROFILES OF DEVELOPMENT AFTER LATE AND MODERATELY PRETERM BIRTH

S. Johnson[1], G. Waheed[1], B.N. Manktelow[1], D. Field[1], N. Marlow[2], E.S. Draper[1], E.M. Boyle[1]

[1]*Department of Health Sciences, University of Leicester, Leicester, UK*

[2]*Institute for Women's Health, University College London, London, UK*

INTRODUCTION

Recent studies show that babies born late and moderately preterm (LMPT; 32-36 weeks' gestation) are at increased risk for adverse neurodevelopmental outcomes compared their term-born peers. However, it is not known whether (1) the neurodevelopmental problems observed after LMPT represent an extension of the very preterm phenotype, or whether they more closely resemble a profile of problems observed in the term-born population; and (2) whether preterm birth has an adverse impact on development among the total LMPT population to a greater or lesser extent, or whether it affects only a sub-group of babies at high risk. This study aimed to address these issues.

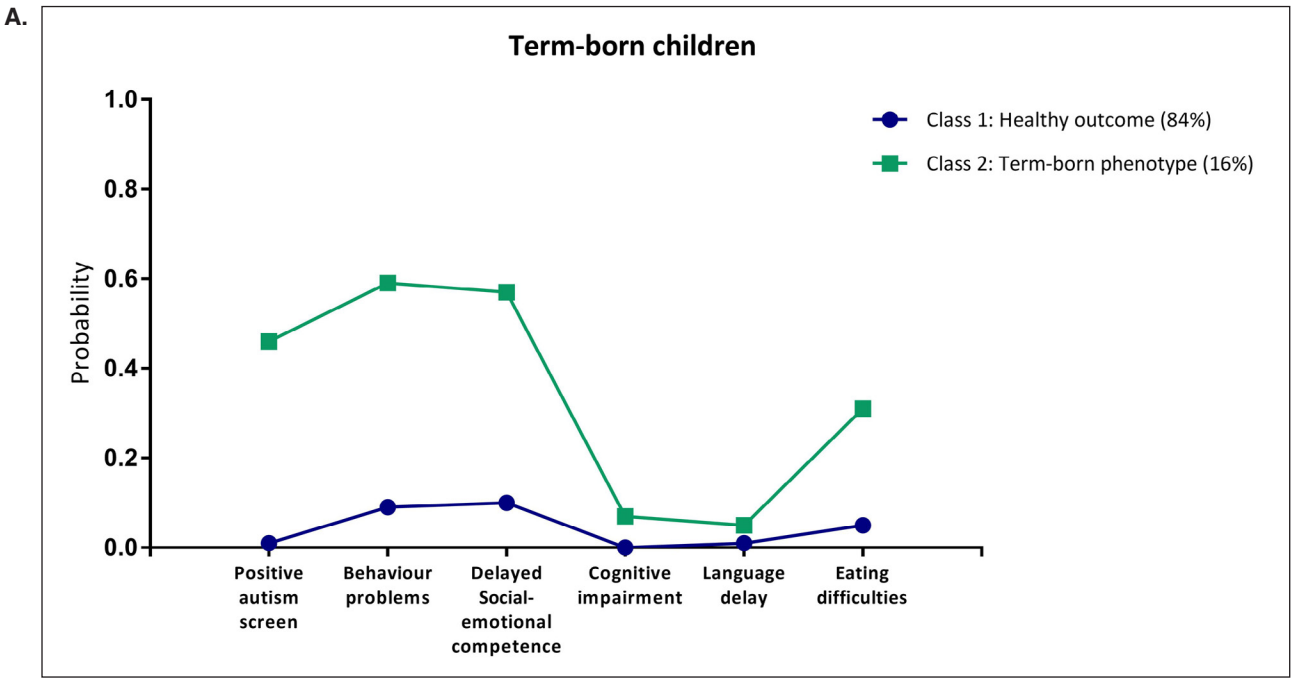
METHODS

A geographical population-based cohort of 1,139 LMPT (32-36 weeks' gestation) and 1,255 term-born (37-42 weeks' gestation) babies were recruited at birth. Neurodevelopmental outcomes were assessed at 24 months corrected age for 638 (57%) LMPT and 765 (62%) term-born children using parent questionnaires. The Parent Report of Children's Abilities-Revised was used to identify cognitive impairment and language delay, Brief Infant and Toddler Social-Emotional Assessment to identify behaviour problems and delayed social-emotional competence, Modified Checklist for

Autism in Toddlers to identify autistic features, and a validated scale to identify eating difficulties.

RESULTS

Latent Class Analysis was used to identify profiles of development. This revealed two classes among the term group: healthy outcome (84%) and term-born phenotype (16%) (**Fig. 1A**). The term-born phenotype comprised risk for behaviour problems and delayed social-emotional competence. In contrast, three classes were identified in the LMPT group: healthy outcome (67%), term-born phenotype (26%) and an additional preterm phenotype (7%) (**Fig. 1B**). The preterm phenotype comprised cognitive impairment, language delay, delayed social-emotional competence and autism spectrum symptoms, representing an extension of the very preterm phenotype. Non-white ethnicity, socio-economic risk and not receiving breast milk



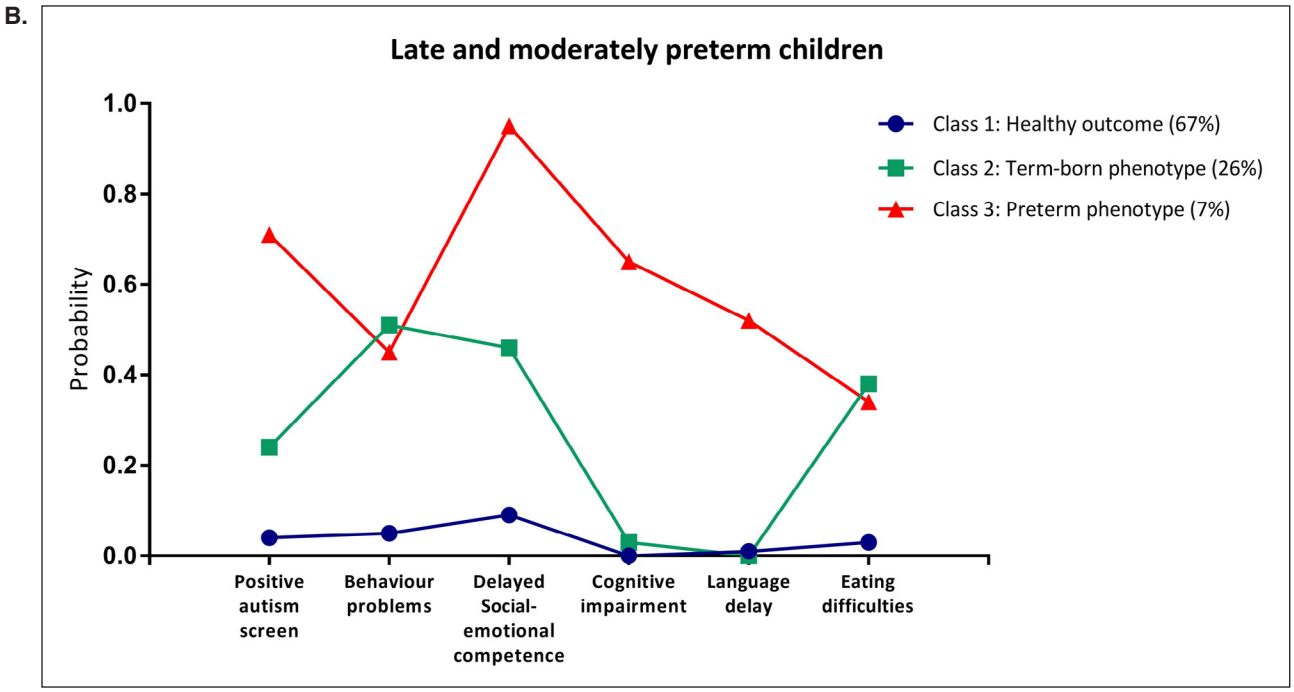


Figure 1 (ABS 68). Profiles of neurodevelopmental outcomes among term (37^{+0} to 42^{+6} week's gestation, **A**), and late and moderately preterm (LMPT, 32^{+0} to 36^{+6} week's gestation, **B**) born children at 2 years corrected age using item response probabilities for latent classes.

at discharge from hospital were risk factors for the term-born phenotype in both groups. Male sex, lower gestational age and preeclampsia were additional risk factors for the preterm phenotype.

CONCLUSIONS

Only a small proportion of LMPT born children have neurodevelopmental problems consistent with the very preterm phenotype, which may have arisen through a 'preterm pathway' similar to more immature children. A larger proportion has a profile of problems similar to children born at term, which may have a different aetiology. This has implications for the targeting of follow-up and intervention services for children born LMPT.

ABS 69

NEONATAL NEUROIMAGING IN SYMPTOMATIC CONGENITAL CMV (CCMV) AND ITS CORRELATION WITH OUTCOME: EMPHASIS ON WHITE MATTER DISEASE

A. Alarcon[1,2], A. Garcia-Alix[2], M. Martinez-Biarge[3], I. van Straaten[4], F. Cabañas[5], J. Quero[5], L. de Vries[6]

[1]*Neonatal Unit, Oxford University Hospitals NHS Foundation Trust, Oxford, UK*

[2]*Department of Neonatology, Sant Joan de Déu University Hospital, Barcelona, Spain*

[3]*Department of Pediatrics, Imperial College, Hammersmith Hospital, London, UK*

[4]*Department of Neonatology, Isala Klinieken, Zwolle, the Netherlands*

[5]*Department of Neonatology, La Paz University Hospital, Madrid, Spain*

[6]*Department of Neonatology, University Medical Center Utrecht, Utrecht, the Netherlands*

INTRODUCTION

Studies on the relationship between cranial ultrasound (cUS) and brain MRI findings and neurodevelopmental outcomes in cCMV include only small numbers of symptomatic infants. While destructive and disruptive lesions associated with cCMV are known to correlate with a poor prognosis, few studies exist aimed at establishing the prognostic significance of milder neuroimaging abnormalities, namely isolated white matter injury (WMI).

Aims: 1) To examine the predictive ability of modern-day neonatal neuroimaging categorization in a large cohort of infants with symptomatic cCMV. 2) To establish the correlation between isolated WMI and outcome.

METHODS

Infants born between 1999-2016 with symptomatic cCMV, referred to 3 European tertiary NICUs and investigated by neonatal cUS and MRI were included. Neuroimaging was classified according to two scales (**Tab. 1**). Extent and location of isolated WMI were described. Moderate/severe disability was defined at ≥ 1y as: cerebral palsy with GMFCS level ≥ II; Griffiths or Bayley scales scores ≤ 85 or global IQ ≤ 70; epilepsy; hearing loss not compensated by aids; visual deficit or behavioral disorders.

RESULTS

36 children were studied. The two neuroimaging scales correlated well with each other ($r_s = 0.967$, $p < 0.001$). Outcome data were available for 31/36 children (86%), 6 of whom died. Mean age at follow-up in survivors was 4.5 ± 2.9 y. Both neuroimaging scales showed a significant association with death or moderate/severe disability ($p < 0.01$). Areas under the ROC curves for the Alarcon and the Cannie scales were 0.955 ± 0.039 and 0.944 ± 0.041, respectively. 11 patients presented WMI

Table 1 (ABS 69). Neuroimaging scales.

Alarcon (2016)		Cannie (2016)	
Score	**Findings**	**Score**	**Findings**
0	None of the following	1	Normal
1	Single punctate periventricular calcification, lenticulostriate vasculopathy, caudothalamic germinolysis, ventriculomegaly (excluding severe) and/or focal/ multifocal white matter signal abnormality on MRI	2	Isolated frontal or parieto-occipital periventricular T2-weighted signal hyperintensity
2	Multiple discrete periventricular calcifications, paraventricular germinolytic cysts, severe ventriculomegaly, diffuse white matter signal abnormality and/or temporal lobe involvement	3	Isolated temporal periventricular T2-weighted signal hyperintensity
		4	Cysts and/or septa in the temporal and/ or occipital lobe
3	Extensive calcifications, brain atrophy, abnormal gyration, cortical malformation, dysgenesis of the corpus callosum and/or cerebellar hypoplasia	5	Migration disorders, cerebellar hypoplasia, microcephaly

as the primary finding (4 diffuse, 4 involving the temporal lobes). Outcome was poor in 3/8 with follow-up ≥ 1 y. An association was found between diffuse WMI and poor outcome (p = 0.018), but not between temporal lobe involvement and outcome.

CONCLUSIONS

Neuroimaging categorization predicts outcome in neonates with symptomatic cCMV. In infants with isolated WMI, its extent is an important predictor of the risk of life-long disabilities.

ABS 70

INTRANASALLY APPLIED MESENCHYMAL STEM CELLS MIGRATE TO INJURED BRAIN REGIONS OF NEWBORN NON-HUMAN PRIMATES

N. Wagenaar[1], F. van Bel[1], M. Benders[1], C. Blanco[2], D. McCurmin[2], S. Mustafa[2], F. Groenendaal[1], L. de Vries[1], C. Heijnen[3], C. Nijboer[4]

[1]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands

[2]Department of Pediatrics, University of Texas Health Science Center, San Antonio, TX, USA

[3]Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4]Laboratory of NeuroImmunology and Developmental Origins of Disease, University Medical Centre Utrecht, Utrecht, the Netherlands

INTRODUCTION

Experimental studies using neonatal rodents provide evidence that intranasally applied mesenchymal stem cells (MSCs) reduce brain lesion size and improve functional outcome after hypoxic-ischemic (HI) brain injury. We have shown that intranasally applied MSCs migrate rapidly and specifically from the nasal cavity towards brain lesions after HI. Whether the intranasal route can be effective for MSC application in human neonates with brain injury is still unknown, as human olfactorial anatomy is different from rodents, so migration routes may differ between rodents and humans. To translate intranasal MSC therapy to clinical application, we investigated whether human MSCs are able to migrate to cerebral lesions when applied via the nose in a non-human primate model of neonatal ischemic brain injury.

METHODS

We used a bilateral carotid artery occlusion model of HI brain damage in two newborn baboons (birth weight 940-1,040 grams) at postnatal day 5-7, as described before [1-3]. Intubated animals were kept in the intensive animal care unit with cardiovascular/aEEG monitoring under the care of an experienced neonatologist. At 24 hours after the insult, the baboons were treated intranasally with 30 x 10^6 human umbilical cord-derived MSCs. Just prior to application, MSCs were labeled with PKH-26 or PKH-67 according to manufacturer's protocol (Sigma-Aldrich). Eighteen hours after intranasal MSC application, animals were sacrificed and their brains removed, dissected and frozen. Coronal sections of 8 μm were cut and counterstained with DAPI. Sections were analyzed for presence of the PKH signal.

RESULTS

At 18 hours after intranasal administration, PKH signal, indicative of MSCs, was detected in the bulbi, forebrain and relatively caudal in the hippocampal area in both animals, indicating a rapid and effective migration of MSCs into the newborn baboon brain.

CONCLUSIONS

This study provides evidence that intranasally administered MSCs migrate rapidly to injured brain regions of newborn primates, in accordance with previous rodent studies. These data warrant the near-future use of non-invasive intranasal MSC administration in treatment of neonatal brain injury in clinical trials.

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DECLARATION OF INTEREST

Umbilical Cord Mesenchymal Stem Cells for this study were kindly provided by Chiesi®. This study was funded by the ZonMW TAS Grant. Facility Support for Experiments was provided by the San Antonio Health System Research Fund.

ABS 71

EARLY CRANIAL ULTRASOUND AND MRI AT TERM IN VERY PRETERM INFANTS: DIAGNOSIS OF BRAIN INJURY VERSUS NEURODEVELOPMENTAL OUTCOME AT 12 AND 24 MONTHS CORRECTED GESTATIONAL AGE

K. Chatzidimitriou[1], A. Chebsey[1], D. Odd[1,3], M. El Brookle[1], M. Likeman[2], A. Heep[1,3]

[1]*Neonatal Intensive Care Unit, Southmead Hospital, Bristol, UK*

[2]*Imaging Department, Southmead Hospital, Bristol, UK*

[3]*Neonatal Neurology Group, School of Clinical Sciences, University of Bristol, Bristol, UK*

INTRODUCTION

Brain injury is frequently seen in preterm infants and is linked with suboptimal neurodevelopment. Cranial ultrasound (CUS) identifies reliably IVH, ventriculomegaly (VM) and parenchymal injury. MRI at term is increasingly performed to study subtle white matter injury (WMI) or cerebellar haemorrhage (CH).

Objective: To describe brain injuries in preterm infants born at less than 28 weeks of gestational age (GA) by CUS at day 7 and MRI at term, following a standard protocol, and to compare them with neurodevelopmental (ND) outcome (Bayley III) at 12 and 24 month of life.

Design: Retrospective observational cohort study in a single Level III neonatal intensive care unit.

METHODS

All infants admitted at less than 28 completed weeks of gestation weeks at a single tertiary neonatal intensive care unit between 2013-2014 were eligible for the study (n = 128). 95 Infants were excluded (neonatal death n = 13; lost to follow up or missing MRI data n = 82) leaving 33 infants for the main analysis. Mean GA was 26 (23.4-28, SD 1.32). Mean birth weight (BW) 778.8 g (453-1,216 g, SD 233.5), 16 (48.5%) were male. The study group did not differ in GA, BW, and gender from the total cohort. CUS at day 7 and 3 TESLA MRI at term were performed according to clinical protocol. CUS IVH classification was based on that of Papile. WMI in MRI was classified based on the extent of injury in T1/T2 sequences and the presence of WM volume loss, cysts, thinning of the corpus callosum and VM. Bayley was classified using composite scores (cut off value 85) and months of ND delay.

RESULTS

On day 7 CUS 13 infants (39.4%) presented with IVH, 7 (21.2%) were stage 1-2, whereas 6 (18.2%) stage 3-4. Parenchymal injury was found in n = 5 (15.2%) and VM in n = 8 (24.2%).

MRI at term showed WMI in 13 infants (39.4%; 7 moderate/severe: 21%), GMI (grey matter injury) in 6 (18.2%) and VM in 16 (48.4%). IVH was present in 14 babies (42.4%), PVL in 3 (9.1%), WM loss in 5 (15.2%) and subarachnoid space changes in 6 (18.2%). CH was only detected on MRI (n = 6 [18%]). Poor Bayley score at 12 months was related to CUS IVH ($p = 0.033$) and possibly to CUS VM ($p = 0.055$). Parenchymal injury on CUS was associated with Motor score < 85 ($p = 0.049$). 24 months poor Bayley score was related to MRI cPVL ($p = 0.001$) and VM in both early CUS and term MRI ($p = 0.018$ and $p = 0.038$). Motor score < 85 was related to CUS VM ($p = 0.028$) and MRI CH ($p = 0.028$).

CONCLUSIONS

MRI adds valuable information to CUS in the detection of cPVL and CH, both strongly linked to ND outcome at 24 months of age. Both early and late detection of VM at term may predict unfavourable ND outcome. Future prospective studies are needed with focus on detection of CH and the evolution of VM in order to stratify indication for neonatal clinical MRI.

ABS 72

CRANIAL ULTRASOUND AT DAY 7 AND CLINICAL MRI AT TERM IN VERY PRETERM INFANTS BORN AT LESS THAN 28 WEEKS: VENTRICULOMEGALY IS RELATED TO SUBTLE BRAIN PATHOLOGY AND UNFAVORABLE DEVELOPMENTAL OUTCOME AT 24 MONTH

K. Chatzidimitriou[1], A. Chebsey[1], D. Odd[1,3], M. El Brookle[1], M. Likeman[2], A. Heep[1,3]

[1]*Neonatal Intensive Care Unit, Southmead Hospital, Bristol, UK*

[2]*Imaging Department, Southmead Hospital, Bristol, UK*

[3]*Neonatal Neurology Group, School of Clinical Sciences, University of Bristol, Bristol, UK*

INTRODUCTION

Brain injury is frequently seen in preterm infants and is associated with suboptimal neurodevelopmental (ND) outcome. While MRI is better for detecting subtle white matter injury (WMI), major WMI and ventriculomegaly (VM) are well detected on both cranial ultrasound (CUS) and MRI.

Objective: To find possible relations between early VM, as assessed by CUS, or late VM, as assessed by MRI, with subtle brain damages on MRI at term and ND outcome (Bayley III) at 12 and 24 months of life in very preterm infants, born at less than 28 weeks of gestational age (GA).

Design: Retrospective observational cohort study in a single Level III neonatal unit.

METHODS

All infants admitted at less than 28 completed weeks of gestation weeks at a single tertiary neonatal intensive care unit between 2013-2014 were eligible for the study (n = 128). 95 Infants were excluded (neonatal death n = 13 ; lost to follow up or missing MRI data n = 82) leaving 33 infants for the main analysis. Mean GA was 26 (23.4-28, SD 1.32), mean birth weight (BW) 778.8 g (453-1,216 g, SD 233.5), 16 (48.5%) were male. The study group did not differ in GA, BW, and gender from cohort. CUS at day 7 and MRI at term were performed according to clinical protocol. CUS IVH classification was based on that of Papile, whereas WMI in MRI was classified based on the extent of injury in T1/T2 sequences and the presence of WM volume loss, cysts, thinning of the corpus callosum and VM. Bayley was classified using composite scores (cut off value 85) and months of ND delay.

RESULTS

At day 7 CUS, VM was seen in 8 babies (24.2%), IVH was diagnosed in n = 13 (39.4%), IVH grades 3-4 n = 6 (18.2%). At MRI performed at term, VM was present in n = 16 (48.5%), WMI in n = 13 (39.4%), gray matter injury (GMI) in n = 6 (18.2%) and cPVL in n = 3 (9.1%). Other subtle MRI changes found are shown in table 1. Early VM on CUS was related to MRI VM (p = 0.001), WM haemorrhage (p = 0.01), WM loss (p = 0.043), WMI (p = 0.009), IVH MRI (p = 0.003), poor Bayley summary and motor scores at 24 months (p = 0.018 and p = 0.028 respectively), but not with cPVL (p = 0.177). Late VM on MRI was related to WM loss (p = 0.012), IVH MRI (p = 0.024) and poor Bayley score at 24 months (p = 0.029) (**Tab. 1**).

CONCLUSIONS

VM is easily detected on both CUS and MRI. Both early and late VM are associated with detected subtle brain changes and unfavorable ND outcome at 24 months.

VM, being easily detected by CUS, could be potentially used either to identify patients at high risk instead of MRI, or as an eligibility criterion for term MRI. Early detection of these babies may favor early intervention measures.

Table 1 (ABS 72). Subtle changes in MRI and Bayley III assessment at 12 and 24 month of corrected gestational age.

VM MRI	16 (48.5%)
WM haemorrhage	9 (27.3%)
Myelin damage	2 (6.1%)
Cerebellar damage	6 (18.2%)
Subarachnoid space enlargement	6 (18.2%)
WM loss	5 (15.2%)
WMI	13 (39.4%)
GMI	6 (18.2%)
IVH	14 (42.4%)
cPVL	3 (9.1%)
Bayley score 12 months	Normal/mild: 18 (54.5%) Moderate/severe: 7 (21.2%) Missing: 8 (24.3%)
Motor component < 85 at 12 months	Yes 16 (64%) Missing: 8 (24.2%)
Bayley score 24 months	Normal/mild: 17 (51.6%) Moderate/severe: 3 (9.1%) Missing: 13 (39.4%)
Motor component < 85 at 24 months	Yes 4 (12.1%) Missing: 13 (39.4%)

VM: ventriculomegaly; WMI: white matter injury; GMI: gray matter injury.

ABS 73

AUTOPHAGY INHIBITION PROTECTS IN A PRETERM RAT MODEL OF EXCITOTOXIC BRAIN INJURY

C. Descloux[1,2], V. Ginet[1], J. Puyal[1], A.C. Truttmann[1,2]

[1]Department of Fundamental Neurosciences (DNF), University of Lausanne, Lausanne, Switzerland

[2]Clinic of Neonatology, Department of Woman, Mother and Child, University Center Hospital, Lausanne, Switzerland

INTRODUCTION

Surviving premature infants frequently develop neurodevelopmental disabilities, some related to cerebral lesions following a perinatal excitotoxic event. The immature brain is highly vulnerable to excitotoxicity, which is one of the main deleterious mechanisms involved in hypoxic/ischemic brain injuries. It has been shown that excitotoxic conditions could lead to excessive activation of autophagy changing this physiological cellular system of degradation to a deleterious process. In the present study, we investigated if enhanced autophagy is involved in the development of cerebral lesions in a rat model of preterm excitotoxic cerebral lesion and its potential functional role.

METHODS

Excitotoxic lesion was induced by injecting a glutamate analogue, ibotenate (ibo, 10 μg), in the right cingulum of P5 rat pups, whose brain maturity corresponds to preterm's of 28-32 weeks. Autophagy was investigated by Western Blots and immunohistochemistry of the autophagic substrate

SQSTM1 and autophagosomal (LC3)/lysosomal (LAMP1, CathD\B) markers, as well as by EM. Cell death was evaluated by fodrin and caspase-3 cleavage at 24h. Cerebral lesion was assessed, by measuring the volume of both the brain and the lateral ventricle (on Nissl stained sections) and the subcortical white matter (WM) thickness (MBP labelling) at P21. The role of autophagy was evaluated by injecting at intracerebroventricular level (i.c.v.), just after ibo, the pharmacological autophagy inhibitor 3-methyladenine (3-MA, 30 mg/ml).

RESULTS

Autophagy is increased at 24 h after ibo injection as shown not only by the increased presence of autophagosomes (more LC3-II [> 1.5x] and LC3-positive dots [> 7x]) but also by enhanced autophagic degradation, SQSTM1 reduction (> 0.75x) and increased of LAMP1- (> 6.5x) and CathB- (> 2.4x) positive vesicles. 3-MA co-injection could efficiently attenuate the enhancement of autophagy as shown by reduced increase in LC3-II (~65%) and SQSTM1 degradation (~125%). Moreover 3-MA injected brain displayed reduced caspase-3 activation (~50%) and calpain-dependent fodrin (~22%) cleavage at 24h. Ibo injection induced typical features of preterm brain injury at P21 such as lateral ventricle dilatation (~15x), cerebral tissue volume loss (~0.88x) and subcortical WM reduced thickness. 3-MA also strongly reduces these brain alterations at long term.

CONCLUSIONS

Our results show for the first time that autophagy is strongly enhanced in a preterm rat model of excitotoxic brain injury. Enhanced autophagy is involved in cell death mechanisms (apoptotic and necrotic) and its inhibition reduces long term brain lesions development. Strategies inhibiting autophagy could represent a promising neuroprotective approach in the context of preterm brain injuries.

ABS 74

VALIDITY OF THE KOREAN DEVELOPMENTAL SCREENING TEST FOR VERY LOW BIRTH WEIGHT INFANTS

C.Y. Kim, J.H. Hwang, E. Jung, B.S. Lee, K.S. Kim, A.R. Kim

Division of Neonatology, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

INTRODUCTION

The importance of neurodevelopmental outcome of very low birth weight (VLBW) infants is emphasized as their mortality rate has dramatically improved. The purpose of this study was to evaluate the validity of the Korean Developmental Screening Test (K-DST), a developmental screening tool acknowledged by Korean Society of Pediatrics for preterm and term babies, for the timely diagnosis of neurodevelopmental delay in VLBW infants.

METHODS

Subjects included VLBW infants visiting outpatient clinic from July 2014 to June 2016 at Asan Medical Center, who had undergone Bayley Scales of Infant Development II (BSID II) and K-DST, filled-out by primary caretaker, at corrected 18-36 months. The statistical analyses were performed by Chi-square test and Spearman's rank correlation analysis (SPSS® version 21.0).

RESULTS

A total of 58 patients were enrolled. Of these infants, 26 (50%) were male. The mean gestational age at birth and birth weight was 27.7 ± 3.5 weeks and 948.6 ± 268.5 g, respectively. Intraventricular hemorrhage (Grade ≥ II), necrotizing enterocolitis (Stage ≥ II) and retinopathy of prematurity (Stage ≥ I) was 24.1%, 6.9% and 41.4%, respectively. The mean age at which both BSID II and K-DST were obtained was at corrected 24.3 ± 6.5 months (range 18-41 months). The frequency of failed MDI < 85 (32.7%) were similar to the frequency of failed at least one domain of K-DST < -1 SD. Failed more than 1 domain of K-DST when compared with MDI < 85 showed sensitivities and NPVs of 0.889 and 0.905, respectively. Failed more than 1 domain of K-DST when compared with PDI < 85 showed sensitivities and NPVs of 0.818 and 0.905, respectively. Each domain of K-DST had stronger correlation in predicting failing MDI < 85 than PDI < 85 ($p < 0.05$).

CONCLUSIONS

The results of this study showed usefulness of K-DST as a screening tool in predicting neurodevelopmental delay among VLBW infants.

ABS 75

INTERACTION BETWEEN ACUTE THERAPEUTIC HYPOTHERMIA AND A DELAYED MESENCHYMAL STEM CELL THERAPY IN NEONATAL HYPOXIA-ISCHEMIA

J. Herz, C. Köster, B.S. Reinboth, M. Dzietko, I. Bendix, U. Felderhoff-Müser

Department of Pediatrics I, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

INTRODUCTION

To date, the only clinically established intervention for hypoxic-ischemic brain injury is a hypothermia treatment (HT). However, 40-50% of cooled infants still suffer from major neurological problems. Thus, new and/or additional treatment strategies are urgently required. Due to the limited therapeutic time window of acute neuroprotective agents, regenerative therapies, such as bone-marrow-derived mesenchymal stem cells (MSC) have gained major interest. In the present study we hypothesized that an immediate mild HT combined with a delayed MSC therapy will result in additive and/or synergistic treatment effects to improve long-term neurological outcome.

METHODS

Postnatal day (PND) 9 C57BL/6 mice were exposed to hypoxia-ischemia (HI, 10% oxygen, rectal temperature (Trectal): 35°C) immediately followed by 4 hours HT at Trectal: 32°C. Control mice (normothermia, NT) were maintained at nesting temperature (Trectal: 35°C). Murine MSC (1 x 10^6 cells/animal) or saline (control) were administered intranasally at PND 12 to HT or NT mice (i.e. 4 experimental groups). Brain tissue injury, microglia activation, endothelial adhesion molecule expression and cerebral leukocyte infiltration were determined by immunohistochemistry and western blot at 7 days post HI (n = 12-16/group). Long-term neurobehavioural outcome was assessed in the Open Field, the Elevated Plus Maze and the Novel Object Recognition test at 5 weeks post injury (n = 16-18/group).

RESULTS

Both, MSC and HT significantly improved motoric function revealed by an increased rearing activity in the Open Field test. HI-induced cognitive deficits expressed as a reduced ability to discriminate familiar and novel object cues were improved by MSC but not by HT. Surprisingly, neither motoric nor cognitive deficits improved by the combined treatment regimen. Furthermore, significant protective effects on histological brain injury and neuroinflammatory responses (i.e. microglia activation, vascular cell adhesion molecule-1 (VCAM-1) expression, cerebral immune cell infiltration) mediated by each single therapy where diminished after combination of both treatments.

CONCLUSIONS

This study has important clinical implications as it demonstrates that in depth pre-clinical analyses on potential interactions between therapies are required before the initiation of clinical trials. Further research is needed on the impact of the brains' microenvironment on the phenotype of MSCs to define the optimal window of opportunity for regenerative therapies as add on therapy for obligatory acute hypothermia treatment.

ABS 76

IMPACT OF NEONATAL WHITE MATTER INJURY AND BRAIN VOLUMES TO SCHOOL-AGE NEURODEVELOPMENT IN CHILDREN WITH CONGENITAL HEART DISEASE

N.H.P. Claessens[1,2,3,4], S.O. Algra[5], T.L. Ouwehand[1], N.J.G. Jansen[3], P. Moeskops[6,7], I. Išgum[6], R. Schappin[8], I.C. van Haastert[1,9], M.J.C. Eijsermans[1,9], F. Groenendaal[1,4], L.S. de Vries[1,4]*, M.J.N.L. Benders[1,4]*

**Authors share last authorship*

[1]*Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, the Netherlands*

[2]*Department of Paediatric Cardiology, Wilhelmina Children's Hospital, Utrecht, the Netherlands*

[3]*Department of Paediatric Intensive Care, Wilhelmina Children's Hospital, Utrecht, the Netherlands*

[4]*Brain Centre Rudolph Magnus, University Medical Centre Utrecht, Utrecht, the Netherlands*

[5]*Department of Radiology, University Medical Centre Utrecht, Utrecht, the Netherlands*

[6]*Image Sciences Institute, University Medical Centre Utrecht, Utrecht, the Netherlands*

[7]*Medical Image Analysis Group, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands*

[8]*Department of Medical Psychology and Social Work, University Medical Centre Utrecht, Utrecht, the Netherlands*

[9]*Child Development and Exercise Centre, University Medical Centre Utrecht, Utrecht, the Netherlands*

INTRODUCTION

Critical congenital heart disease (CHD) is associated with neonatal brain injury and delayed brain growth. To date, the impact of neonatal brain abnormalities to long-term neuropsychological outcome in children with CHD has not been reported.

METHODS

In this study, 34 children (median gestation 39.1 weeks, 79% male) who required neonatal open-

heart surgery for CHD underwent preoperative (median 8 days after birth) and postoperative MRI of the brain (median 7 days after surgery). MRI scans were analysed qualitatively for the presence of moderate-severe white matter injury (WMI, if > 3 lesions 2 mm), grey matter focal infarctions and cerebral sinovenous thrombosis. Volumes of cerebellum, basal ganglia and thalami, unmyelinated white matter, cortical grey matter and total brain were calculated with inner cortical surface and gyrification index as cortical measures, based on automated segmentation. Neurodevelopmental outcome was assessed at the age of two years (n = 32, using Bayley Scales of Infant and Toddler Development-III-NL to obtain cognitive composite score (normative mean 100 ± 15) and six years (n = 26, using Wechsler Preschool and Primary Scales of Intelligence-III-NL to obtain intelligence quotient (IQ, normative mean 100 ± 15) and Teacher Report Form to obtain attention problem score (score > 65 is within clinical range). Cognitive outcome parameters were corrected for maternal education level (classified as low, middle or high). Median two year cognitive composite score was 100 (IQR: 95-110), median six year full-scale IQ 89 (IQR: 82-106), median performance IQ 96 (IQR 84-109), median verbal IQ 93 (IQR: 85-115), median processing speed 88 (IQR: 73-94) and median attention problem score was 53 (IQR 50-62).

RESULTS

Children with preoperative neonatal WMI (35%) showed lower cognitive score at the age of 2 years (-10 points, 95% CI 7;12), and decreased full-scale IQ (-18 points, 95% CI 14;22), performance IQ (-14 points, 95% CI 10;18), processing speed (-13 points, 95% CI 9;17) and higher teacher report of attention problems (64 versus 53, $p < 0.001$) at the age of six. Children with postoperative WMI (62%) showed lower two year cognitive score (-10 points, 95% CI 7;13) with lower six year full-scale IQ (-14 points, 95% CI 9;19) and higher teacher report of attention problems (58 versus 52, $p = 0.03$). Presence of neonatal grey matter focal infarction or cerebral sinovenous thrombosis did not result in different neurodevelopmental outcome parameters. In linear regression analysis, no associations of neonatal brain volumes and cortical measures with cognitive or behavioural outcome parameters were seen. Children with below average full-scale IQ (115, 12%).

CONCLUSIONS

Our findings demonstrate unfavourable neuro-psychological outcome in school-aged children with critical CHD who acquired neonatal WMI. Neonatal WMI seems to be more predictive of childhood cognitive abilities and behavioural functioning than neonatal brain volumes and cortical measures. The consequences of neonatal WMI on neuropsychological performance at an older age should be taken into account in parent-counselling, perioperative management and follow-up of children with CHD.

ABS 77

ASYNCHRONY AND SPECTRAL EEG COHERENCE IN TERM NEONATES WITH INTRAUTERINE GROW RESTRICTION

B. Reyes Millán[1], J.R. Castro Conde[2], C. González Campo[2], I. Quintero Fuentes[3], N.L. González González[4], D. González Barrios[5]

[1]Neonatology Department, Hospital Universitario Nuestra Señora de la Candelaria, S/C Tenerife, Spain

[2]Neonatology Department, Hospital Universitario de Canarias, S/C Tenerife, Spain

[3]Neuropsychology Department, Universidad de La Laguna, S/C Tenerife, Spain

[4]Gynecology and Obstetrics Department, Hospital Universitario de Canarias, S/C Tenerife, Spain

[5]Neuropediatrics Department, Hospital Universitario Nuestra Señora de la Candelaria, S/C Tenerife, Spain

INTRODUCTION

Term infants with intrauterine grow restriction (IUGR) have a longer-term risk of neurological deficits and lower scores than controls in validated neurodevelopmental tests. To date there are no neurophysiological studies performed in the neonatal period in term infants with IUGR. Neuroimaging studies have demonstrated significantly altered development of the corpus callosum in fetuses with late-onset CIR. In the present study we analyzed the inter-hemispheric asynchrony by visual analysis and the inter- and intra-hemispheric coherence with the objective of assessing the neonatal brain connectivity in this group of babies.

METHODS

Eighty-two term infants were recruited (41 with IUGR and 41 matched controls by gestational age). All underwent video-EEG recording lasting > 3 hours min at 48-72 h of life. Two experienced neonatal neurophysiologists select all segments of quiet sleep with *tracé alternant* and/or discontinuity. Main outcome measures: 1) the EEG visual analysis

included the percentage of bursts with inter-hemispheric asynchrony and asymmetry; and 2) the EEG spectral analysis included EEG coherence in the following frequency bands: delta 0.5-4 Hz; theta 4-8 Hz; alpha 8-13 Hz and beta 13-30 Hz.

RESULTS

Infants with IUGR showed 12.1% (range: 0-34.7) of bursts with inter-hemispheric asynchrony and only 4.6% (range: 0-10.6) ($p = 0.004$). The neonates with CIR had significantly lower EEG coherence ($p < 0.05$) than the babies of control group (**Fig. 1**). These differences were observed mainly in the alpha and beta frequency ranges and between central-temporal and fronto-occipital areas for intra-hemispheric coherence, and in all frequency ranges in the temporo-central areas for inter-hemispheric coherence

CONCLUSIONS

Video-EEG records revealed significant changes in background tracing and EEG coherence in term

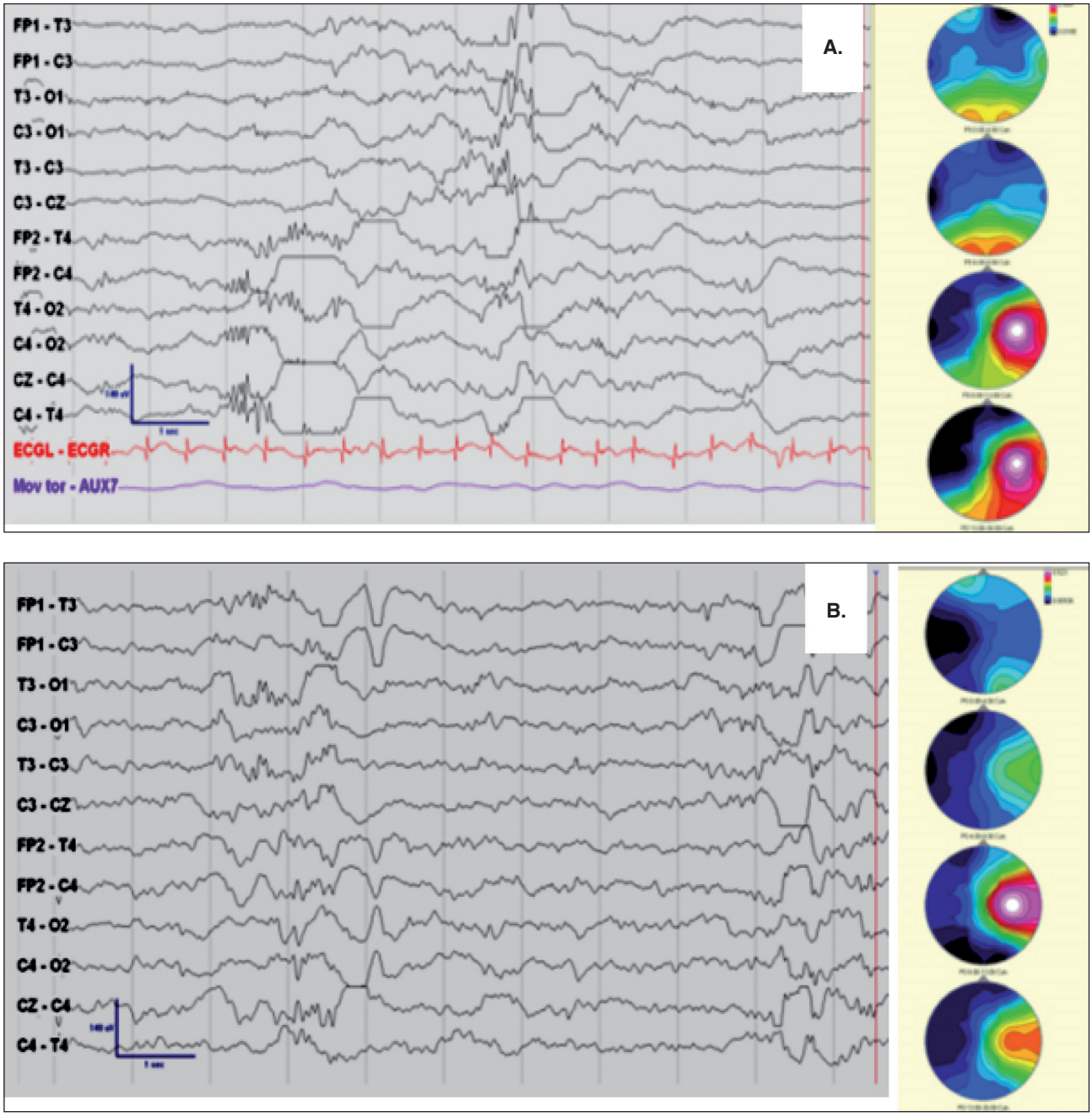

Figure 1 (ABS 77). A. Inter-hemispheric asynchrony of a burst on a discontinuous background in a neonate with CIR of 39 weeks gestational age. **B.** *Tracé alternant* in a neonate of 39 weeks of gestational age of the control group. Next to each EEG tracing, in descending order (delta, theta, alpha and beta) topographic maps shows in color scale inter-hemispheric coherence of each of them.

newborn infants with late-onset IUGR. These findings suggest a deterioration or underdevelopment of the more complex talamocortical and corticocortical connections accompanied by faster frequencies.

DECLARATION OF INTEREST

Funding: This study is part of a research project entitled "Neurophysiological and short-term neurodevelopmental assessment of newborn infants with intrauterine growth restriction". Entity: University of La Laguna. Funding Entity: CajaCanarias Foundation.

ABS 78

MUSIC EFFECTS IN PRETERM INFANTS' BRAIN: A STRUCTURAL NEUROIMAGING INVESTIGATION

J. Almeida[1], N. Kunz[2], L. Lordier[1], A. Darque[1], F. Lazeyras[3], P. Hüppi[1]

[1]Pediatrics Department, University Hospital of Geneva, Geneva, Switzerland
[2]Center of BioMedical Imaging (CIBM), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[3]Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland

INTRODUCTION

Preterm birth can result in long-term complications, namely neurodevelopmental disorders since occurs when the human brain is maturing rapidly and thus highly vulnerable to environmental stressors, leading to a heavy burden on families and society. Music, an extrinsic multisensory stimulus, was shown to modulate neural networks and functions formed early in development and affected by prematurity, by triggering distinct neural substrates later implied in learning and socio-emotional regulation. Using diffusion tensor imaging (DTI), a tool to study brain microstructure *in vivo*, we aimed to assess if music exposition had a positive impact in premature babies' brain development and maturation.

METHODS

We recruited 29 preterm ($24^{0/7}$ to $32^{6/7}$ gestational age [GA]) and 15 term newborns ($37^{0/7}$ to $42^{6/7}$ GA). From the preterm group, 14 listened to music (PTM) with headphones (10 minutes, 5 times/ week) and 15 were exposed to same headphones but without music (PTNM) (10 minutes, 5 times/ week). Both preterm groups underwent a magnetic resonance imaging (MRI) with DTI sequence at term equivalent age and term controls completed MRI shortly after birth. Using a template based region of interest (ROI) method for a quantitative analysis of DTI studies, 19 ROIs were drawn manually in the study template and back transformed to each subject space to compute ROI-average estimates of DTI measures. One-way ANOVA analysis with Bonferroni correction was performed to compare differences between groups.

RESULTS

DTI measures quantification considering the average of all 19 ROIs: fractional anisotropy (FA) is significantly higher in term newborns in comparison with PTNM, at $p < 0.05$ level. This significant difference is absent between term vs PTM. No significant differences in mean diffusivity (MD) are found between groups. DTI measures quantification per ROI: FA values are higher in all ROIs of PTM vs PTNM, except for one where is equal. FA is significantly higher, at $p < 0.05$ level, in corpus callosum (cc) genu and acoustic radiations of term vs PTNM, a difference not significant between term vs PTM. Additionally, FA is significantly higher at $p < 0.0.1$ level in cc splenium and body of term vs both PTNM and PTM. MD values are lower in PTM vs PTNM in the majority of evaluated ROIs. MD is significantly lower, at $p < 0.001$ level, in term vs both PTNM and PTM, in cc splenium and body and fornix major. Results are presented in **Tab. 1**.

CONCLUSIONS

The present study reveals that preterm newborns exposed to music have higher white matter FA, being closer to term values. According to the literature, this supports a beneficial effect in white matter maturation, myelin and axonal integrity, as well as in neurocognitive skills and development. Music might therefore constitute an effective non-invasive early postnatal neuroenhancement intervention to preterm infants during their stay in NICU.

ABS 79

CONGENITAL HEART DEFECTS AND ACADEMIC PERFORMANCE IN A NATIONWIDE COHORT OF 458,318 DANISH CHILDREN

N.B. Matthiesen[1,2], S.H. Larsen[3], T.B. Henriksen[1], C.C. Bach[1], J.R. Ostergaard[4], V. Hjortdal[5]

[1]Perinatal Epidemiology Research Unit and Department of Pediatrics & Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Pediatrics, Herning Regional Hospital, Herning, Denmark
[3]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark
[5]Department of Cardiothoracic Surgery, Aarhus University Hospital, Aarhus, Denmark

Table 1 (ABS 78). Mean diffusion tensor imaging (DTI) measurements (mean ± SD): fractional anisotropy (FA) and mean diffusivity (MD) average of all regions of interest (ROIs) and distributed by ROI. One way ANOVA was performed with Bonferroni post hoc test.

GROUP ROI	FA						MD					
				p-value						p-value		
	A	B	C	AC	BC	AB	A	B	C	AC	BC	AB
All ROIs	0.279 ± 0.018	0.286 ± 0.020	0.304 ± 0.028	**0.013**	0.107	1.000	4.137 ± 0.173	4.122 ± 0.040	4.091 ± 0.025	0.113	0.191	1.000
cc-sp	0.488 ± 0.063	0.508 ± 0.046	0.578 ± 0.044	**< 0.001**	**0.002**	0.945	4.425 ± 0.331	4.271 ± 0.287	3.791 ± 0.385	**< 0.001**	**< 0.001**	0.417
cc-bd	0.363 ± 0.066	0.388 ± 0.065	0.461 ± 0.069	**0.001**	**0.016**	0.954	4.137 ± 0.223	4.061 ± 0.207	3.780 ± 0.266	**0.001**	**0.007**	1.000
cc-ge	0.460 ± 0.047	0.470 ± 0.056	0.512 ± 0.062	**0.048**	0.137	1.000	4.014 ± 0.264	3.879 ± 0.206	3.829 ± 0.262	0.172	1.000	0.460
scr	0.217 ± 0.030	0.217 ± 0.039	0.216 ± 0.044	1.000	1.000	1.000	4.129 ± 0.346	4.179 ± 0.379	4.650 ± 0.379	1.000	1.000	1.000
fmin	0.222 ± 0.028	0.232 ± 0.032	0.243 ± 0.033	0.323	1.000	0.982	4.582 ± 0.318	4.544 ± 0.239	4.485 ± 0.236	1.000	1.000	1.000
ac	0.184 ± 0.034	0.200 ± 0.051	0.215 ± 0.043	0.202	1.000	1.000	3.257 ± 0.180	3.272 ± 0.119	3.202 ± 0.144	0.984	0.629	1.000
fmaj	0.337 ±0.058	0.341 ± 0.048	0.365 ± 0.036	0.364	0.555	1.000	4.511 ± 0.272	4.440 ± 0.341	4.102 ± 0.187	**0.001**	**0.006**	1.000
plic	0.456 ± 0.024	0.459 ± 0.029	0.466 ± 0.038	1.000	1.000	1.000	3.090 ± 0.100	3.058 ± 0.023	3.105 ± 0.089	1.000	0.549	1.000
alic	0.305 ± 0.026	0.307 ± 0.032	0.322 ± 0.044	0.605	0.742	1.000	3.402 ± 0.141	3.422 ± 0.169	3.477 ± 0.052	0.707	1.000	1.000
ilf-ifof	0.306 ± 0.030	0.303 ± 0.022	0.301 ± 0.034	1.000	1.000	1.000	4.149 ± 0.264	4.090 ± 0.174	4.050 ± 0.193	0.651	1.000	1.000
ec	0.222 ± 0.024	0.223 ± 0.020	0.235 ± 0.030	0.580	0.647	1.000	3.658 ± 0.140	3.712 ± 0.151	3.642 ± 0.127	1.000	0.566	0.895
slf	0.247 ± 0.029	0.250 ± 0.028	0.252 ± 0.027	1.000	1.000	1.000	3.942 ± 0.282	4.080 ± 0.251	3.900 ± 0.161	1.000	0.144	0.365
or	0.281 ± 0.026	0.286 ± 0.035	0.302 ± 0.042	0.354	0.665	1.000	4.358 ± 0.241	4.350 ± 0.231	4.262 ± 0.208	0.788	0.920	1.000
ar	0.169 ± 0.018	0.174 ± 0.026	0.193 ± 0.026	**0.023**	0.116	1.000	3.739 ± 0.199	3.761 ± 0.206	3.813 ± 0.174	0.941	1.000	1.000
fg-wm	0.188 ± 0.038	0.191 ± 0.038	0.216 ± 0.044	0.204	0.307	1.000	4.311 ± 0.314	4.310 ± 0.314	4.150 ± 0.261	0.476	0.482	1.000
fpc	0.097 ± 0.016	0.100 ± 0.026	0.096 ± 0.018	1.000	1.000	1.000	4.967 ± 0.344	5.038 ± 0.334	4.962 ± 0.264	1.000	1.000	1.000
opc	0.162 ± 0.028	0.166 ± 0.028	0.170 ± 0.033	1.000	1.000	1.000	5.057 ± 0.336	5.135 ± 0.354	4.953 ± 0.282	1.000	0.423	1.000
cg	0.253 ± 0.028	0.260 ± 0.040	0.264 ± 0.036	1.000	1.000	1.000	3.870 ± 0.163	3.897 ± 0.212	3.792 ± 0.109	0.657	0.297	1.000
fx	0.336 ± 0.056	0.354 ± 0.038	0.364 ± 0.070	0.528	1.000	1.000	4.997 ± 0.610	4.826 ± 0.434	4.822 ± 0.602	1.000	1.000	1.000

FA: fractional anisotropy; MD: mean diffusivity; Cc-sp: splenium part of corpus callosum; cc-bd: body part of corpus callosum; cc-ge: genu part of corpus callosum; scr: superior corona radiata; fmin: forceps minor; ac: anterior comissure; fmaj: forceps major; plic: posterior limb of the internal capsule; alic: anterior limb of the internal capsule; ilf-ifof: inferior longitudinal fasciculus and inferior fronto-occipital fasciculus; ec: external capsule; slf: superior longitudinal fasciculus; or: optic radiation; ar: acoustic radiation; fg-wm: superior part of the frontal gyrus white mater; fpc: frontal periventricular crossroad; opc: occipital periventricular crossroad; cg: cingulum; fx: fornix.

INTRODUCTION
Congenital heart defects (CHD) are the most common birth defects, present in up to 1% of all children. Over the last decades, survival has improved immensely, but CHDs remain a leading cause of both mortality and severe childhood morbidity. Concurrently, it has become clear that up to 50% of the children present with abnormal neurodevelopment, the most common and distressful long-term complication associated with CHDs. Nonetheless, studies of long term follow up are sparse and the association between specific anatomic subtypes of CHD and different aspects of academic achievement of the children remains widely unknown. We aimed to assess these associations in a large nationwide cohort.
METHODS
We identified a cohort of 458,318 liveborn, singleton, Danish children born from 1997-2005. CHDs were present in 3,201 children. Reading and mathematics skills were assessed by mandatory national public school tests. CHD and potential confounders were identified in national registries. We estimated the association between subtypes of CHDs and the standardized mean test scores in reading and mathematics by random effects linear mixed models adjusted for potential confounders, comparing children with CHD to the general population. Potential confounders included parental origin, maternal age, body mass index, smoking, parity, diabetes, and hypertension, as well as newborn factors including gender, year of birth, extracardiac malformations, teratogenic, chromosomal, and genetic syndromes.
RESULTS
Overall, compared to the general population, the presence of CHD was associated with a standardized mean difference in reading of -0.10 (95% CI -0.13 to -0.07). In mathematics, the estimate was -0.11 (95% CI -0.14 to -0.07). Several subtypes of CHD were associated with even lower scores in both reading and mathematics, including hypoplastic left heart syndrome, reading: -0.67 (95% CI -1.13 to -0.21), mathematics: -0.63 (95% CI -1.17 to -0.08), other single ventricle defects, reading: -0.31 (95% CI -0.51 to -0.10), transposition of the great arteries, reading: -0.32 (95% CI -0.49 to -0.16), mathematics: -0.22 (95% CI -0.42 to -0.02) tetralogy of Fallot, reading: -0.25 (95% CI -0.42 to -0.09), anomalous pulmonary venous return, reading: -0.34 (95% CI -0.64 to -0.04), and major atrial septal defects, reading: -0.26 (95% CI -0.37 to -0.14), mathematics: -0.23 (95% CI -0.36 to -0.10).
CONCLUSIONS
Children with CHD constitute a distinct population prone to impaired neurodevelopment, including poor academic achievement. Overall, the presence of CHD was associated with discrete difficulties within both reading and mathematics. Several subtypes were associated with markedly poorer academic achievement, including the most severe subtype, hypoplastic left heart syndrome, but also one of the most common subtypes, major atrial septal defects.

ABS 80

PROGNOSTIC VALUE OF EARLY CONVENTIONAL PROTON MAGNETIC RESONANCE SPECTROSCOPY IN COOLED ASPHYXIATED NEWBORNS

H. Barta[1], A. Jermendy[1], M. Kolossvary[2], L.R. Kozak[3], A. Lakatos[3], U. Meder[1], G. Rudas[3], M. Szabo[1]

[1]1st Department of Paediatrics, Semmelweis University, Budapest, Hungary
[2]MTA-SE Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[3]MR Research Center, Semmelweis University, Budapest, Hungary

INTRODUCTION
Neonatal hypoxic-ischemic encephalopathy (HIE) commonly leads to neurodevelopmental impairment, raising the need for prognostic tools that may guide future therapies in the early phase of the disease. Prognostic value of proton MR spectroscopy (H-MRS) between 1-46 days of life has been extensively studied, however, the reproducibility and generalizability of these methods are controversial. Therefore, we investigated the prognostic performance of conventional H-MRS during first 96 hours of life in hypothermia-treated asphyxiated neonates.
METHODS
Fifty-one consecutive hypothermia-treated HIE neonates were examined by H-MRS using three different echo-times (TE = 35, 144, 288 ms) between 6-96 hours of age. Patients were divided into favorable (n = 38) and unfavorable (n = 17) outcome groups based on psychomotor and mental developmental index (PDI and MDI, Bayley Scales of Infant Development II) scores (≥ 70 vs. < 70 or death, respectively), assessed at 18-26 months of age. Associations between 36 routinely measured metabolite ratios and outcome were studied after

correction for multiple testing. Age-dependency of metabolite ratios in whole patient population was assessed. Prognostic performance of metabolite ratios was evaluated by Receiver-operating characteristics (ROC) analysis.

RESULTS

Three metabolite ratios showed significant difference between outcome groups after correction for multiple testing ($p < 0.0014$): myo-inositol (mIns)/N-acetyl-aspartate (NAA) height, mIns/creatine (Cr) height, both at TE = 35 ms, and NAA/Cr height at TE = 144 ms. Assessment of age-dependency showed that 2 out of 3 metabolite ratios (mIns/NAA and mIns/Cr) had weak correlation with timing of MR scan during first 96 hours of life. ROC analysis revealed that mIns/NAA gives better prediction for outcome than mIns/Cr with cut-off values 0.6798 and 0.7977, respectively, (AUC 0.9084 and 0.8462, respectively, $p < 0.00001$); mIns/NAA had the highest specificity (95.24%) and sensitivity (84.62%) for predicting outcome of neonates with HIE any time during the first 96 hours of life.

CONCLUSIONS

Our findings suggest that during first 96 hours of life H-MRS could be a useful and generalizable prognostic tool in predicting the outcome of asphyxiated neonates; mIns/NAA was found to be the most accurate and possibly age-independent predictor.

ABS 81

CYTOKINES TRAJECTORIES IN NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY: THE ROLE OF HYPOTHERMIA

S. Perrone[1], S. Cornacchione[1], M.D. Weiss[2], R. Candace[2], M. Longini[1], F. Proietti[1], M. Calderisi[3], G. Buonocore[1]

[1]Department of Molecular and Developmental Medicine, General Hospital "Santa Maria alle Scotte", University of Siena, Siena, Italy

[2]Department of Pediatrics, University of Florida, Gainesville, FL, USA

[3]Kode-solution Pisa, Italy

INTRODUCTION

Despite the recent introduction of hypothermia (HT) as a mandatory standard of care, the incidence of neonatal hypoxic-ischemic encephalopathy (HIE) in full-term newborns remains to be a major cause of neonatal mortality and morbidity. It is unclear why HT is effective in alleviating neonatal HIE in some, but not all, newborns. Part of the neuroprotective effect of HT is due to proinflammatory pathway blockade. However, the effect of HT on the inflammatory response triggered by hypoxia is still at early stage of discovery. Our aims were to identify a panel of cytokines involved in the HIE process and possibly modulated by HT and to investigate the cytokines trajectories in the setting of HT.

METHODS

Eighteen newborns were enrolled: 10 with clinical signs of hypoxic ischemic encephalopathy and 8 healthy babies as controls. For each patient of HIE group, 5 samples at 5 different times points were collected: time 1: between 0 and 6 hours of life, time 2: at 12 hours, time 3: at 24 hours, time 4: at 48 hours and time 5: at 72 hours of life (therefore respectively before, during and after the hypothermic treatment). For each patient of control group only one sample (time 0) was collected. A default panel of 48 inflammatory cytokines was determined in all samples. All statistical analyses were performed using Principal component analysis (PCA).

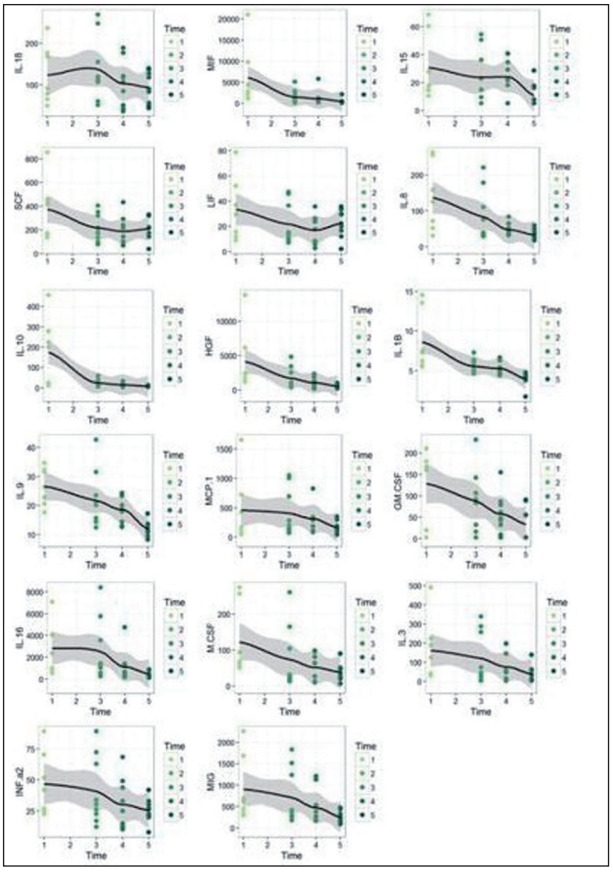

Figure 1 (ABS 81). All 17 cytokines showed a descending trend: they were higher in hypoxic ischemic patients at time 1, and then they decreased during the hypothermia treatment.

RESULTS
Seventeen cytokines, among 48 analyzed, allowed to distinguish babies with HIE from controls: 11 cytokines with pro-inflammatory effects and 6 with anti-inflammatory effects. All 17 cytokines showed a descending trend: they were higher in hypoxic ischemic patients at time 1, and then they decreased during the hypothermia treatment (**Fig. 1**). At time 5 cytokines levels were similar to controls.
CONCLUSIONS
Hypothermia inhibits both pro-inflammatory and anti-inflammatory cytokines probably avoiding beneficial responses and protective effects in response to hypoxia. Data support the hypothesis babies with HIE undergoing to hypothermia need to be protected with additional drugs. The identification of cytokines trajectories during TH allows to identify possibile targets for intervention.

ABS 82

COLD-INDUCIBLE RBM3 AUGMENTS IGF2 EXPRESSION IN NEURAL STEM CELLS BY INTERACTING WITH IMP2 IN AN RNA-DEPENDENT MANNER

J. Yan[1], X. Zhu[1], A. Zelmer[1], J. Kapfhammer[2], S. Wellmann[1]

[1]Neonatology Department, University Children's Hospital Basel (UKBB), University of Basel, Basel, Switzerland

[2]Biomedicine Department, University of Basel, Basel, Switzerland

INTRODUCTION
Cold-inducible RNA-binding motif protein 3 (RBM3) is expressed in neural stem cells (NCSs) and mediates neuroplasticity and neuroprotection but the underlying molecular mechanisms are poorly understood. In a previous screening approach for RBM3 protein interactors we identified a group of insulin like growth factor 2 (IGF2) mRNA binding proteins (IMPs). Among them, IMP2 is found in many long-lasting proliferating cells including immortal cell lines, cancer cells and stem cells. As a downstream effector of IMP2, IGF2 has been reported as a positive regulator of stem cell self-renewal. Thus, we investigated whether RBM3 regulates NSC proliferation by promoting IGF2 expression through interaction with IMP2.
METHODS
RBM3 overexpression or knock-down was performed in Hep3B cells, a cell line with high endogenous IGF2 expression. NSCs were isolated from RBM3 WT or KO mice (P1) and subjected to oxygen glucose deprivation/reoxygenation (OGD/R) when indicated. Cultured cells were harvested to perform co-immunoprecipitation (co-IP), RNA-immunoprecipitation (RIP) assay and proximity ligation assay (PLA). For immunoprecipitation (IP), anti-RBM3, anti-IMP2 antibodies or normal IgG were used to precipitate target protein and bound RNAs from cell lysates. In RIP assay, co-precipitated RNAs were purified and subjected to RT-PCR and qPCR. In co-IP assay, co-precipitated proteins were analyzed by Western blot.
RESULTS
In co-IP assay of Hep3B cells, RBM3 could pull down IMP2 butIMP2 band was absent when cell lysates were pre-treated with RNase. These results were confirmed in RBM3 KO/WT NSCs indicating that RBM3 interacts with IMP2 via RNA molecules. Next, RIP assay was performed and IGF2 mRNA enrichment on RBM3 and IMP2 proteins were detected in Hep3B cells. When silencing RBM3 expression by different specific siRNAs, IGF2 mRNA was down-regulated in input. In NSCs isolated from RBM3 KO mice IMP2 protein recruited less IGF2 mRNA than in WT mice with or without OGD/R. Moreover, IGF2 expression was lower in NSCs from RBM3 KO mice than in WT mice. PLA experiment demonstrated RBM3-IMP2 protein interactions present in both Hep3B cells and NSCs. These interactions occurred in both nucleus and cytoplasm of the cell.
CONCLUSIONS
RBM3 interacts physically with IMP2 in Hep3B cells and NSCs in an RNA-dependent manner. RBM3 facilitates the recruitment of IGF2 mRNA by IMP2 protein interaction and thereby regulates positively IGF2 expression. Thus, IGF2 is a downstream effector of RBM3 and a valid candidate of RBM3 mediated neuroplasticity and neuroprotection.

ABS 83

EARLY POSTOPERATIVE AMPLITUDE-INTEGRATED ELECTROENCEPHALOGRAPHY: BIOMARKER OF NEW BRAIN INJURY IN NEONATES WITH CONGENITAL HEART DISEASE

N.H.P. Claessens[1,2,3], L. Noorlag[1,2], L. Weeke[1], M. Toet[1], J.M.P.J. Breur[3], M.J.N.L. Benders[1], F. Groenendaal[1], N.J.G. Jansen[2], L.S. de Vries[1]

[1]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
[2]Department of Paediatric Intensive Care, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Department of Paediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands

INTRODUCTION

Neonates with critical congenital heart disease (CHD) are at risk for developing brain injury after cardiac surgery. Amplitude-integrated electroencephalography (aEEG) is used for continuous brain function monitoring and may predict new brain injury at an early stage. The objective of our study is to evaluate whether early postoperative aEEG can identify neonates at risk of new brain injury after neonatal cardiac surgery.

METHODS

Nineteen neonates with critical CHD (single ventricle pathology [n = 7], transposition of great arteries [n = 7], and aortic arch obstruction [n = 5]) who underwent neonatal cardiac surgery were enrolled. Postoperative aEEG was evaluated for background pattern at 5 time points (4h, 12h, 18h, 24h and 48h after surgery) and presence of ictal discharges. Presence of new postoperative moderate-severe brain injury (white matter injury (> 3 lesions 2 mm), grey matter focal infarction and/or intra-parenchymal haemorrhage) was assessed using preoperative and postoperative MRI of the brain (median 7 days after surgery).

RESULTS

No differences in clinical parameters were present between neonates with new brain injury (63%) and without new brain injury (37%). In the first 18 hours postoperatively, background pattern was more depressed in neonates with new brain injury (**Fig. 1**), particularly at 12 hours (p = 0.02). Neonates with new brain injury also needed longer time to recover to continuous normal voltage after surgery (median 18 versus 10 hours, p = 0.06). All neonates with postoperative burst suppression showed new brain injury. Postoperative ictal discharges were seen in 11%, with presence of new brain injury in all.

CONCLUSIONS

Early postoperative aEEG background pattern can be used to identify neonates at risk of new brain injury after cardiac surgery for critical CHD. Presence of postoperative burst suppression or ictal discharges is associated with new postoperative brain injury.

ABS 84

STABILITY OF AUTISM DIAGNOSIS IN CHILDREN BORN VERY-PRETERM FROM AGE 2 TO 4 YEARS

M. Pritchard[1,2], H. Haydon[1,2], T. de Dassel[3], E. Beller[4], F. Bogossian[5], L. Johnston[6], J. Paynter[5], S. Russo[7], J.G. Scott[5]

[1]Australian Catholic University, Brisbane, Queensland, Australia
[2]Mater Hospital, Brisbane, Queensland, Australia
[3]Royal Brisbane Women's Hospital, Brisbane, Australia
[4]Bond University, The University of Queensland, Robina, Queensland, Australia
[5]Griffith University, Brisbane, Queensland, Australia
[6]University of Toronto, Toronto, Canada
[7]Better Life Psychology, Brisbane, Queensland, Australia

INTRODUCTION

Although children born very preterm are at increased risk of autism, the diagnostic stability in these children is unknown. This study aimed to determine the diagnostic stability of Autism using the Autism Diagnostic Observation Schedule-Generic (ADOS-G) classifications in children born very preterm from age 2 to 4 years' corrected age (CA).

METHODS

Child-survivors born < 29 weeks' gestation were enrolled at age 2 years in a hospital-based prospective longitudinal Autism study. Measures included the Modified Checklist of Autism in Toddlers-Follow-up Interview (M-CHAT-FI™), ADOS-G and developmental assessments. The ADOS-G was conducted on toddlers who screened positive on the M-CHAT-FI™. Outcomes were assessed at ages 2 and 4 years.

RESULTS

Data were available on 85% (74/87) of VPT children at age 4 years. At age 2 years the rates of no autism, sub-clinical autism and autism were respectively 91.7%, 5.6% (n = 4) and 2.8% (n = 2) and at 4 years 91.7%, 1.4% (n = 1) and 6.9% (n = 5). The Kappa agreement was 0.39. Three new autism cases were diagnosed at 4 years of age; one was subclinical and two were classified as no autism at 2 years.

CONCLUSIONS

Autism outcomes at 2 years of age are only moderately predictive of outcomes at 4 years of age. Children diagnosed at 2 retained a diagnosis at 4 years of age. This demonstrates the need for ongoing diagnostic vigilance for autism in young children born very preterm.

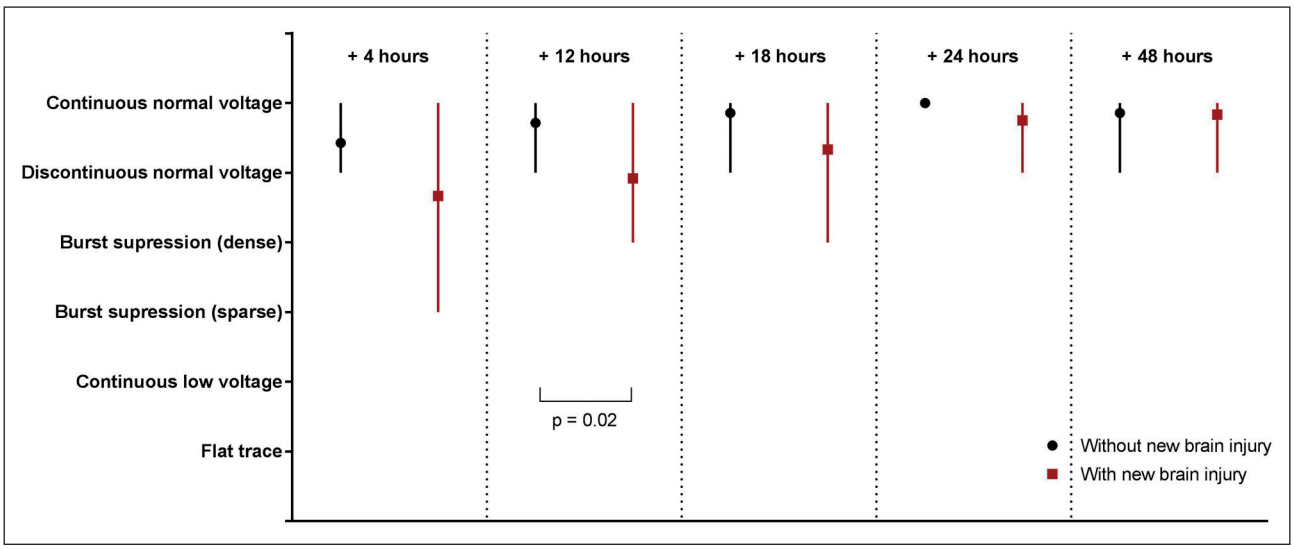

Figure 1 (ABS 83). Mean aEEG background pattern (and range) at 5 postoperative time points in neonates with critical CHD. Background patterns are listed from normal (continuous and discontinuous normal voltage) to abnormal.

ABS 85

ASSOCIATION BETWEEN TRANSIENT NEONATAL HYPOGLYCEMIA AND ADVERSE NEUROLOGICAL DEVELOPMENT AT 2-6 YEARS OF AGE

R. Wickström[1], B. Skiöld[1], G. Petersson[2], O. Stephansson[1,2], M. Altman[2,3]

[1]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[2]Department of Medicine Solna, Clinical Epidemiology Unit, Karolinska Institutet, Stockholm, Sweden

[3]Humanitas University, Milan, Italy

INTRODUCTION

Severe or prolonged neonatal hypoglycemia may damage the newborn brain. There is controversy regarding the possible long-term effects of moderate neonatal hypoglycemia. We aimed to determine whether moderate neonatal hypoglycemia (blood glucose < 40 mg/dL, < 2.2 mmol/L) treated with extra feedings in the postnatal ward is associated with adverse neurodevelopmental outcome in pre-school children.

METHODS

All singletons born 1st July 2008-31st December 2012 (n = 101,060) in the Stockholm-Gotland region in Sweden were included. Infants with congenital malformations, infants treated in the neonatal intensive care unit, infants with an inborn error of metabolism and infants to mothers with diabetes were excluded. Exposure was neonatal transient hypoglycemia, as defined by the ICD-10 diagnoses P70.4, P70.4A and/or P70.4B. Infants were followed-up until 2014 and regarding specified neurodevelopmental disorders registered in the Swedish National Patient Registry and/or the Swedish Cause of Death Registry. Main outcomes were a compound adverse outcome; any developmental delay; motor developmental delay; and cognitive developmental delay.

RESULTS

Among the 101,060 included infants, 1,500 (1.5%) had transient hypoglycemia. In regression analyses adjusted for mode of delivery; birth weight for gestational age, gestational age, sex, Apgar score at 5 minutes, and birth year, the odds ratio (OR) of compound adverse outcome was 1.48 (95% confidence interval 1.17-1.88) in hypoglycemic compared to normoglycemic infants. The adjusted risk of any developmental delay was more than doubled (OR 2.53 [1.71-3.73]), the adjusted risk of motor developmental delay was almost doubled (OR: 1.91 [1.06-3.44]) and the adjusted risk of cognitive developmental delay was almost tripled (OR 2.85 [1.70-4.76]). Infants with early neonatal hypoglycemia (< 6 hours) had a double risk (adjusted OR 1.94 [1.30-2.89]) of compound adverse outcome and a tripled risk of cognitive developmental delay (adjusted OR 3.17 [1.35-7.43]), compared to normoglycemic infants.

CONCLUSIONS

Moderate neonatal hypoglycemia requiring treatment with extra oral feedings is associated with negative effects on neurodevelopment in pre-school children. Our data do not support the notion that

early transient neonatal hypoglycemia is a harmless physiologic state. Clinical guidelines with screening of symptomatic and high-risk infants should be followed and immediate treatment of hypoglycemia should be provided when necessary.

ABS 86

PERINATAL ASSOCIATIONS WITH BRAIN GROWTH EVALUATED BY SEQUENTIAL CRANIAL ULTRASONOGRAPHY IN VERY PRETERM INFANTS

R. Cuzzilla[1,2,5], A.J. Spittle[1,4,5], K.J. Lee[1,3], S. Rogerson[2,5], F.M. Cowan[6], L.W. Doyle[1,2,5], J.L.Y. Cheong[1,2,5]

[1]Victorian Infant Brain Studies, Murdoch Children's Research Institute, Melbourne, Australia

[2]Department of Obstetrics and Gynaecology, The University of Melbourne, Melbourne, Australia

[3]Department of Paediatrics, The University of Melbourne, Melbourne, Australia

[4]Department of Physiotherapy, The University of Melbourne, Melbourne, Australia

[5]Neonatal Services, The Royal Women's Hospital, Melbourne, Australia

[6]Department of Paediatrics, Imperial College, London, UK

INTRODUCTION

Preterm infants are at risk of long-term neurodevelopmental impairment related to perinatal brain injury and aberrant brain growth and maturation. Whilst cranial ultrasonography (cUS) is commonly used to screen preterm infants for major brain injury, its use in assessing early postnatal brain growth has not been well described. We aimed to: (1) evaluate early postnatal brain growth in preterm infants using sequential cUS linear measures; and (2) explore perinatal variables that are associated with early postnatal brain growth.

METHODS

This prospective longitudinal cohort study recruited 144 infants born at < 30 weeks' gestational age (GA) at a single centre between January 2011 and December 2013. Infants with congenital or chromosomal anomalies were excluded, as were infants with major preterm brain injury detected on cUS. Linear measurements were made on sequential cUS performed as part of routine clinical care (**Fig. 1**). Perinatal variables were chosen on the basis of their known associations with preterm brain injury and long-term developmental outcomes. Data were analysed using mixed-effects modelling to allow for repeated measurements from the same infant. Models were adjusted for GA, birth weight (BW) z-score and sex.

RESULTS

429 scans were assessed for 144 infants included in this study. Mean (standard deviation) GA was 27.7 weeks (1.5), mean BW was 1,017 g (259) and mean number of scans per infant was 3 (range 1-8). Almost two-thirds of scans were performed < 28 days' postnatal age (PNA) but most infants had scans up to 33 weeks' postmenstrual age. Biparietal diameter (BPD), corpus callosum length (CCL), transcerebellar diameter (TCD) and vermis height (VH) increased with PNA, except the BPD in the first postnatal week. Slower BPD and ventricular width growth was associated with higher GA. Slower CCL, TCD and VH growth was associated with postnatal corticosteroids, and slower TCD growth was associated with sepsis and necrotising enterocolitis (NEC).

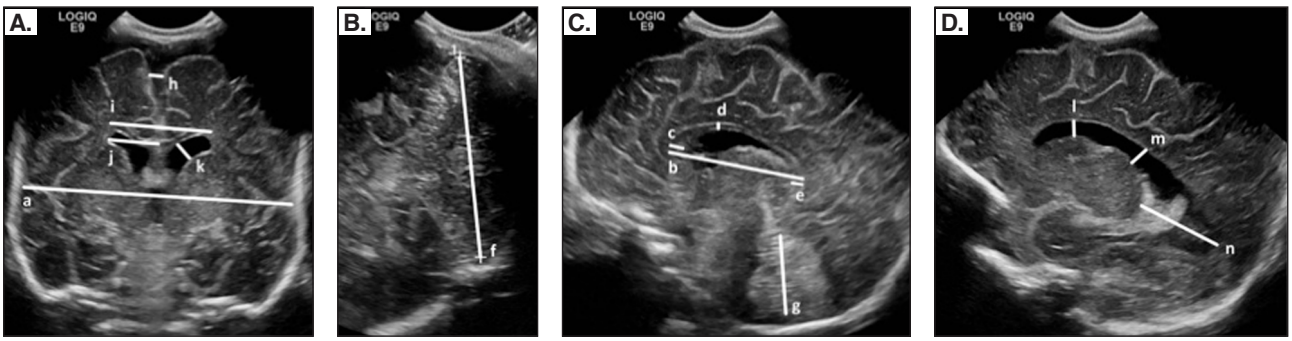

Figure 1 (ABS 86). Cranial ultrasonography linear measures (images through the anterior fontanelle in the coronal plane at the level of foramina of Monroe [**A**] and the sagittal [**C**] and para-sagittal [**D**] planes, and image through the mastoid fontanelle in the coronal plane posterior to the fourth ventricle [**B**]).

Brain tissue: (a) biparietal diameter; (b) corpus callosum length; (c) corpus callosum genu width; (d) corpus callosum body width; (e) corpus callosum splenium width; (f) transcerebellar diameter; (g) vermis height.
Fluid spaces: (h) interhemispheric distance; (i) ventricular width; (j) ventricular index; (k) anterior horn width; (i) anterior horn height; (m) ventricular midbody width; (n) thalamo-occipital distance.

CONCLUSIONS

Brain growth in very preterm infants can be assessed using simple linear measurements made on cUS. Several perinatal variables associated with long-term development, including GA, postnatal corticosteroids and sepsis/NEC, were associated with poorer early postnatal brain growth. Further research is needed to evaluate the utility of brain growth, as evaluated on cUS, as a marker of long-term developmental outcome.

ABS 87

NEUROFILAMENT SERUM LEVELS AS BIOMARKER OF NEURONAL INJURY IN VERY PRETERM BORN INFANTS

A. Depoorter[1], C. Barro[2], R. Neumann[3], J. Kuhle[2], S. Wellmann[3]

[1]Division of Neuropediatrics and Developmental Medicine, University of Basel Children's Hospital (UKBB), Basel, Switzerland

[2]Neurology, Departments of Medicine, Biomedicine and Clinical Research, University Hospital Basel, Basel, Switzerland

[3]Division of Neonatology, University of Basel Children's Hospital (UKBB), Basel, Switzerland

INTRODUCTION

Neurofilament light chains (NfL) are part of the unique cytoskeletal proteins of neurons, are shed to the cerebrospinal fluid, are detectable at low concentrations in peripheral blood of healthy adults and represent a highly promising serum biomarker of neuronal injury in adults. Prematurity is worldwide the leading cause of infant death and an important risk factor for neurodevelopmental deficits. Therefore early identification is needed to detect premature infants with an elevated risk for later neurodevelopmental disorders. The present pilot study investigates for the first time NfL serum levels in very preterm infants, aiming to understand the impact of prematurity on brain development.

METHODS

We performed a prospective observational study enrolling 99 very preterm infants with 28.6 ± 2.4 weeks of gestational age (GA) born at the University Hospital of Basel. Blood samples were taken at 7 days of life and NfL concentrations were measured using a newly developed ultrasensitive single-molecule array (Simoa). Clinical data and cranial ultrasound were recorded serially until discharge home. Statistical analyses included descriptive statistics, Spearman correlation analyses and multiple linear regression using NfL as dependent variable and GA, birth weight (BW), oxygen supply duration and intraventricular hemorrhage (IVH) as explanatory variables.

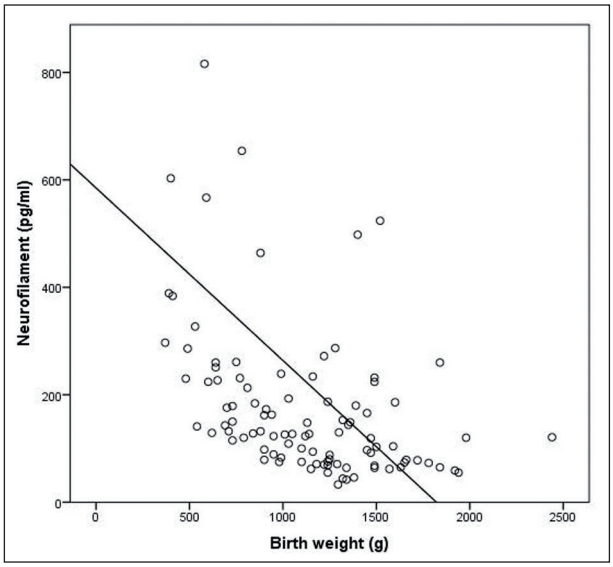

Figure 1 (ABS 87). NfL levels are negatively correlated with birth weight (BW).

RESULTS

The mean serum concentration of NfL was 224.12 (range 30 to 5,116) pg/ml. The NfL levels significantly ($p < 0.001$) correlated with GA ($r = -0.48$), BW ($r = -0.54$), Apgar score at 5 minutes ($r = -0.26$), duration of oxygen supply ($r = 0.38$), IVH ($r = 0.27$) and bronchopulmonary dysplasia (BPD) at 36 weeks GA ($r = 0.34$). A significant linear regression was found ($F[4,93] = 9.36$, $p < 0.001$) with an R^2 of 0.29. In particular GA ($\beta = 0.68$), BW ($\beta = -0.46$) and oxygen duration ($\beta = 0.57$) explained the most of the NfL serum levels.

CONCLUSIONS

Serum levels of the neuronal injury marker NfL are in very preterm born infants on average 10-fold higher than in healthy adults. NfL levels are negatively correlated with GA and BW (**Fig. 1**). Brain immaturity with high turnover of neurons, leakage of the blood brain barrier or the existence of neuronal injury associated with prematurity are possible explanations for the high serum NfL levels in preterm infants.

ABS 88

PREDICTING THE DEVELOPMENT OF CEREBRAL PALSY: A COMPARISON BETWEEN DTI-MRI AND EARLY HAND ASSESSMENT

IN INFANTS WITH UNILATERAL PERINATAL BRAIN INJURY

B. van Gasselt[1], N. Wagenaar[1], C. Verhage[2], M. Benders[1], F. Groenendaal[1], L. de Vries[1], N. van der Aa[1]

[1]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, the Netherlands

[2]Child Development and Exercise Center, Wilhelmina Children's Hospital, Utrecht, the Netherlands

INTRODUCTION

Unilateral perinatal brain injury, including periventricular hemorrhagic infarction and perinatal arterial ischemic stroke, is still a common problem in the neonatal intensive care unit. Both preterm and term born infants with unilateral perinatal brain injury are at risk for developing unilateral spastic cerebral palsy (USCP). Diffusion Tensor Imaging (DTI) performed within the first months after birth has been shown to predict USCP in later life. The Hand Assessment for Infants (HAI) is a promising new instrument to aid in the clinical quantification of hand asymmetry before the first year of age. This study aims to investigate the additional value of HAI in the prediction of USCP in infants suffering from unilateral perinatal brain injury.

METHODS

We included 22 preterm born and 22 term born infants with unilateral perinatal brain injury. Preterm born infants were scanned at term equivalent age (TEA), while term born infants were scanned during the first week after birth and again at three months of age. Fractional anisotropy (FA) was calculated from DTI-based tractography derived from manually placed region-of-interests in the corticospinal tracts. HAI was performed by an occupational therapist at 3, 6 and 9 months of age. Asymmetry indices (calculated as follows: 100*[score affected side – score non-affected side]/ score non-affected side) were derived from both techniques and the predictive values for USCP of both instruments were compared.

RESULTS

Assessment of the FA of the corticospinal tracts at TEA correctly predicted the development of USCP in all (PPV and NPV 100%) of 20 preterm born infants. HAI at three months correctly predicted motor impairment in all infants with abnormal CST measurements (PPV 100%), but had a low NPV (50%). All other HAI epochs had a PPV and NPV of 100%. For the term born infants, 16 (72.7%) neonatal DTI scans were available. The neonatal DTI correctly predicted development of USCP in 8 of 10 (PPV 80%, NPV 80%). At three months, a DTI was available in 19 (86.4%) infants and 9 out of 12 infants were accurately predicted to develop USCP in later life (PPV 75%, NPV 100%). HAI at 3 month had a PPV of 100%, but a low NPV of 69%. The HAI at 6 months predicted USCP correctly in 11 of 12 children (PPV 91.6%, NPV 100%). Every other HAI epoch correctly predicted USCP in all children (PPV 100%, NPV 100%).

CONCLUSIONS

Both DTI-based tractography of the corticospinal tract and early quantification of hand function by HAI are able to predict the development of USCP in children with unilateral perinatal brain injury. In preterm infants, DTI at TEA is the best predictor of USCP. In term infants, DTI is able to predict USCP correctly before 3 months of age. In health centers that are not able to offer DTI, HAI can be performed for prediction of USCP from 3 months onwards.

ABS 89

MICRORNA PANEL VALIDATION IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

M.P. O'Sullivan[1,2], A.M. Looney[1,2], G. Moloney[3], B. Hallberg[4], G. Clarke[5,6], G.B. Boylan[1,2], D.M. Murray[1,2]

[1]NBRG, Irish Central for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland

[2]Department of Pediatrics and Child Health, University College Cork, Cork, Ireland

[3]Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

[4]Neonatal department, CLINTEC, Karolinska Institutet and the Karolinska University Hospital, Stockholm, Sweden

[5]Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland

[6]APC Microbiome Institute, University College Cork, Cork, Ireland

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is one of the leading causes of neonatal death and long-term neurological disability. A reliable biomarker for early detection and grading of HIE remains elusive. We wished to examine the potential of microRNAs (miRs) to predict HIE.

METHODS

A discovery cohort of term infants was recruited at birth from 2009-2011; a validation cohort was recruited from 2013-2015 in Cork and Karolinska

using identical recruitment criteria and methods. Whole blood was biobanked at birth from the umbilical cord. Infants were grouped as perinatal asphyxia without HIE (PA), HIE and healthy controls. An exploratory microarray was followed by validation using RT-qPCR.

RESULTS

The discovery cohort consisted of 70 infants: 18 control, 33 PA, and 19 HIE (13 mild, 2 moderate and 4 severe). The validation cohort consisted of 74 infants: 24 control, 24 PA and 26 HIE (16 mild, 9 moderate and 1 severe). Following an exploratory microarray of 996 miRs, 13 miRNAs were chosen for validation in the discovery cohort. Of these 7/13 showed altered expression on RT-qPCR and were tested again in our validation cohort. Of these 2/7, showed persistent down-regulation compared to controls; miR-374a [median RQ (IQR) = 0.75 (0.31-1.86) vs 1.74 (1.25-2.18), $p < 0.03$], and miR-181b [0.39 (0.16-1.13) HIE vs 0.99 (0.84-1.32), $p < 0.04$ PA and 1.91 (0.87-2.88) controls, $p < 0.001$].

CONCLUSIONS

We have validated 2 miRNAs in umbilical cord blood in two separate well-defined cohorts which may have potential as diagnostic biomarkers for early detection of HIE and grade of injury at birth.

ABS 90

OUTBORN PRETERM INFANTS WITH POST-HAEMORRHAGIC VENTRICULAR DILATATION: ARE THEY TRANSFERRED TOO LATE?

A. Parodi[1], M. Malova[1], A. Sannia[1], A. Cama[2], M. Ravegnani[2], C. Bellini[1], L.A. Ramenghi[1]

[1]*Neonatal Intensive Care Unit, Istituto Giannina Gaslini, Genoa, Italy*

[2]*Neurosurgery Unit, Istituto Giannina Gaslini, Genoa, Italy*

INTRODUCTION

Post-haemorrhagic ventricular dilatation (PHVD) is a complication of intraventricular haemorrhage in preterm neonates. Timely neurosurgical intervention is often needed to resolve PHVD and prevent further brain injury. In line with the Levene criteria for ventricular indices, intervention is suggested and usually performed when the lateral ventricle reaches a diameter > 4 mm above the 97th percentile. However, surgical timing may sometimes be influenced by a delay in transferring the patient to a center with adequate neurosurgical expertise. The aim of this study was to assess the degree of PHVD among outborn preterm infants who were transferred to a third level NICU to receive treatment.

METHODS

A retrospective search through the clinical electronic database at Gaslini Institute of Genoa, Italy, was performed in order to identify outborn preterm infants transferred to our NICU from January 2012 to October 2016 because of PHVD. Subjects with fetal post-haemorrhagic hydrocephalus and subjects who had already received any kind of neurosurgical treatment were excluded. Collected data included gestational age at birth, age at transport, and ventricular size (i.e. Ventricular Index according to Levene), assessed by cranial ultrasound at admission to our NICU.

RESULTS

12 outborn patients with PHVD were transferred to our NICU in the selected period in order to receive neurosurgical treatment. Two of them were excluded because they had undergone a previous neurosurgical treatment, while one was excluded because born at term. Among the 9 selected preterm infants, mean GA at birth was 27.8 weeks. Mean postnatal age at transport was 4.8 weeks. Ventricular

Table 1 (ABS 90). Outborn preterm infants with post-haemorrhagic ventricular dilatation.

Patients	Gestational age at birth (weeks)	Gestational age at transport (weeks)	Right Ventricular Index (mm above 97th centile)	Left Ventricular Index (mm above 97th centile)
1	31	33	14.3	N/A (PVHI)
2	33	40	5.3	5.4
3	25	30	9.9	11.5
4	31	33	9	11
5	24	36	N/A (-3.5)	16.5
6	25	30	8.7	N/A (PVHI)
7	26	30	8.8	9.7
8	31	33	5	8.4
9	24	26	4.5	4.5

PVHI: periventricular haemorrhagic infarction.

Index of both lateral ventricles was available in 7 patients, while in 2 patients it was available only for one ventricle because of the presence of periventricular haemorrhagic infarction (PVHI) resulting in porencephaly on the contralateral side. All Ventricular Indexes (with the exception of the contralateral ventricle in one patient with monoventricular hydrocephalus) resulted largely higher than the conventional surgical cut-off of 4 mm above the 97th percentile (mean 8.8 mm; range 4.5-16.5 mm) (**Tab. 1**).

CONCLUSIONS

The degree of ventricular dilatation at admission was surprisingly very severe among outborn patients transferred to our NICU in order to undergo neurosurgical treatment. These data suggest that these infants should be transferred earlier to a center with adequate neurosurgical expertise in order to prevent brain injury deriving from not timely management of hydrocephalus.

ABS 91

CEACAM1 EXPRESSION IN THE CEREBELLUM

S. Prager[1], B.B. Singer[2], I. Bendix[1], J. Herz[1], U. Felderhoff-Müser[1]

[1]Department of Pediatrics 1 – Neonatology, University Hospital Essen, Essen, Germany

[2]Department of Anatomy, University Hospital Essen, Essen, Germany

INTRODUCTION

CEACAM1, a member of the Carcinoembryonic Antigen-related Cell Adhesion Molecules with functions in cell proliferation and differentiation, is expressed in oligodendrocytes of the developing rat forebrain in a spatio-temporal correlation with myelination. In addition, *in vitro* stimulation of primary oligodendrocytes of the forebrain with a CEACAM1 ligand resulted in increased myelination, suggesting a role of CEACAM1 in regulation of myelination. Cerebellar CEACAM1 expression was not analyzed yet. Aim of this work was to define CEACAM1 expression in the developing rat cerebellum.

METHODS

Ontogenetic CEACAM1 expression in the developing rat cerebellum was analyzed in paraffine sections of the cerebellum of Wistar rats from P3 (postnatal day 3) to P28 by immunohistochemistry (IHC). CEACAM1 expressing neural cell types were identified by co-staining of CEACAM1 and cell-type specific markers. Cerebellar primary oligodendrocyte cell cultures of Sprague-Dawley rats were cultured according to protocols well-established for forebrain primary oligodendrocytes. Immunocytochemistry (ICC) was performed according to standard protocols.

RESULTS

CEACAM1 is expressed in the developing cerebellum of the rat. CEACAM1 positive structures emerge between P7 and P11. Co-staining with MPB revealed CEACAM1 expression on oligodendrocytes in a spatio-temporal congruency to myelination, like in forebrain. CEACAM1 expression on oligodendrocytes was verified in primary cerebellar oligodendrocyte cell cultures by ICC.

CONCLUSIONS

Like in forebrain, CEACAM1 is expressed on oligodendrocytes of the developing rat cerebellum. Expression patterns of CEACAM1 and MPB, a protein of the myelin sheath, are almost congruent in the analyzed period of cerebellar development (P3-P28), supposing a role of CEACAM1 in myelination of the developing rat cerebellum. Identification of the underlying mechanisms is part of our current examinations.

ABS 92

LONG-TERM NEURODEVELOPMENTAL OUTCOMES AMONG YOUNG ADULTS BORN PRETERM

M. Tei[1], S. Negro[1], M.C. Muraca[1], M.G. Gatti[1], D. Urilli[2], G. Buonocore[1], S. Perrone[1]

[1]Department of Molecular and Developmental Medicine, General Hospital "Santa Maria alle Scotte", University of Siena, Italy

[2]Department of Psychiatry, University of Siena, Siena, Italy

INTRODUCTION

Advances in obstetric and neonatal medical care during the last two decades paved the way to increased survival rates of preterm and low birth weight infants. Nevertheless survival at the borderline of viability resulted in high risk for developmental problems including cognitive deficits, poor academic achievement, and behavior disorders. While numerous studies evaluated the prevalence of neurodevelopmental disability in early childhood, poor literature is available for infants born preterm or low birth weight in adolescence and adulthood.

METHODS

Fifty-five young adults, ranging from 16 to 23 years, who were born < 33 weeks of gestational age and/or with a birth weight < 1,500 grams, admitted to the NICU of Siena Hospital, were enrolled. All subjects with genetic or malformative syndromes, metabolic diseases and severe motor disabilities were previously excluded. The Verbal Intelligence Quotient (vIQ), Performance Intelligence Quotient (pIQ) and Total Intelligence Quotient (tIQ) were assessed through the Wechsler Adult Intelligence Scale – Revised (WAIS-R). Personality profiles were also investigated using the Rorschach test. Both WAIS-R and Rorschach results were subsequently compared to 6 controls of the same age range born at term. Data were analyzed with the SPSS® v20 for Windows® statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

The descriptive analysis of the population is reported in **Tab. 1**. Mann-Whitney's non-parametric test for independent samples with a 95% significance level was applied. Statistically significant differences between case and control group for vIQ (89.85 ± 21.85 versus 109.33 ± 11.73, respectively; p = 0.018) and tIQ (90.95 ± 22.46 versus 107.17 ± 7.91, respectively; p = 0.038) were found while there were no significant differences in pIQ (92.40 ± 22.9 versus 102.83 ± 12.89, respectively; p = 0.184). Regarding the Rorschach test, no differences emerged in personality profile as most subjects showed adequate internal resources in both groups (1.02 ± 1.13 versus 0.33 ± 0.52, respectively; p = 0.209). A trend towards anxiety and insecurity has been identified in the case group with regard to controls (1.36 ± 0.93 versus 0.67 ± 1.03, respectively; p = 0.153).

CONCLUSIONS

The present preliminary data highlight that extreme prematurity and very low birth weight may cause a wide range of neurodevelopmental disabilities including learning disorders, intellectual impairments and behavior disorders in adolescence and adulthood.

Table 1 (ABS 92). Descriptive analysis of the population.

	Cases (n = 55)	Controls (n = 6)
Age at evaluation time (years)	18.58 ± 2.42	20.83 ± 2.79
Sex (M/F)	31/24	3/3
Gestational age (weeks)	31.25 ± 2.72	38.67 ± 1.37
Birth weight (grams)	1,431.91 ± 319.15	3,183.33 ± 471.83
APGAR score at 1'	4.84 ± 2.57	9 ± 0
APGAR score at 5'	8.09 ± 1.76	10 ± 0

Data are presented as mean ± SD.

ABS 93

LOW-GRADE IVH AND LOW-GRADE CBH: WHICH INFLUENCE ON GRIFFITHS SCORE AT 2 YEARS OF AGE?

A. Parodi[1], M. Malova[1], S. Uccella[2], L. Boeri[2], E. De Grandis[2], A. Sannia[1], M. Severino[3], G. Morana[3], D. Tortora[3], A. Rossi[3], E. Veneselli[2], L.A. Ramenghi[1]

[1]*Neonatal Intensive Care Unit, Istituto Giannina Gaslini, Genoa, Italy*

[2]*Child Neuropsychiatry Unit, Istituto Giannina Gaslini, Genoa, Italy*

[3]*Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy*

INTRODUCTION

How low-grade intraventricular haemorrhage (LG-IVH) diagnosed with ultrasound impacts neurological outcome remains uncertain, as no significant influence have been shown in previous studies. Cerebellar haemorrhage (CBH) can share similar risk factors and pathogenesis with IVH, but two lesions could have different consequences for neurological outcome. Brain MRI performed at term-equivalent age (TEA) provides more accurate diagnosis of LG-IVH and low-grade CBH (LG-CBH) than ultrasound. The goal of present study was to investigate the influence of MRI-diagnosed isolated LG-IVH and LG-CBH on mental development at 2 years of age in a cohort of very preterm infants (gestational age ≤ 32 w).

METHODS

Very preterm infants admitted to our NICU who underwent brain MRI at TEA and completed Griffiths Mental Developmental Scale (GMDS) at 2 years of age were retrospectively identified and included in the study. MRI scans were performed at 1.5 T system and included T1, T2, diffusion and susceptibility weighted (SWI) sequences. LG-IVH was defined as presence of hemosiderin deposits inside germinal matrix and/or along the ependyma of the ventricles (as seen on SWI), in absence of ventricular dilatation or periventricular infarction. LG-CBH was defined as presence of punctate haemorrhagic lesions within cerebellum. GMDS scores were obtained by a single operator blinded to MRI results and analysed by comparing mean values in the group with isolated LG-IVH versus one with LG-CBH.

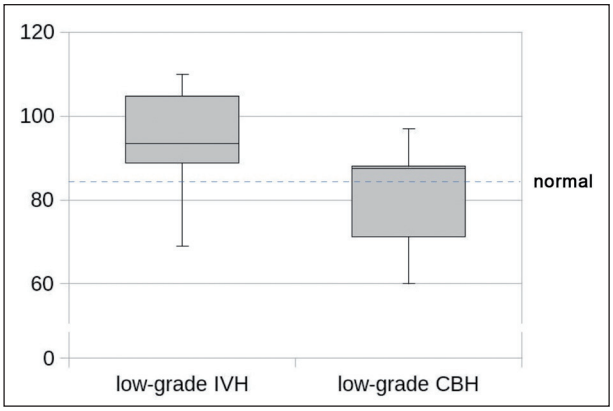

Figure 1 (ABS 93). Griffiths scale at 2 years of age.

RESULTS

The study group consisted of 173 patients (mean gestational age 28 weeks). When all grades of lesions were considered, prevalence of IVH (57 patients, 32.9%) was higher than prevalence of CBH (35 patients, 20.2%). Isolated low-grade IVH was found only in 8 patients (prevalence 4.6%), and isolated low-grade CBH in 10 (prevalence 5.8%). A Griffiths score of 85 was used as cut off for normal outcome. Mean Griffiths score was 94 in the group of low-grade IVH and 82 in the group of low-grade CBH (**Fig. 1**), but this difference did not reach statistical significance (p = 0.08), probably due to small group size. Mean gestational age was 28 and 27.5 weeks, respectively, in LG-IVH and LG-CBH groups (non-significant difference, p = 0.7).

CONCLUSIONS

Babies with LG-CBH show a trend for a more compromised neurological outcome at 2 years compared to those with LG-IVH. This finding seems not to be related to gestational age and may help to further investigate the contribution of each single disease to the development of very premature babies. Longer follow-up on this population is recommended in order to confirm higher risks for neurological impairments due to LG-CBH.

ABS 94

GENETIC CAUSES IN NEWBORNS WITH EPILEPTIC ENCEPHALOPATHIES

A. Soltirovska Salamo, D. Paro-Panjan

Division of Paediatrics, Department of Neonatology, University Medical Centre Ljubljana, Slovenia

INTRODUCTION

Early onset epileptic encephalopathies (EOEE) encompass a heterogeneous group of epileptic syndromes that manifest with seizures starting from early infancy, severe electroencephalographic (EEG) abnormalities, neurologic, cognitive and behavioural deficits and sometimes early death. Although they are mostly associated with perinatal asphyxia, structural brain malformations and inherited metabolic disorders, pathogenic gene mutations may also be involved. Based on the current literature, single gene variants explain at least 20 to 30% of epileptic encephalopathies (EE). Our aim was to determine the contribution of genetic aetiologies in a cohort of patients with EOEE.

METHODS

Seventy-eight newborns with EE and neonatal seizures where admitted to the Department of Neonatology between January 2012 and December 2016. After exclusion of children with perinatal asphyxia and dysmorphic features five (6.4%) newborns were studied retrospectively: time of occurrence and type of seizures, results of electroencephalography, magnetic resonance imaging and metabolic workup. Next-generation DNA sequencing was performed for patients without previously identified aetiologies from clinical or diagnostic work up evaluation.

RESULTS

Several genes including KCNQ2, TBC1D24, SPTAN1 and SCN1A have been found to be associated with EOEE. Suppression-burst EEG pattern and normal extensive metabolic work-up was present in all. Signal changes in the globus pallidus and hypomielinisation on brain MRI were present in two but were unremarkable in the rest. The initial seizures, which were mainly clonic and myoclonic, occurred within 1 h after birth in two siblings with heterozygous mutations in the TBC1D24 gene. The other three developed seizures during the first week of life including tonic in association with KCNQ2 and myoclonic in others. Seizures were resistant to treatment in all children but one. Severe developmental delay developed and severe progressive encephalopathy led to full deterioration in all and death during the first year in two children. Additionally profound sensory neural deafness in both siblings and coloboma-like optic discs were observed in children with SPTAN1 mutation.

CONCLUSIONS

Our data clearly demonstrated that genetic aetiologies are frequently involved in suppression-

burst EEG pattern in newborns, diagnosed as EOEE. Thus primary genetic causes should be included in the diagnostic approach of EE in newborns as increasing knowledge about EE in infancy influenced not only the diagnostic approach but also therapeutic guidelines.

ABS 95

OUTCOME AT FIVE YEARS OLD IN A SWISS NATIONAL COHORT OF VERY PRETERM INFANTS BORN IN 2006

M.P. Pittet[1], M. Adams[2], M. Bickle-Graz[3], S. Grunt[4], I. Mürner-Lavanchy[4], R.E. Pfister[1], G. Natalucci[2,5], C. Borradori Tolsa[1]

[1]Department of Child and adolescent, University Hospital, Geneva, Switzerland

[2]Department of Neonatology, University Hospital Zurich and University of Zurich, Zurich, Switzerland

[3]Clinic of Neonatology, Department Woman-Mother-Child, University Hospital Lausanne, Lausanne, Switzerland

[4]Division of Neuropaediatrics, Development and Rehabilitation, University Children's Hospital, University of Bern, Berne, Switzerland

[5]Child Development Center, University Children's Hospital, Zurich, Switzerland

INTRODUCTION

Although progresses in obstetric management and neonatal intensive care have improved the survival of very preterm (VP) infants, neurodevelopmental outcome of survivors remains a major concern. The Swiss Neonatal Network and Follow-up Group have prospectively collected neonatal and follow-up data of VP infants since 2000. Here we present the first evaluation of neurodevelopmental outcome at the age of 5 in a Swiss national cohort of VP infants. We focus on cognitive aspects and perinatal factors associated with cognitive outcome and the need for therapeutic intervention.

METHODS

Design: retrospective analysis of a prospective national cohort study. Population: 381 children born alive between $23^{0/7}$-$29^{6/7}$ weeks in Switzerland in 2006. Perinatal and demographic data were recorded online by each center. At 5 years of age, children underwent a neurologic examination and a cognitive assessment with the Kaufman Assessment Battery for Children, first edition. Main outcomes were measured with the Composite Mental Processes (CMP) score (expected mean [SD] of 100 [15]) and the main subscales of the test. Secondary outcomes were cerebral palsy (CP) graded with the Gross Motor Function Classification System, visual or hearing impairment and need for any type of therapy. Factors associated with CMP score < 1 SD below the mean were analyzed with logistic regression models.

RESULTS

Survival rate of VP at 5 years of age was 76% (289/381). Follow-up information was available for 235/289 (81% of eligible children), with 199 K-ABC results available. The mean CMP score was 92.5 (SD 12, range 62-121); 16% of the children had a CMP score < 1 SD and 9% has a score II on Papile classification), male sex and lower familiar socio-economic status (SES) were associated with a CMP score < 1 SD ($p = 0.001$, $p = 0.03$ and $p = 0.001$ respectively). Subtests of short-term memory showed that 118 (59%) children born VP had scores in number recall and word order that fell ≥ 1 SD below the mean. CP was diagnosed in 14 (6%) VP children, abnormal vision in 36 (15%), and hearing loss in 12 (5.5%). At 5 years of age, 26% of the subjects needed one or multiple therapies.

CONCLUSIONS

We provide the first data on neurodevelopmental outcome of children born VP in Switzerland at preschool-age. Compared to other cohorts, morbidity at 5 years in our population was similar. Brain injuries, male sex and SES were associated with cognitive difficulties. Short-term memory was affected with possible associations with later academic difficulties. Children born VP need a long-term follow-up with a special attention to short term memory.

ABS 96

PLACENTAL HISTOLOGY FINDINGS AS POSSIBLE RISK FACTORS FOR MRI-DETECTED BRAIN LESIONS IN VLBW INFANTS

A. Parodi[1], M. Re[1], D. Brignole[1], M.P. Brisigotti[2], M.G. Calevo[3], M. Malova[1], A. Sannia[1], M. Severino[4], G. Morana[4], D. Tortora[4], A. Rossi[4], E. Fulcheri[2], L.A. Ramenghi[1]

[1]Neonatal Intensive Care Unit, Istituto Giannina Gaslini, Genoa, Italy

[2]Feto-Perinatal Pathology Unit, Istituto Giannina Gaslini, Genoa, Italy

[3]Epidemiology, Biostatistics and Committees Unit, Istituto Giannina Gaslini, Genoa, Italy

[4]Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy

INTRODUCTION

Various perinatal factors can influence development of prematurity-related brain lesions, but their

Table 1 (ABS 96). Perinatal risk factors for germinal matrix-intraventricular haemorrhage (GMH-IVH).

Risk factors	GMH-IVH (n = 68)	Controls (n = 218)	OR (95% CI)	p-value
Apgar score at 5th min ≤ 5	10.3%	1.8%	6.62 (1.48-29.6)	0.01
Incomplete or no antenatal steroids	24.4%	19.2%	2.45 (1.17-5.16)	0.02
Maternal hypertension/preeclampsia	11.8%	21.6%	0.26 (0.09-0.72)	0.009
Mechanical ventilation in the first 72 hours of life	72.1%	45.9%	2.14 (1.09-4.20)	0.03
Surgical ligation of ductus arteriosus	23.5%	6.9%	3.45 (1.45-8.18)	0.005
Umbilical vein vasculitis	22.1%	9.2%	3.80 (1.59-9.06)	0.003
Villous infarction	25%	10.5%	5.94 (2.49-14.2)	0.0001

precise individual roles are yet to be defined. In particular, the role of placental inflammation in the development of ultrasound-detected white matter lesions and intraventricular haemorrhage is still matter of debate. The goal of our study was to identify perinatal risk factors, with particular attention to placental histopathology, for MRI-diagnosed brain lesions in a cohort of VLBW infants.

METHODS

All VLBW infants born in our hospital between January 2012 and October 2016 who had received a term equivalent age brain MRI scan as a part of follow-up program were retrospectively identified. Scans were performed at 1.5 T system and included T1, T2, diffusion and susceptibility weighted sequences. Among the identified patients, only newborns with an available placental histology were included in the study. Perinatal data including placental histology were collected from NICU electronic database and clinical charts. Univariate and multivariate analyses of potential risk factors were performed for germinal matrix-intraventricular haemorrhage (GMH-IVH), cerebellar haemorrhage (CBH), cystic periventricular leukomalacia (c-PVL) and punctate white matter lesions (PWML).

RESULTS

The study group consisted of 286 patients. Independent risk factors for GMH-IVH (prevalence: 23.8%) identified by multivariate analysis are shown in **Tab. 1**. As for CBH (prevalence: 16.8%), multivariate analysis identified the use of inotropic support within 72 h after birth (OR 5.24) and contemporary presence of GMH-IVH (OR 6.38) as independent risk factors. In our study, placental characteristics, including chorioamnionitis, were not identified as independent risk factors for white matter lesions, including both c-PVL (prevalence: 2.4%) and punctate white matter lesions (prevalence: 19.9%).

CONCLUSIONS

Our study shows that placental inflammation or infarction is risk factor for the development of GMH-IVH, a disease occurring in the first days of life. Moreover, Apgar score and incomplete or absent antenatal steroid prophylaxis are confirmed risk factors for GMH-IVH. Interestingly, chorioamnionitis is not associated to MRI-diagnosed white matter lesions, in contrast with previous studies based mainly on ultrasound findings.

ABS 97

SYSTEMIC INFLAMMASOME ACTIVATION IN NEONATAL ENCEPHALOPATHY

M. O'Dea[1-5], L. Kelly[1-3], J.J. O'Leary[2,3], E.J. Molloy[1-6]

[1]Department of Paediatrics and Child Health, Trinity College Dublin, Dublin, Ireland

[2]Trinity Translational Medicine Institute, St James Hospital, Dublin, Ireland

[3]Coombe Women and Infant's University Hospital, Dublin, Ireland

[4]National Maternity Hospital, Dublin, Ireland

[5]National Children's Hospital, Tallaght, Dublin, Ireland

[6]Our Lady's Children's Hospital Crumlin, Dublin, Ireland

INTRODUCTION

Systemic inflammation has been demonstrated in both animal and human models of neonatal brain injury. The inflammasome is a multiprotein complex in immune cells that has been implicated in a range of inflammatory disorders and has not been studied in Neonatal Encephalopathy (NE). Components of the Inflammasome need exploration as potential therapeutic targets in NE, as an adjunctive treatment to Therapeutic Hypothermia. Our aim was to profile the Inflammasome components, Interleukin (IL)-1β and ASC (Apoptosis-associated Speck-like protein containing a carboxy-terminal CARD), and NLR Family Pyrin Domain Containing 3 (NLRP3) in week one of life in patients with NE.

METHODS
This was a prospective observational study in Infants with NE grade II/III requiring therapeutic hypothermia. Serial blood samples were analysed at two timepoints on day 1 to 3 of life and compared to healthy term neonatal controls. Quantitative real time PCR analysis of inflammasome components IL-1β, NLRP3 and ASC in infants with NE (n = 10) was compared to healthy neonatal controls (n = 5) in response to endotoxin stimulation (Lipopolysaccharide: LPS). RT-PCR analysis was carried out on the ABI 7900 with analysis using GraphPad Prism Version 7.
RESULTS
IL-1β expression was increased on day 1 and day 3 and very responsive to LPS stimulation, day 1 (p-value 0.009) and day 3 (p-value 0.01). NLRP3 was increased day 1 and decreasing by day 3 in NE. It is upregulated in response to LPS stimulation on day 1 (p-value 0.15) and day 3 (p-value 0.009). ASC was increased day 1 NE and further increased on day 3 life. It is further upregulated in response to LPS stimulation on day 1 (p-value 0.3) but not day 3 (p-value 0.4).
CONCLUSIONS
The results add evidence of inflammasome activation in NE and its upregulation in response to LPS. The inflammasome and inhibition of systemic inflammation may have a role as a future immunomodulatory therapeutic target in NE.
DECLARATION OF INTEREST
Health Research Board Ireland Funding.

ABS 98

LONGITUDINAL STUDY OF BRAIN TISSUE VOLUMES IN PRETERM INFANTS AND THEIR RELATION WITH NEONATAL RISK FACTORS AND NEURODEVELOPMENTAL OUTCOME

L. Gui[1], F. Lazeyras[2], P.S. Hüppi[1], C. Borradori[1]

[1]Division of Development and Growth, Department of Child and adolescent, University Hospital, Geneva, Switzerland
[2]Department of Radiology and Medical Informatics, University Hospital, Geneva, Switzerland

INTRODUCTION
Compared with full term, preterm infants are at risk for adverse neurodevelopmental outcomes. However, it is still not well established whether abnormalities in brain structure at birth or term equivalent age (TEA) are associated with subsequent neurodevelopmental outcome. Longitudinal analyses are sparse, limiting our understanding of how preterm birth affects brain growth from birth to TEA. The aim of this study was to explore the relationship between brain volumes at birth and at TEA with perinatal factors and neurodevelopmental outcome at 2 and 5 years of age in a cohort of preterm children free of major brain lesions.
METHODS
MRI data of infants (n = 84) born between 26 and 36 GA were acquired at birth and at TEA. Volumes of cortical gray matter (CGM), unmyelinated white matter, subcortical gray matter (SGM), cerebellum, brainstem, and cerebrospinal fluid (CSF) were measured with the method of Gui1. Volume growth speed (GS) between birth and TEA was calculated. Neurodevelopmental outcome was assessed via the BSID II at 24 months and the K-ABC at 5 years. Association between developmental outcome and perinatal factors, tissue volumes and GS were investigated via multivariate linear regression by comparing (F-test) R^2 values of two linear regression models: a) outcomes versus family socio-economic status (SES), GA at birth, gender, birth weight z-score and perinatal risk factors; b) model a) adding as regressors 3 groups of variables: volumes at birth, at TEA and volume GS.
RESULTS
At birth, all cerebral volumes were significantly associated with GA and with birth weight z-score. At TEA, infants who were diagnosed with patent ductus arteriosus had lower volumes of SGM (MD 2.33 ml, 95% CI 0.93-3.74) and cerebellum (MD 3.05 ml, 95% CI 1.15-4.94). Sepsis was related with lower intracranial (MD 34.56 ml, 95% CI 7.23-61.91) and CSF volumes (MD 23.31 ml, 95% CI 12.51-34.1). Volume GS of CGM, SGM and cerebellum were significantly associated with GA at birth. SES was associated with cognitive outcome at 2 and 5 years (model a), but not with motor outcome. The addition of volumes at birth and at TEA, and volumes GS in the analysis (model b) yielded an increase of the model R^2 for motor outcome at 2 years by adding the volumes at birth (R^2 difference = 0.159, p .023), and for cognitive outcome at 5 years by adding the volume GS (R^2 difference = 0.171, p .045).
CONCLUSIONS
Several perinatal factors are associated with brain volume changes at TEA and SES is associated with cognitive outcome. Brain volume GS is dependent on GA at birth. This may indicate that

the longitudinal brain growth trajectory is different between extremely and moderately preterm children. Our results suggest that the volumetric assessment at birth and TEA contributes to the prediction of outcomes, but their relevance remain limited.

ABS 99

DELINEATING THE BEHAVIOURAL PHENOTYPE AMONG CHILDREN BORN EXTREMELY PRETERM

J. Trickett[1], D. Wolke[2], C. Hollis[3], N. Marlow[4], S. Johnson[1]

[1]*Department of Health Sciences, University of Leicester, Leicester, UK*

[2]*Department of Psychology and Health Sciences Research Institute, University of Warwick, Coventry, UK*

[3]*School of Medicine, University of Nottingham, Nottingham, UK*

[4]*Institute for Women's Health, University College London, London, UK*

INTRODUCTION

A recent review has suggested that there is a consistent "preterm behavioural phenotype" comprising a high risk for anxiety, inattention and autism spectrum symptoms relative to term-born controls [1]. Whilst this pattern of outcomes has been reported across a number of different studies, the extent to which the preterm behavioural phenotype describes a homogenous group of extremely preterm children has not been established.

METHODS

We used data from 182 children born < 26 weeks gestation from the EPICure study who were evaluated at 11 years. An exploratory hierarchical cluster analysis was conducted using Ward's method and the squared Euclidean distance with these variables: the social communication, reciprocal social interaction, and repetitive and restrictive interests subscales of the Social Communication Questionnaire (SCQ), three items from the Strengths and Difficulties Questionnaire (SDQ) emotional subscale that refer to anxiety, and the inattention subscale of the Du Paul ADHD Rating Scale IV (ADHD-RSIV). Outcomes on the SCQ, SDQ conduct, peer problems, prosocial behaviour, anxiety, ADHD-RSIV inattention and hyperactivity subscales were compared between each extremely preterm cluster and a term-born control group.

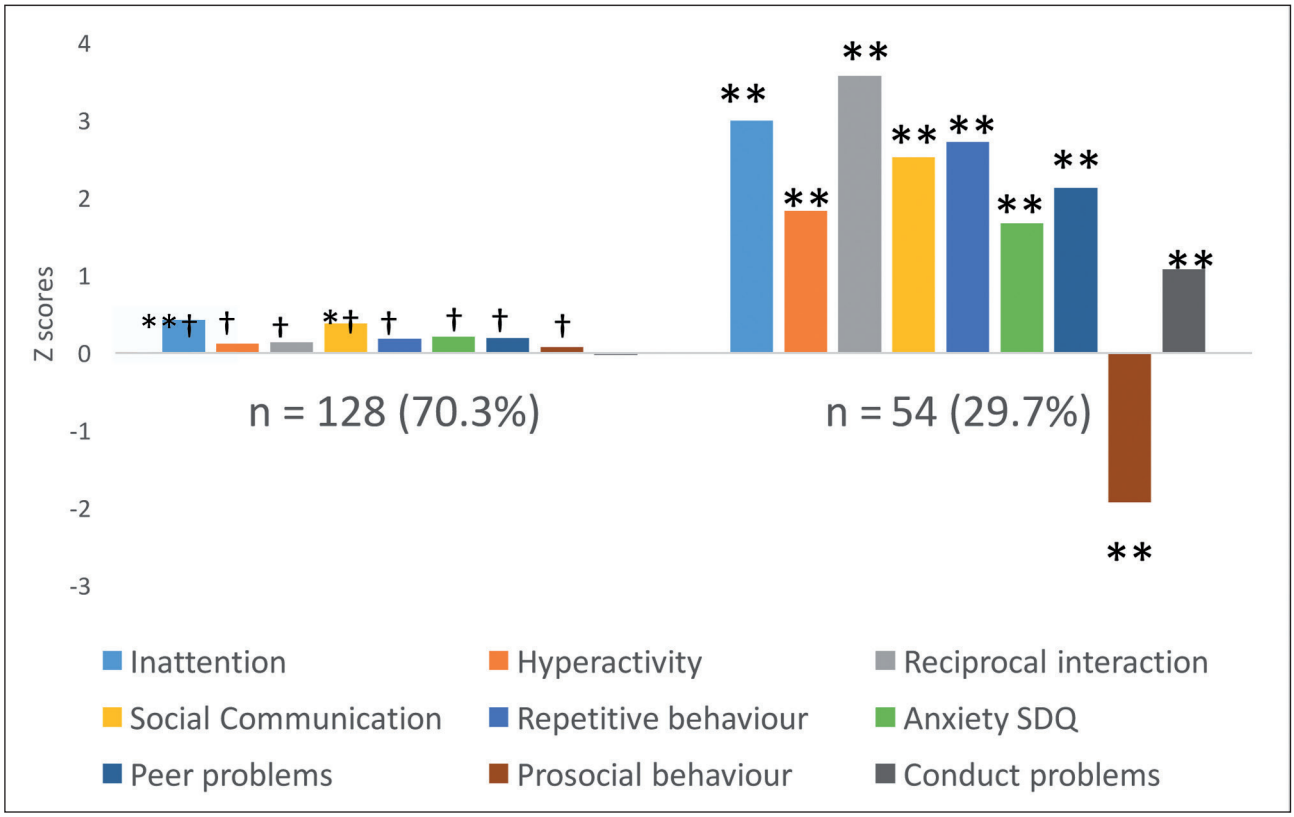

Figure 1 (ABS 99). Comparison of Social Communication Questionnaire, DuPaul ADHD Rating Scale IV, Strengths and Difficulties Questionnaire and subscales between two extremely preterm (EP) clusters and children born at term.

*p < 0.05 difference between cluster and control group; **p < 0.001 difference between cluster and control group; † p < 0.001 difference between large and small cluster; Z score 0= mean score children born at term, 1= SD of children born at term.

RESULTS

These preliminary analyses identified two clusters of extremely preterm (EP) children. The larger cluster (n = 128, 70.3%) had significantly poorer social communication, lower IQ scores (mean difference -12.8; 95% CI -15.6, -10.0) and showed greater inattention than term-born children, but no significant excess of other autism spectrum symptoms, conduct, anxiety, peer problems, prosocial behaviour or hyperactivity. The smaller cluster (n = 54, 29.7%) had significantly lower IQ scores than both the larger EP cluster (mean difference -16.2; CI -20.8, -11.6) and the term-born group (mean difference -29.0; CI -34.0, -24.0), and greater inattention, hyperactivity, autism spectrum symptoms, social and behavioural difficulties than either the term born group or the larger EP cluster (**Fig. 1**).

CONCLUSIONS

Two behavioural phenotypes are associated with extremely preterm birth, the more severe of which comprises 30% of children with comorbid problems across a range of dimensions. Further research is needed to identify predictors of this poorer outcomes cluster at age 11, the persistence of these problems and whether the translation of standard interventions for social, emotional and behavioural difficulties is appropriate for this group.

REFERENCE

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ABS 100

NANOMOLECULAR SIGNALLING IN THE DEVELOPING BRAIN: CHARACTERISTICS OF EXOSOMES IN THE CEREBROSPINAL FLUID OF PRETERM INFANTS

R. Spaull[1]*, B. McPherson[1]*, A. Clayton[2], J. Uney[1], O. Cordero-Llana[1], A. Heep[1,3]

**Joint responsibility as first author*

[1]Stem Cells and Neuroregeneration Research Group, School of Clinical Sciences, University of Bristol, Bristol, UK

[2]Division of Cancer & Genetics, School of Medicine, Cardiff University, Cardiff, Wales, UK

[3]Southmead Hospital, North Bristol NHS Foundation Trust, Bristol, UK

INTRODUCTION

Extracellular vesicle signalling has been recognised to play a key role in cellular interaction both in neurogenesis and neuroregeneration. Exosomes present the endosome-derived category of extracellular vesicles, released from a variety of cells contributing to intercellular communication. Exosomes are enriched in small non-coding RNAs (sncRNAs), in particular micro RNAs (miRNAs). Exosome signalling is crucial for maintaining neuronal integrity [1].

METHODS

Cerebrospinal fluid (CSF) was taken from ventricular access devices placed in the lateral ventricles of preterm infants with evolving posthaemorrhagic ventricular dilatation (Ethics: NHS REC: 15-YH-0251). CSF was centrifuged to remove cellular material and frozen within 1 hour of collection at -80°C. Concentration of extracellular vesicles (EVs) in thawed CSF was determined using a NanoSight NS300 nanoparticle tracking analyser (NTA). EVs were isolated using differential ultracentrifugation, and characterised using transmission electron microscopy (TEM) using negative staining with uranyl acetate and gold immunolabelling of CD63 and CD81. RNA was extracted from lysed EVs using the mirVana miRNA isolation kit. Specific candidate miRNA expression (serum exosome-specific: miR-17; Brain/CSF specific: miR-9, miR-26a, miR-124, miR-1911) were analysed using real-time PCR (qRT-PCR; TaqMan MicroRNA assays).

RESULTS

NTA analysis of thawed CSF (n = 11 samples) from 3 preterm infants across 26 to 42 weeks corrected gestational age consistently demonstrated particles in the exosomal fraction (30-100 nm) (1.48-1.59 x 10^{10} particles per mL of CSF; **Fig. 1A**). The size of these particles increased with corrected gestational age (83.6 nm (mode) at 26 weeks to 122.6 nm (mode) at 42 weeks CGA; $R^2 = 0.74$, $p = 0.027$) while particle concentration declined with time following injury.

TEM with negative staining of EVs isolated by differential ultracentrifugation demonstrated multiple spheroids with lipid bilayers meeting the size and expected morphology of exosomes (**Fig. 1B**). Further, immunogold staining for CD63 and CD81 demonstrated these EVs express these exosomal markers. miRNAs were successfully detected by qPCR in all 3 patients and at all time-points. Relative concentration of serum exosome-specific miRNA reduced with time post haemorrhage. Brain and CSF exosome-specific miRNAs could be detected at all time points further suggesting the central nervous system as the origin of these EVs.

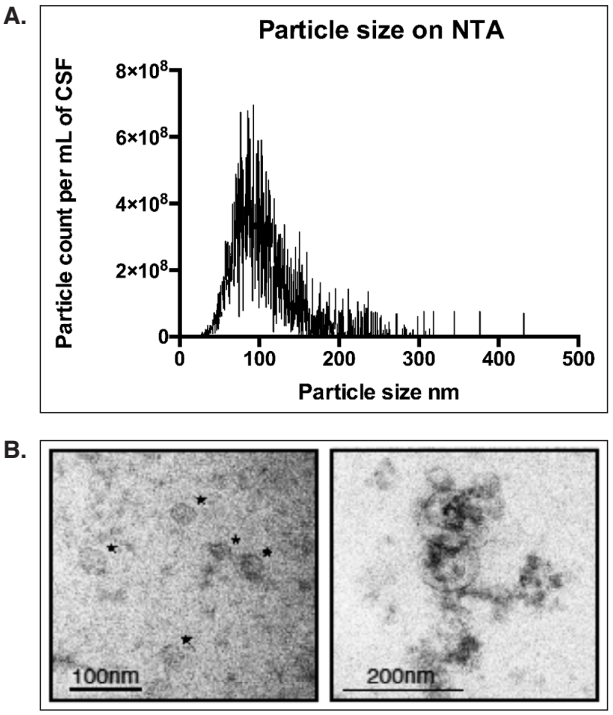

Figure 1 (ABS 100). A. Nanotracking analysis (NTA) of CSF nanoparticles. Particle concentration by size of particle, vertical bars represent standard error of measurement. **B.** Transmission electron micrographs using a uranyl-acetate negative stain demonstrating extracellular vesicles consistent with exosomes.

CONCLUSIONS

This is the first report of isolation and characterisation of brain-specific exosomes from the CSF of preterm infants combining NTA, TEM and immunogold labelling of exosome-specific proteins. Our results describe a time course of microRNA expression and support the idea that exosome signalling is involved in early brain development, potentially supporting the importance of maintaining integrity following perinatal brain injury.

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ABS 101

BEDSIDE MONITORING OF CEREBRAL METABOLISM IN NEONATES AT RISK FOR HYPOXIC-ISCHEMIC ENCEPHALOPATHY

M. El-Dib[1], S.J. Blackwell[2], F. Yi[2], R. Vyas[2], C.G. Ha[2], B. Walsh[1], T.E. Inder[1], P.E. Grant[2], S.L. Ferradal[2]

[1]*Brigham and Women's Hospital, Boston, MA, USA*

[2]*Boston Children's Hospital, Boston, MA, USA*

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) occurs in 1-6/1,000 live term births with devastating neurological consequences. Therapeutic hypothermia (TH), the only available treatment with proven efficacy, is primarily effective via decreasing cerebral metabolism. Current monitoring tools lack the ability to track cerebral metabolism and thus fail to provide individualized treatment. Herein, we use two non-invasive optical techniques to quantify cerebral oxygen saturation (SO_2), cerebral blood flow (CBFi) and cerebral oxygen metabolism ($CMRO_2i$) in term neonates at risk of HIE undergoing TH and compare to healthy controls.

METHODS

Two cohorts of term infants were recruited from the NICU and well-baby nurseries at Boston Children's Hospital and Brigham and Women's Hospital: 12 neonates undergoing TH (GA = 36.1-40.1 weeks; 9M/3F) and 15 healthy neonates (GA = 36.6-40.6 weeks; 9M/6F). Daily measurements of SO_2, CBFi and $CMRO_2i$ were performed at the bedside during the first week of life. Frequency-domain NIRS (FD-NIRS) and diffuse correlation spectroscopy (DCS) systems were used for measuring SO_2 and CBFi, respectively. Cerebral metabolism was computed as $CMRO_2i = 1.39 \times Hgb \times CBFi \times (SaO_2\text{-}SO_2)$, where arterial oxygen saturation (SaO_2) was recorded from clinical pulse oximetry and hemoglobin concentration (Hgb) was measured from blood samples. Fractional tissue oxygen extraction (FTOE) is defined as $(SaO_2\text{-}SO_2)/SaO_2$.

RESULTS

In neonates undergoing TH, CBFi and $CMRO_2i$ were lower during the cooling stage when compared with healthy neonates, with the $CMRO_2i$ decrease reaching statistical significance. Compared to the hypothermic state, significant increases in CBFi and $CMRO_2i$ occurred during both rewarming and normothermia stages (**Fig. 1**). In contrast, measurements of SO_2 and FTOE did not show a clear trend (**Fig. 1**). A qualitative comparison with temperature also suggests that $CMRO_2i$, and to a lesser degree CBFi, are positively correlated with core temperature values.

CONCLUSIONS

Despite the limited sample size, our results suggest that $CMRO_2i$ reflects longitudinal changes in metabolic activity during different stages of TH treatment. In contrast, traditional

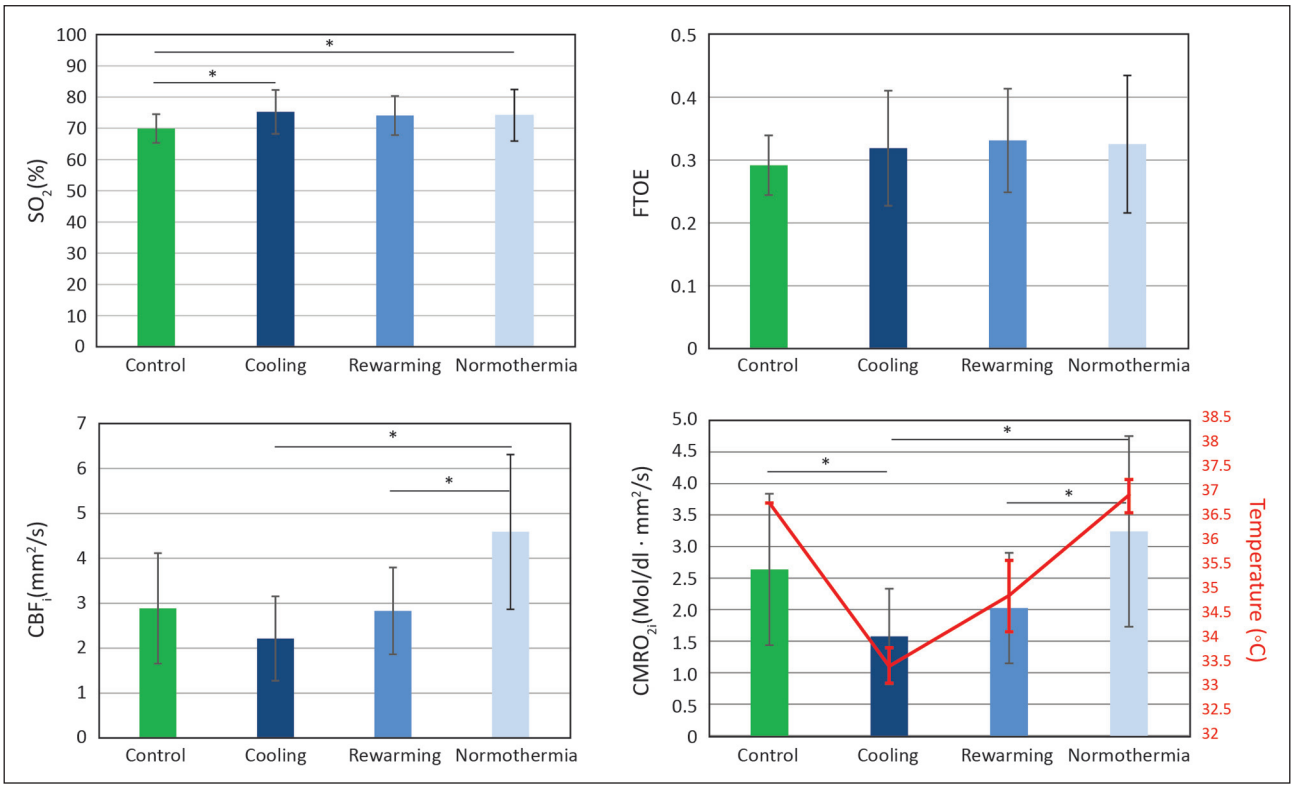

Figure 1 (ABS 101). Cerebral hemodynamic variables measured in a cohort of healthy controls (green) and in neonates at risk of HIE during different stages of TH treatment: cooling (dark blue), rewarming (blue) and normothermia (light blue). Control measurements were taken daily for the first three days of life and averaged together. Mean temperature is overlaid onto $CMRO_2i$ values obtained at each stage. Standard deviations from the mean are shown for each category. Statistical significance is denoted by *.

parameters such as SO_2 and FTOE provided by commercial devices may not be sensitive to different stages of treatment. FD-NIRS/DCS technology can potentially offer a biomarker for tracking treatment progress and individual optimization for neonates at risk of HIE.

ABS 102

POSTNATAL MR-IMAGING AND ADC MEASURES IN CONGENTIAL CYTOMEGALOVIRUS INFECTION PROVIDE AN ADDED DIAGNOSTIC VALUE ON CEREBRAL ULTRASOUND IN CHARACTERIZING WHITE MATTER DISEASE

C. Martins[1], J. Schneider[2], M. Bickle Graz[3], M. Kobas[1], S. Asner[4], A.C. Truttmann[5]

[1]*University of Lausanne, Lausanne, Switzerland*

[2]*SickKids Hospital, University of Toronto, Canada*

[3]*Follow up Unit, Department of Mother Women and Child, University Hospital Center, Lausanne and University of Lausanne, Lausanne, Switzerland*

[4]*Infectious Disease Unit, Department of Mother Women and Child, University Hospital Center, Lausanne and University of Lausanne, Lausanne, Switzerland*

[5]*Clinic of Neonatology, Department of Mother Women and Child, University Hospital Center, Lausanne and University of Lausanne, Lausanne, Switzerland*

INTRODUCTION

Congenital Cytomegalovirus (cCMV) infection carries heavy long term clinical neurological burden, but not much has been reported so far regarding the most appropriate diagnostic imaging tools and which lesions would qualify for treatment. One of the cerebral affections seen postnatal in cCMV is white matter disease (WMD), often temporal, developing in the late trimester, which could potentially benefit from early postnatal treatment. The objective of this retrospective cohort study was to compare in cCMV infants the respective diagnostic values of postnatal cerebral ultrasound (cUS) and MRI in relation to the lesions seen in cCMV and particularly WMD, and to determine the added value of ADC values measured in 6 different regions of interest (ROIs) of the WM.

METHODS

All patients born between 2004 and 2016 with confirmed cCMV infection using postnatal PCR

(urinary or saliva), evaluated with both postnatal cUS (GE, Vivid) and MRI (3T, conventional T1 and T2 sequences and Diffusion Weighted Imaging) were included. Clinical, epidemiological and imaging data were collected and analyzed. Measures of ADC were performed according to a standardized protocol in 6 different ROIs of the frontal, parietal and temporal WM (left and right).

RESULTS

26 newborns (19 f) were included, 1 patient died at DOL 8; 14 were neurologically symptomatic (≥ 2 symptoms: microcephaly < P3 [n = 7], abnormal: cUS [n = 12], MRI [n = 14], evoked auditory potentials [n = 8]). Cerebral findings were germinolytic pseudocysts in 62% (n = 16), WMD in 50% (n = 13) and ventricular dilatation in 35% (n = 9). When considering all cerebral findings, 15 cUS (58%) against 23 MRIs (88%) were pathological. After a second look on cUS, 80% were considered pathological. Mean ADC values were significantly increased in all cCMV patients, compared to normative values, with 189 (± 16), 180 (± 14) and 175 (± 25) mm^2/sec in parietal, frontal and temporal WM respectively. In the presence of WMD, mean ADC values were 198 (± 26), 185 (± 24) and 194 (± 35) mm^2/sec in parietal, frontal and temporal WM respectively, significantly higher than patients without WMD ($p < 0.05$) in frontal and temporal WM.

CONCLUSIONS

In a cohort of patients with cCMV infection, WMD reported from patients represented 50% of all anomalies found. While MR imaging was concordant to cUS for usual findings such as pseudocysts or ventriculomegaly, it was definitively superior and provided an added value to cUS for the diagnosis of temporal lesions (cysts) and particularly WMD, not only temporal but also frontal, suggesting to be a valuable tool for WMD identification and quantification and possible tailoring to the postnatal treatment. The definitive clinical long-term value of WMD has yet to be determined.

ABS 103

COMPARISON OF 1-DIMENSIONAL AND 2-DIMENSIONAL SONOGRAPHIC (US) AND MRI MEASUREMENTS OF THE CEREBELLUM IN TERM NEWBORNS

B. Reulecke[1], R. Fernandez[1], M. Mills[2], V. Pelling[2], H. Rabe[3], L. Harris[2]

[1]Department of Neonatology, Royal Sussex County Hospital, Brighton & Sussex University Hospitals NHS Trust, Brighton, UK

[2]Department of Medical Physics, Royal Sussex County Hospital, Brighton & Sussex University Hospitals NHS Trust, Brighton, UK

[3]Academic Department of Paediatrics and Neonatology, Brighton & Sussex Medical School, Brighton, UK

INTRODUCTION

Developmental abnormalities and acquired postnatal injuries of the cerebellum are linked to neuro-developmental disorders. Neonatal neuroimaging may allow earlier diagnosis and intervention. MRI is often considered the most sensitive imaging modality. However, MRI is lengthy, expensive and requires patient sedation. Conversely, US can repeatedly be performed at the bedside and is inexpensive. If measurements obtained from cranial US correspond well to their MR counterparts they may be used for the same diagnostic purposes. We therefore aimed to assess the level of correspondence between MRI and US measurements of the cerebellum.

METHODS

Images of 10 term, appropriate for gestational age neonates with a diagnosis of hypoxic ischaemic encephalopathy were analysed, for which 2D T1 and T2 MRI and cranial US images existed. The structure of the neonatal cerebellum visualised in MRI and with a phased array US probe was compared in different planes. Both modalities were compared for linear measurements in two dimensions as well as perimeter and surface area (in sagittal plane: anterior-posterior, cranio-caudal, perimeter and surface area; in coronal: bilateral diameter). Measurements were repeated 3x for each variable for each patient by two different examiners. Perimeter measurements in sagittal plane were also compared to a sonographically determined gestational age dependent formula. Image viewing and measurements were performed using ImageJ1.48v Software, USA. Data are presented as median and IQR and statistical significance was assessed using Mann-Whitney U test and Pearson Correlation Coefficient; $p < 0.001$ was considered statistically significant.

RESULTS

There were no statistically significant differences in all measurements between US and MRI. However, correlation was weak for linear measurements and moderate for perimeter and surface area (**Tab. 1**). The perimeter formula did have a weak correlation to our US measurements and a moderate correlation to MRI. An analysis

Table 1 (ABS 103). Displayed are median, interquartile range (IQR) and correlation coefficient between MRI and US; p < 0.001 significant.

	US	MRI	r-value	p-value
AP (cm)	1.9 (1.6-2.2)	1.7 (1.4-2)	0.4890	0.0106
CC (cm)	2.9 (2.7-3.1)	2.8 (2.3-3.2)	0.4638	0.1707
Area (cm^2)	5.1 (4.3-6.4)	4.9 (2.9-5.3)	0.5959	0.0016
Perimeter (cm)	9.3 (8.8-10)	9.1 (7-9.5)	0.6282	0.0080
Width (cm)	5.8 (5.5-6.4)	5.6 (4.9-6.2)	0.3565	0.0574

of intra- and inter-observer variability was not available at the time of submission, but is in process.

CONCLUSIONS

US measurements of the cerebellum correlate at best moderately well with MRI and should therefore be used with caution. The use of perimeter and surface area of the vermis appears to be the most encouraging and warrants further investigation in relation to recent literature from antenatal assessments of specific diseases. The use of a perimeter formula appears to be feasible up to term age and might help reduce assessment bias in comparison to MRI.

ABS 104

MILD HYPOXIC ISCHAEMIC ENCEPHALOPATHY AND LONG TERM NEURODEVELOPMENTAL OUTCOME – A SYSTEMATIC REVIEW

J. Conway[1,2,3], B.H. Walsh[4,5], M. Dozier[3], G.B. Boylan[1,2], D.M. Murray[1,2]

[1]Irish Central for Fetal and Neonatal Translational Research, University College Cork, Cork, Ireland

[2]Department of Pediatrics and Child Health, University College Cork, Cork, Ireland

[3]University of Edinburgh, Erskine Medical Library, Edinburgh, UK

[4]Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Boston, MA, USA [5]Division of Newborn Medicine, Boston Children's Hospital, Boston, MA, USA

INTRODUCTION

Despite the introduction of therapeutic hypothermia (TH) Hypoxic Ischaemic Encephalopathy (HIE) remains a significant cause of long term neurodisability. Approximately 50% of infants with HIE are graded as mild are traditionally perceived to have a low risk of disability and not currently eligible for TH. This review aims to examine the available evidence for outcome in term infants with mild HIE.

METHODS

Medline, Embase and *Cochrane* Clinical Trials databases were searched from inception to March 2017. Only studies with clear grading at birth and standardised neurodevelopmental assessment at 18 months or older were included. Both non-randomised, observational studies (non-RCT) and randomised control trials (RCT) of mild HIE were included. As the non-RCT were highly heterogeneous, a meta-analysis was inappropriate. Within the RCT studies, we conducted a meta-analysis of neurodevelopmental outcomes. Abnormal outcome was defined as death, cerebral palsy or a cognitive score less than 1 standard deviation below the expected mean.

RESULTS

Across the 15 non-RCT studies, outcome was reported in 186 mild HIE infants. Of this group, 55 (30%) had any abnormal outcome at 18 months of age or older. Within the RCT studies, 87 infants with mild HIE were included for analysis; 40 cooled and 47 uncooled. Abnormal outcome in the cooled vs uncooled groups was 27.5% vs 34% (p = 0.336), with an odds ratio of 0.735 (0.29-1.84). By combining both RCT and non-RCT studies, outcome was reported in a total of 273 mild HIE infants, with 82 (30%) having an abnormal outcome. Results are presented in **Fig. 1**.

CONCLUSIONS

In the most recent *Cochrane* review of cooling results of 1,505 moderate to severe HIE infants have been reported compared to just 251 mild HIE infants studied in this review. We have shown that the outcome for infants with mild HIE at birth is not normal in one third of cases. There is insufficient evidence to recommend cooling in infants with mild HIE at present and adequately powered RCT is required to answer this question.

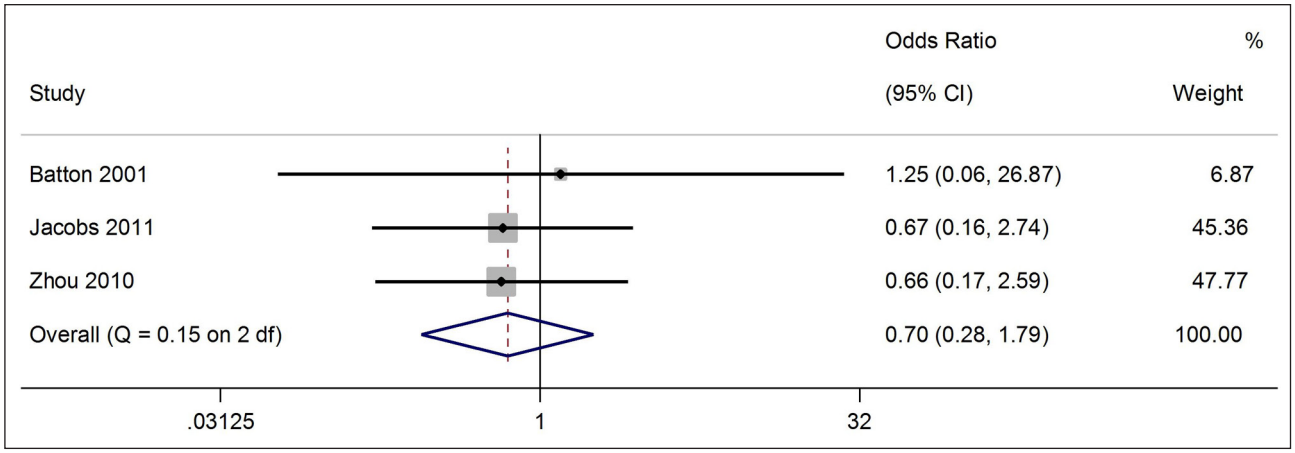

Figure 1 (ABS 104). Metanalysis of neurodevelopmental outcomes studies within the randomised control trials (RCT) of mild Hypoxic Ischaemic Encephalopathy (HIE).
Weights are from Mantel-Haenszel model.

ABS 105

NEURODEVELOPMENTAL AND SENSORY OUTCOME AT TWO YEARS IN VLBW BABIES: CORRELATIONS WITH BRAIN LESIONS DETECTED AT TERM MRI

M. Malova[1], L. Ceschi[1], C. Traggiai[1], S. Uccella[2], A. Parodi[1], A. Sannia[1], L. Boeri[2], E. De Grandis[2], M. Severino[3], G. Morana[3], D. Tortora[3], M.G. Calevo[4], A. Rossi[3], E. Veneselli[2], C. Bellini[1], L.A. Ramenghi[1]

[1]Neonatal Intensive Care Unit, Istituto Giannina Gaslini, Genoa, Italy
[2]Child Neuropsychiatry Unit, Istituto Giannina Gaslini, Genoa, Italy
[3]Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy;
[4]Epidemiology, Biostatistics and Committees Unit, Istituto Giannina Gaslini, Genoa, Italy

INTRODUCTION

Short and long-term outcomes of high prematurity are a matter of constant attention in scientific literature and health care. Major challenge in the field is finding early predictors of developmental disabilities in order to be able to intervene and improve the outcome. The purpose of the present study was to evaluate developmental outcomes and major sensory deficits at two years of age in a cohort of VLBW newborns and investigate correlations of these data with brain MRI performed at term equivalent age.

METHODS

Our retrospective observational study included all VLBW infants admitted to our NICU between January 2012 and December 2013 who underwent brain MRI at term equivalent of age and completed the follow-up program at two years of age. A database was created with: clinical and auxological data, evidence of cerebral lesions connected with prematurity at brain MRI, visual, audiological and neurological outcome (including Griffiths Mental Developmental Scale, GMDS) at two years of age. Prematurity related brain lesions seen on MRI were tested as possible risk factors for negative outcome at two years using logistic regression analysis. Results were reported as odds ratio (OR) with their confidential intervals (CI).

RESULTS

Seventy four patients matched inclusion criteria and thus became the cohort of our study. Their average weight at birth was 982.8 ± 275.1 g, and average gestational age was 28^{+1} weeks. At two years of age, 1 patient presented auditory deficits, 13 patients (17.6%) visual deficits, 6 (8.1%) were diagnosed with cerebral palsy and 2 (2.7%) with autism spectrum disorders. Twenty-eight patients (37.8%) were receiving some type of rehabilitation therapy during first two years of life. GMDS scores resulted normal (> 85) in 59 infants (79.7%). In regression analysis, cerebellar haemorrhage increased the risk for developing ROP (OR = 3.9, 95% CI [1.1; 13.3], p = 0.03). Cerebellar and intraventricular haemorrhages were correlated to an incremented risk for developing visual deficits at the age of 12-18 months (OR = 9.1, 95% CI [2.4; 34.0], p = 0.001 and OR = 4.5, 95% CI [1.2; 16.4], p = 0.02 respectively).

CONCLUSIONS

Connection between haemorrhagic lesions seen on term equivalent age MRI and visual defects at 12-18 months asks for further follow-up studies in order to corroborate role of MRI as a possible

instrument to predict sensory outcome in VLBW newborns.

ABS 106

PREVALENCE OF AUTISM IN EXTREME PRETERM CHILDREN BORN IN STOCKHOLM 2004-2007

E. Eklof[1], A. Hedfors Moretti[2], H. Lagercrantz[1], S. Bolte[3], U. Aden[1]

[1]Neonatology Unit, Karolinska Institutet, Stockholm, Sweden

[2]BUP, Stockholm, Sweden

[3]Pediatric Neuropsychiatry Unit, Karolinska Institutet (KIND), Stockholm, Sweden

INTRODUCTION

Extremely preterm (EPT) children (< 28 weeks) are at increased for Autism Spectrum Disorder (ASD). Joseph et al. [1] recently reported a prevalence of 7.1% in a cohort of EPT children when the Autism Diagnostic Observation Schedule (ADOS) was used as diagnostic tool after screening with the Social Communication Questionnaire (SCQ). The prevalence increased with lower gestational age, and a prevalence of 15% at week 23-24 was reported. The present study aims to estimate the prevalence of ASD in a regional cohort of EPT children at the age 6.5 years using the Social Responsiveness Scale (SRS) and the SCQ, and at 9-11 years using the ADOS-2.

METHODS

The study population is a regional cohort of EPT children (< 27 weeks) born in Stockholm 4/2004-12/2007 (n = 104). It is part of the national prospective research study on extreme prematurity, the EXPRESS study. Clinical diagnoses (DSM-IV) were retrieved from medical charts. At 6.5 years 91 children participated in a follow-up study and were screened for ASD with SCQ and SRS. Mean gestational age was 25.6 months (SD 1.0); 93% completed the SRS and 94% the SCQ. At age 9-11 years, 51 children were assessed by ADOS-2, module 3.

RESULTS

At 6.5 years, 26% (22/85) screened positive on SRS and 9% (8/86) screened positive on SCQ. SRS had a sensitivity of 100% and a specificity of 82% to predict a clinical diagnosis of ASD at 6.5 years. The SCQ had a sensitivity of 44% and a specificity of 95% to predict ASD in EPT born children. At 9-11 years, 29% (15/51) of the EPT children scored above the cut-off level of 7 on the ADOS-2, module 3. The ADOS-2 had a sensitivity of 89% and a specificity of 83% to predict a clinical diagnosis of ASD. In the cohort, 16% of the children had a clinical diagnosis of ASD. Out of 53 children who were not assessed by ADOS-2, 15% had a clinical diagnosis of ASD. Thus the prevalence of ASD was almost equal in the drop out group.

CONCLUSIONS

EPTs have an increased risk of developing ASD. Reports on the prevalence vary. This may be caused by differences in methodology and age at which screening instruments are used, illustrating the importance of not relying solely on screening and diagnostic instruments. Multiple sources of information are necessary when diagnosing ASD. The high incidence in present cohort may also be due to low gestational age.

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ABS 107

CEREBRAL AUTOREGULATION IN ASPHYXIATED NEONATES TREATED WITH HYPOTHERMIA

A. Hendriksen, L. Dix, W. Baerts, F. van Bel, F. Groenendaal, P. Lemmers

Department of Neonatology, Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht, the Netherlands

INTRODUCTION

Hypoxic ischemic encephalopathy due to perinatal asphyxia is a major cause of neurodevelopmental disability and mortality. Cerebral autoregulation is an important protective mechanism to maintain perfusion during fluctuations in blood pressure. Cerebral autoregulation can be estimated by calculating the correlation between near-infrared spectroscopy monitored regional cerebral oxygen saturation ($rScO_2$) and mean blood pressure (MABP). A correlation > 0.5 is indicative of impaired autoregulation. The aim of this study is to assess the relation between absence of cerebral autoregulation and severity of brain injury on magnetic resonance imaging (MRI) after perinatal asphyxia.

METHODS

Neonates with perinatal asphyxia born between 2014 and 2016 and treated with hypothermia

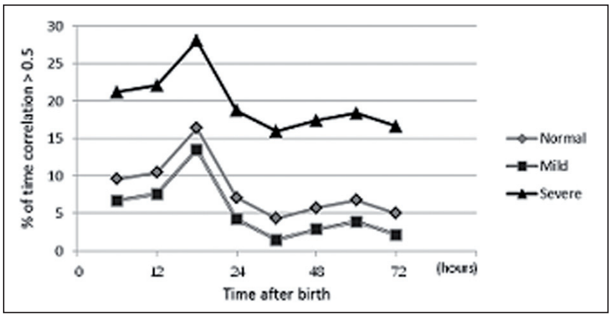


Figure 1 (ABS 107). Cerebral autoregulation.
Percentage of time spent with impaired autoregulation (correlation > 0.5) in infants with normal, mildly and severely abnormal MRI outcome.

during the first 72 hours after birth were included. The correlation between $rScO_2$ and MABP was calculated to estimate cerebral autoregulation. Heart rate and arterial oxygen saturation were measured simultaneously. Infants were divided in 3 groups based on MRI outcome: normal (no injury), mildly abnormal (watershed injury) or severely abnormal (basal ganglia-thalamus or near-total injury). Percentage of time with autoregulation correlation > 0.5 and % of time with $rScO_2$ > 85% were studied over time in the 3 groups with mixed model analysis (**Fig. 1**).

RESULTS

42 asphyxiated neonates with hypothermia were included. MRI outcome was normal in 20, mildly abnormal in 6 and severely abnormal in 16 infants. Of those 16, 12 neonates died due to neurologic deterioration. MRI outcome and time as a categorical variable had a significant effect on cerebral autoregulation ($p < 0.05$). For $rScO_2$, MRI outcome and time as a continuous variable had a significant effect (p 85%).

CONCLUSIONS

Impaired autoregulation is significantly related to cerebral injury as measured on MRI in asphyxiated neonates under hypothermia. Moreover, infants with severe cerebral injury have higher cerebral oxygenation values compared to infants with mild or no MRI abnormalities. Bedside monitoring of cerebral oxygenation and autoregulation calculation may have prognostic value and aid in identifying infants at risk of cerebral injury.

ABS 108

HYPERECHOGENICITY OF THE LENTICULO-STRIATE ARTERIES: INCIDENCE AND CLINICAL IMPACT IN A TERTIARY NICU

P. Triantafyllidou[1], M. Papadopoulou[1], S. Gantseva-Patsoura[1], F. Kokkori[1], E. Varxalama[1], M. Theodoraki[1], A. Gounaris[2]

[1]*NICU, General Hospital of Nikaia "Agios Panteleimon", Nikaia, Greece*

[2]*NICU, University Hospital of Larissa, Larissa, Greece*

INTRODUCTION

Neonatal screening with cranial ultrasound as a common practice in NICUs has revealed a relative new entity: Lenticulostriate vasculopathy (LSV) seen as linear areas of echogenicity in the thalami and basal ganglia with an incidence estimated to 0.4% of all live born neonates and 1.9-5.8% of ill neonates. Lenticulostriate arteries are normally not apparent in ultrasound and pathogenically LSV is attributed to maternal-fetal and perinatal factors.

METHODS

Our aim was to record the incidence of LSV in our NICU, to define possible causes and to compare our results with those of other centers. We conducted a retrospective descriptive study during five-year period in our tertiary NICU. Maternal, gestational, perinatal data, clinical neonatal variables and medical interventions were collected from our files. All neonates were tested with routine cranial ultrasound performed with Sony logiqP5, probe 7.5 MHz. Ultrasound examination included coronal and bilateral parasagittal views of the brain performed from radiologist. Developmental follow up was performed at 3, 6 and 24 months corrected gestational age.

RESULTS

During this study period 30 neonates presented with LSV with an incidence of 2.4% (in agreement with the literature). Demographic characteristics: 80% of neonates with LSV were males, 50% were born at term, 71% born with cesarean section, 34.6% at 32-36^{+6} weeks gestational age, 15.4% at 28-31^{+6} weeks gestational age. Mean gestational age 35.6 weeks (SD 3.4), mean birth weight 2,655 g (SD 913), median length of stay was 15 days (25-75 P 10-30). 12 neonates had perinatal infection (40%), 1 had CMV infection, 1 chromosomal aberration, 2 twin-twin transfusion, 1 placenta aberration and 4 suffered severe asphyxia. 61% of the pregnancies were at high risk. 6 out of 30 (20%) neonates presented with neurological deficit during hospital stay attributed to their disease. With most of our patients lost to follow up two more presented with mild developmental deficit.

CONCLUSIONS
Hyperechogenity of the lenticulostriate arteries is not a rare finding in hospitalised neonates. Cranial screening ultrasound should be performed to reveal this finding in order to have sufficient investigation of possible causal factors. Even in the absence of severe underlying condition a high level of awareness is required to reveal mild neurodevelopmental discrepancies in long term follow up.

ABS 109

A MIXED LIPID EMULSION – RICH IN DOCOSAHEXAENOIC ACID (DHA) – AND ITS EFFECT ON BRAIN MATURATION IN EXTREMELY LOW BIRTH WEIGHT INFANTS

C. Binder[1], A. Repa[1], V. Giordano[1], M. Thanhaeuser[1], A. Kreissl[1], N. Haiden[1], A. Berger[1], N. Longford[2], K. Klebermass-Schrehof[1]

[1]Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Pediatric Intensive Care Medicine and Neuropediatrics, Medical University Vienna, Vienna, Austria

[2]Department of Medicine, Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster Campus, London, UK

INTRODUCTION
Preterm infants have a limited capacity to synthetize docosahexaenoic acid (DHA) from precursor fatty acids and accumulate substantial DHA deficits. Studies demonstrated that enteral DHA-supplementation improves neurodevelopment in preterm infants. Preterm infants may depend on long-term parenteral nutrition but standard lipid emulsions (LE) based on soybean oil do not contain DHA. A new mixed parenteral LE (soybean, MCT, olive and fish oil – rich in DHA-) was recently marketed. As yet, no studies evaluated the effect of parenteral DHA supply on brain maturation. The aim of this study was to evaluate the effect of a mixed LE containing DHA compared to soybean oil based LE on brain maturation.
METHODS
In a double-blind randomized controlled trial conducted between 2012-2015 that investigated parenteral nutrition associated cholestasis as its primary outcome, extremely low birth weight infants received either a mixed LE rich in DHA (SL-group) or a soybean oil based LE (IL-group) for parenteral nutrition. Brain maturational score according to Burdjalov et al. (range 0-13), background pattern and sleep-wake cycles (SWC) measured by serial amplitude-integrated EEG were analysed as a secondary outcome. Amplitude-integrated EEG records were performed on a bi-weekly basis from birth until discharge, transfer or death.
RESULTS
317 aEEG records (IL-group: n = 152, SL-group: n = 165) of 121 infants (IL-group: n = 58, SL-group: n = 63) between the postmenstrual ages of 24 to 41 weeks were analyzed. Median (interquartile range) duration of the recordings was 180 min (140, 240) in the IL-group and 180 min (150, 260) in the SL-group ($p = 0.30$). Brain maturational scores and percentages of continuous pattern were significantly higher in the SL- than in the IL-group at every postmenstrual age after 27 weeks. Infants in the SL-group (median: 36.4 weeks; IQR: 35.4-37.5) reached the maximum maturational score significantly earlier than infants in the IL-group (median: 38.4 weeks; IQR: 37.1-42.4) ($p < 0.001$). SWC did not show significant differences between the groups at any postmenstrual age.
CONCLUSIONS
Brain maturation was significantly accelerated in preterm infants who received parenteral nutrition using a lipid emulsion, rich in DHA compared to a lipid emulsion based on soybean oil. These results support the hypothesis that DHA enriched parenteral lipid emulsions positively affect brain maturation.

ABS 110

IMPACT OF PARTURITION ON MATERNAL NEURONAL INTEGRITY

K.S. Evers[1], S. Fouzas[2], C. Barro[3], J. Kuhle[3], U. Fisch[3], O. Lapaire[4], S. Wellmann[1]

[1]Division of Neonatology, University of Basel Children's Hospital (UKBB), Basel, Switzerland

[2]Department of Neonatology, Paediatric Respiratory Unit, University Hospital of Patras, Patras, Greece

[3]Neurology, Departments of Medicine, Biomedicine and Clinical Research, University Hospital Basel, Basel, Switzerland

[4]Division of Obstetrics and Gynecology, University Hospital Basel, Basel, Switzerland

INTRODUCTION
Parturition has a major influence on the mother-infant dyad being a great challenge for physiological adaptation of both. The aim of this study was to investigate the impact of parturition on maternal serum biomarkers that reflect neuronal injury, individual stress levels and hemodynamic effects in order to better understand the physiological changes

along parturition. We used progesterone as a well-established control biomarker for parturition.

METHODS

We performed a prospective cohort study in women at risk of developing preeclampsia at the University Hospital of Basel to determine serum neurofilament light chain (NfL), copeptin, mid-regional pro-ANP (MR-proANP), progesterone, placental growth factor (PlGf) and soluble fms-like tyrosine kinase-1 (sFlt-1) levels shortly before and shortly after parturition (6-24 hours in both cases). In total 56 women were enrolled with complete paired antepartal and postpartal samples. Clinical data of mothers and neonates were recorded and statistics were calculated, including univariate and multivariate regression analysis.

RESULTS

As expected, our study showed a 5-fold decrease of progesterone from antepartal to postpartal measurements ($p < 0.001$). In contrast to copeptin, MR-proANP, PlGf and sFlt-1 which all showed no significant changes, only NfL levels changed significantly by 2-fold during parturition with a mean of 32.5 pg/ml (confidence interval [CI] 24.4-40.7) when measured before birth vs. 63.8 pg/ml (CI 51.6-75.9) when measured after birth ($p < 0.001$). In the combined regression model we identified antepartal NfL levels, maternal age, systolic blood pressure and preterm birth as the major determinants of NfL increase. Delivery mode, time to birth of blood sampling and other clinical characteristics as well as biomarkers had no impact on NfL levels.

CONCLUSIONS

Parturition *per se* causes a significant increase of serum NfL indicating a profound impact of giving birth on maternal neuronal integrity. This finding was unexpected and must be seen in the context of very recently identified long-lasting changes in gray matter architecture of the maternal brain.

ABS 111

THE EFFECT OF MORPHINE ON EARLY BRAIN ACTIVITY IN EXTREMELY PRETERM INFANTS: AN OBSERVATIONAL MULTICENTER STUDY

M.L. Tataranno[1], L.S. de Vries[1], L. Hellström-Westas[2], O. Dammann[3], M. Toet[1], F. Groenendaal[1], N.H.P. Claessens[1], V. Fellman[4], K. Sävman[5], M.J.N.L. Benders[1]

[1]*Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands*

[2]*Department of Women's and Children's Health, University Hospital, Uppsala University, Uppsala, Sweden*

[3]*Perinatal Neuroepidemiology Unit, Hannover Medical School, Hannover, Germany*

[4]*Department of Pediatrics, Clinical Sciences, Lund University, Lund, Sweden*

[5]*Department of Pediatrics, Perinatal Center, Institute of Clinical Sciences, University of Gothenburg, Sahlgrenska Academy, Gothenburg, Sweden*

INTRODUCTION

Amplitude-integrated EEG (aEEG) provides a continuous and bedside assessment of brain activity in preterm infants. Several studies report the effect of sedative medication, widely used in neonatal intensive care units, on aEEG/EEG background pattern. Our aim was to study the effect of morphine and its cumulative dose on aEEG quantitative measures in extremely preterm infants recorded over the first three days after birth.

METHODS

174 extremely preterm infants (mean GA 26, SD 1) were enrolled in 3 European NICUs and monitored with continuous 2 channel aEEG (BrainZ, Natus, Seattle). Six epochs of aEEG recordings were selected at 4-6 h, 10-12 h, 20-24 h, 32-36 h, 44-48 h, 68-72 h. Minimum amplitude EEG (min aEEG), percentage of time < 5 μV (% of time < 5 μV), interSAT interval (ISI), spontaneous activity transients (SAT rate i.e. SAT/min) were calculated using an in-house developed program. For babies receiving morphine for clinical indications, the cumulative dosage was calculated in the first three days after birth. Multivariable models were chosen to check the association between morphine administration/cumulative dose and aEEG/EEG measures.

RESULTS

Eighty-nine neonates (51.1%) received morphine during the study period. Morphine administration (yes/no) and cumulative dose had a significant effect on all quantitative aEEG/EEG measures, causing depression of early brain activity in all epochs. A significant negative association between SAT rate and both morphine administration and dosage was seen (OR resp: -1.38; -1.70). In addition, a significant positive association was observed between ISI and both morphine (yes/no) and cumulative dose (OR resp: 2.90; 5.64). A negative association was found between min aEEG and morphine administration and cumulative dose (OR resp: -0.78; -1.14). A positive association was observed for the % of time < 5 μV (OR resp: 14.80; 15.18). A significant effect of GA and postnatal age on both aEEG/EEG measures was also observed.

CONCLUSIONS

Our findings suggest that morphine administration and cumulative doses are strongly associated with a reduction in brain activity in extremely preterm infants, thus the administration of sedative drugs should be considered when interpreting aEEG/EEG. Both acute and long-term consequences of morphine on brain development should be investigated to optimize neurodevelopmental outcome of the extremely preterm infant.

ABS 112

PERSISTENT MONOCYTE AND NEUTROPHIL ACTIVATION IN SCHOOL AGE CHILDREN POST NEONATAL ENCEPHALOPATHY

Z. Zareen[1-3,5], V. Mc Eneaney[5], N.A. Taher[5], L. Kelly[5], D. Sweetman[3], D. Doherty[5], E. Molloy[1-5]

[1]Paediatrics, Trinity College Dublin, Dublin, Ireland

[2]National Children's Hospital, Tallaght, Dublin, Ireland

[3]National Maternity Hospital, Holles Street, Dublin, Ireland

[4]Coombe Womens and Infants University Hospital, Dublin, Ireland

[5]Trinity Translational Medicine Institute (TTMI), Trinity College Dublin, Dublin, Ireland

INTRODUCTION

Persistent inflammation may be associated with brain injury in animal models. We explored monocyte and neutrophil activation in response to endotoxin (LPS) and melatonin in children with Neonatal Encephalopathy (NE) at school age compared to age-matched controls and children with severe cerebral palsy (CP).

METHODS

School-age children who had NE were compared to age-matched controls and children with severe CP. The expression of neutrophil and monocyte markers of function CD11b (neutrophil activation) and Toll like receptor (TLR)-4 (endotoxin recognition) before and after treatment, *in vitro* with Lipopolysaccharide (LPS) and Melatonin using flow cytometry.

RESULTS

The expression of neutrophil CD11b was significantly increased in children with NE ($p = 0.04$) and CP after LPS stimulation in comparison to children in the control groups. This was reduced with *in vitro* treatment with melatonin. Similarly, expression of TLR4 in neutrophil was seen to be high in children with NE and CP especially after LPS stimulation *in vitro*.

CONCLUSIONS

Children with NE and those with sever CP had significantly altered neutrophil and monocyte responses to endotoxin (LPS) and melatonin at school age. This suggests that dysregulated inflammation seen in newborns with NE may persist into childhood and is amenable to immunomodulation with melatonin.

ABS 113

BLOOD BASED PROTEINS THAT DIFFERENTIATE INFLAMMATION-SENSITIZED HYPOXIA VERSUS HYPOXIA ALONE WITHIN THE 6 H THERAPEUTIC WINDOW IN A PIGLET MODEL

I. Lingam[1], A. Avdic-Belltheus[1], K. Martinello[1], C. Meehan[1], S. Ragab[1], I. Tachtsidis[1], C. Tann[1], M. Hristova[1], B. Fleiss[2], T. Wolfs[3], B. Kramer[3], N. Klein[1], H. Hagberg[2], P. Gressens[2], N.J. Robertson[1]

[1]Institute for Women's Health, University College London, London, UK

[2]Centre for the Developing Brain, King's College London, London, UK

[3]Maastricht University, Department of Pediatrics, Maastricht, the Netherlands

INTRODUCTION

The combination of antenatal infection and birth-asphyxia dramatically increases the risk of cerebral palsy. A blood marker that could differentiate babies with neonatal encephalopathy (NE) due to hypoxia or a combined insult may allow tailored treatments to optimise hypothermic neuroprotection. We evaluated blood cytokine/chemokine and brain biomarkers over 48 h following *E. coli* lipopolysaccharide (LPS), hypoxia (H) and both combined (LPS-H) in a piglet model of NE.

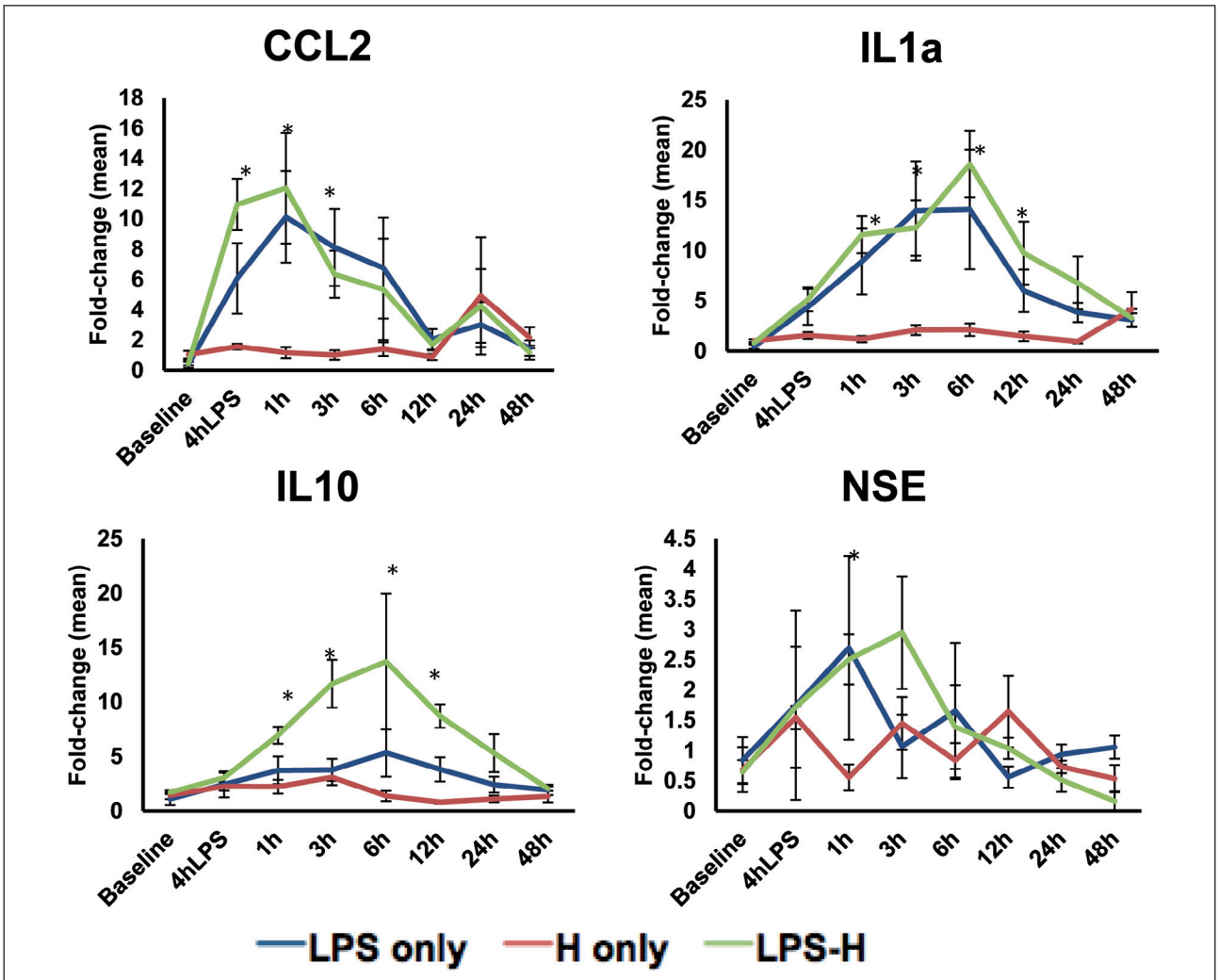
METHODS

16 Large White piglets, aged under 48 h, were randomised to: (i) LPS ($n = 5$), (ii) H ($n = 6$) and (iii) LPS-H ($n = 5$). LPS and LPS-H received *E. coli* LPS (Sigma LPS O55:B5; Bolus 2 mcg/kg, continuous infusion 1 mcg/kg/h), starting 4 h before H in LPS-H animals. H was titrated according to the duration of hypotension < 27 mmHg, isoelectric EEG and relative changes in the oxidation of cytochrome oxide on near-infrared spectroscopy. Serum was taken at baseline, 4 h after LPS and at 1, 3, 6, 12, 24 and 48 h after H. RNA was isolated using a standardised kit (mirVana, Thermo Fisher Scientific) and porcine-specific primers were used to derive relative mRNA expression using the

comparative CT method. Animals were sacrificed at 48 h and regional cell death (TUNEL counts) assessed.

RESULTS

H insult parameters were similar between H only and LPS-H. LPS-H group had higher mortality



		Baseline	4hLPS	1h	3h	6h	12h	24h	48h
CCL2	LPS	0.41	6.08	10.15^{X}	**8.12**^{X}	**6.77**^{X}	2.06	3.03	1.47
	H	1.04	1.57	1.17	1.02	1.41	0.89	4.92	2.16
	LPS-H	0.47	**10.97***	**12.04***	**6.36***	5.36	1.73	4.26	1.18
IL1a	LPS	0.45	4.40	**8.92**^{X}	**13.97**^{X}	**14.09**^{X}	6.00	3.85	3.12
	H	1.05	1.56	1.20	2.09	2.13	1.48	0.97	4.16
	LPS-H	0.83	5.14	**11.59***	**12.26***	**18.61***	**9.77***	6.79	3.29
IL10	LPS	1.11	2.45	3.74	3.78	**5.35**^{X}	3.83	2.42	1.94
	H	1.44	2.26	2.23	3.11	1.39	0.82	1.12	1.33
	LPS-H	1.73	3.06	**6.97***	**11.70***	**13.73***	**8.73***	5.32	2.06
NSE	LPS	0.84	1.75	**2.70**^{X}	1.07	1.65	0.56	0.94	1.06
	H	0.69	1.55	0.55	1.45	0.84	1.65	0.73	0.54
	LPS-H	0.65	1.72	**2.51***	2.95	1.39	1.04	0.51	0.16

Figure 1 (ABS 113). Mean fold-change in mRNA expression of CCL2, IL1a, IL10 and NSE over 48 hours (error bars represent standard error).

* $p < 0.05$ comparing LPS-H vs H; ^{X} $p < 0.05$ comparing LPS vs H.

(0% versus 60%, p = 0.04) and brain TUNEL cell death than LPS (p = 0.001) and H alone (p = 0.04). Two animals in the LPS-H group died early at 24 hours post-insult, limiting analysis of the 48 hour time point. Neuron-specific enolase (NSE) was significantly upregulated in LPS (3.3-fold, p = 0.01) and LPS-H (2.5-fold, p = 0.03) than H (0.83-fold) at 1 h. Chemokine CCL2, interleukin (IL) 1a, 8 and 10 were all increased in LPS-H compared to H at 3 and 6 h (p < 0.001). IL-10 demonstrated significant upregulation in LPS-H compared to either LPS (13.7 vs 6.7, p < 0.01) or H alone (13.7 vs 1.4-fold, p < 0.01) at 6 h, distinguishing between all three pathological processes. Tau and TNFα were late biomarkers, increasing 4.2 and 1.5-fold in LPS-H compared to 0.8 and 0.7-fold in H (p = 0.04) (**Fig. 1**).

CONCLUSIONS

A combination of inflammation and H was associated with higher mortality and neuronal death than either process alone. Early expression of NSE in LPS-H may indicate severity of neuronal injury in a combined insult. Upregulation of CCL2, IL1, 8 and 10 by 3 h in LPS-H were also seen in LPS but not H, thus may indicate an infective discriminator of NE. Upregulation of Tau and TNFα at 24 h in LPS-H may reflect ongoing neuronal injury not evident in H.

ABS 114

BLOOD PLASMA PROFILE OF TEMPORAL MICRORNA EXPRESSION OF INFLAMMATION IN LIPOPOLYSACCHARIDE SENSITISED PORCINE MODEL OF HYPOXIC ISCHAEMIC ENCEPHALOPATHY

A. Avdic-Belltheus[1], I. Lingam[1], C. Meehan[1], K. Martinello[1], S. Ragab[1], I. Tachtsidis[1], C. Tann[1], M. Hristova[1], B. Fleiss[2], T. Wolfs[3], B. Kramer[3], N. Klein[1], H. Hagberg[2], P. Gressens[2], N.J. Robertson[1]

[1]*Institute for Women's Health, University College London, London, UK*

[2]*Centre for the Developing Brain, King's College London, London, UK*

[3]*Maastricht University, Department of Pediatrics, Maastricht, the Netherlands*

INTRODUCTION

Infection is thought to exacerbate hypoxic ischaemic injury in neonatal encephalopathy (NE) and attenuate the efficacy of therapeutic hypothermia. Infants with combined infection and NE may warrant alternative treatment strategies to improve outcomes. There are however, no clinical or biochemical markers to distinguish infants with NE from hypoxia (H) to those with infection sensitised H. MicroRNA (miRNA) are small non-coding RNAs involved in post-transcriptional regulation of gene expression. Several miRNA have been assessed as biomarkers of injury with limited success. We hypothesise that serum miRNA levels can distinguish between infection (LPS), H and a combined insult (LPS-H).

METHODS

16 large white piglets were randomised to receive LPS (n = 5), H (n = 6) and LPS-H (n = 5). Piglets in the LPS and LPS-H group received *E. coli* LPS (Sigma LPS O55:B5; 2 mcg/kg bolus, 1 mcg/kg/h infusion) for 52 hours; commencing 4 h prior to hypoxia in the LPS-H group. H was titrated according to the duration of hypotension < 27 mmHg, isoelectric EEG and NIRS (total fall in oxidised cytochrome oxidase during insult). Blood was taken at baseline, 4 hours after LPS and at 0, 1, 3, 6, 12, 24. 48 hours following hypoxia. RNA was isolated using a standardised kit (mirVana, Thermo Fisher Scientific). Significant human and porcine miRNA populations were identified using a multiple-correction ANOVA (FDR p < 0.05) and fold-changes compared from baseline.

RESULTS

One animal in H group was excluded due to methodological changes in RNA extraction. Three animals in the LPS-H group died; one soon after H and two at 24 hours, limiting the analysis of miRNA levels at 48 h. 4929 miRNA human and porcine species were identified with significant differences seen in 20 of the LPS group and in 5 of the LPS-H group. There were no significant changes in miRNA levels in the H group. Hsa-mir-27a-5p and hsa-mir-23a-5p were upregulated in LPS-H compared to H at 1, 3, 6 and 12 h post-insult (p < 0.01). They also differentiated LPS from LPS-H at 6 h (p < 0.01). Hsa-mir-193a-5p, hsa-mir-31-5p and ssc-mir-31 were downregulated (p = 0.02) after LPS (LPS-H and LPS groups) and post-H in LPS-H, however not significantly different from H after insult. Upregulation of hsa-mir-150-5p (p < 0.01) and downregulation of hsa-mir-181c-3p (p = 0.03) and hsa-mir-330-3p (p < 0.03) occurred at 24 h (**Fig. 1**).

CONCLUSIONS

We identified several miRNA that differentiate LPS-H from H at different timepoints following insult. Hsa-150-5p has been associated with T and B cell differentiation and its upregulation at 24 h may indicate ongoing pro-inflammatory processes. Hsa-mir-27a-5p and hsa-mir-23a-5p have pre-

LPS	H	LPS-H
Human Hsa-mir-150-5p Hsa-mir-27a-5p Hsa-mir-23a-5p Hsa-mir-31-5p Hsa-mir-5100 Hsa-mir-193a-5p Hsa-mir-339-5p Hsa-mir-214-3p Hsa-mir-199a-5p Hsa-mir-99b-5p Hsa-mir- 215-5p Hsa-mir-181c-3p **Porcine** Ssc-mir-150-5p Ssc-mir-193a-5p Ssc-mir-31 Ssc-mir-339 Ssc-mir-339-5p Ssc-mir-199a-5p Ssc-mir-99b Ssc-mir-215	None	**Human** Hsa-mir-150-5p Hsa-mir-27a-5p Hsa-mir-23a-5p Hsa-mir-330-3p **Porcine** Ssc-mir-150-5p

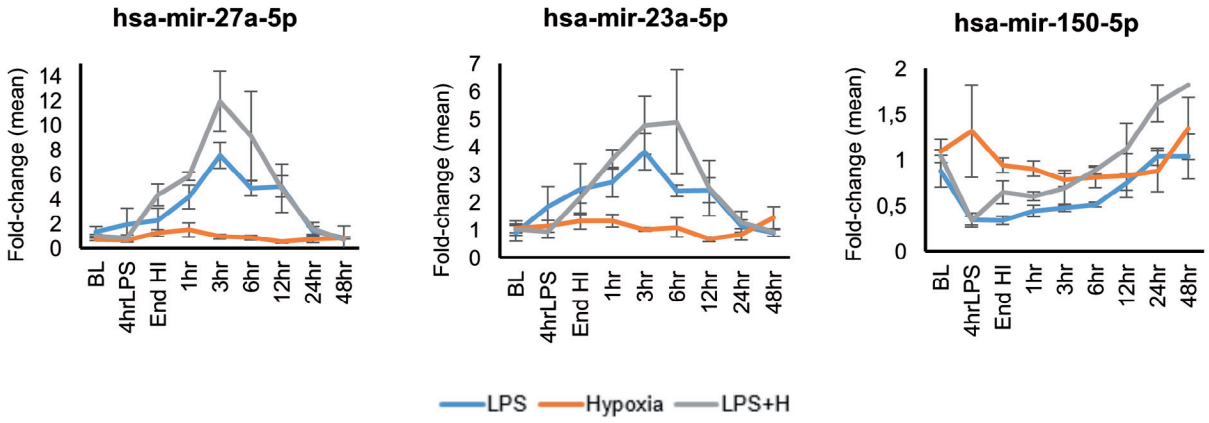


Figure 1 (ABS 114). Significant microRNA identified in animals administered LPS, hypoxia and combined LPS with hypoxia (FDR $p < 0.05$).

viously been associated with hypoxia and appear promising biomarkers to differentiate LPS-H from H, within the 6 h timeframe of initiating therapeutic hypothermia.

ABS 115

ARE THE 2 YEAR GRIFFITHS SCORES OF BABIES WITH CEREBELLAR HAEMORRHAGE (CBH) AND INTRAVENTRICULAR HAEMORRHAGE (IVH) SIGNIFICANTLY DIFFERENT COMPARED TO THOSE OF BABIES SUFFERING FROM ISOLATED IVH?

S. Uccella[1], A. Parodi[2], M. Malova[2], L. Boeri[1], E. De Grandis[1], C. Traggiai[2], A. Sannia[2], M. Severino[3], G. Morana[3], D. Tortora[3], A. Rossi[3], E. Veneselli[1], L.A. Ramenghi[2]

[1]*Child Neuropsychiatry Unit, Istituto Giannina Gaslini, Genoa, Italy*

[2]*Neonatal Intensive Care Unit, Istituto Giannina Gaslini, Genoa, Italy*

[3]*Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy*

INTRODUCTION

Intraventricular Haemorrhage (IVH) and Cerebellar Haemorrhage (CBH) are known pathologies affecting the developing brain of very premature infants (VPI). MRI is known to be superior in detecting all grades of these lesions, but little is known about the influence on neurological outcome of IVH and CBH diagnosed exclusively with MRI. In addition, influence of both lesions occurring

Table 1 (ABS 115). Griffiths Mental Developmental Scales (GMDS-ER) scores at 2 years of age.

GMDS-ER scores	IVH	IVH + CBH	p
Total DQ	90.91 ± 2.70	84.27 ± 0.36	0.149
A DQ Locomotor	88.63 ± 2.97	78.32 ± 3.21	**0.038**
B DQ Personal-Social	90.21 ± 2.58	83.59 ± 3.89	0.155
C DQ Hearing and Language	84.46 ± 2.90	78.18 ± 4.09	0.166
D DQ Eye and Hand Coordination	97.06 ± 3.21	91.27 ± 3.24	0.301
E DQ Performance	93.37 ± 3.16	86.54 ± 4.77	0.195

Results are presented as mean ± standard error.
GMDS-ER: Griffiths Mental Developmental Scales; DQ: Developmental Quotient; IVH: Intraventricular Haemorrhage; CBH: Cerebellar Haemorrhage.

together (frequent phenomenon) on neurological outcome, when compared to influence of isolated IVH, is still a matter of debate. The aim of our study is to investigate the potential adding value of CBH coexisting with IVH as an aggravating factor of the outcome in a cohort of VPI (< 32 weeks of gestational age).

METHODS

We revised data of VPI who underwent brain MRI on a 1,5T system at term equivalent age and a complete neurological examination and Griffiths Mental Developmental Scales (GMDS-ER) at 2 years of corrected age. Two groups were selected: first consisted of VPI with only IVH (any grade); second – of VPI presenting IVH together with CBH (any grade). GMDS-ER was administered by a 10-year experienced single operator blinded to MRI results. Total Developmental Quotient (DQ) relates to global development, scale A assess gross motor skills, B – adaptive behaviour and social development, C – receptive/expressive language, D – fine motor functions, E – precursors of reasoning and planning. DQ above 85 was considered normal. T-student test was performed to compare mean values in IVH vs IVH+CBH groups.

RESULTS

Data about 173 VPI were revised: 35/173 (20.2%) presented with isolated IVH (first group) and 22/173 (12.7%) – with IVH+CBH association (second group). In the first group mean gestational age was 28 ± 0.4 and total developmental quotient (tDQ) was 90.91 ± 2.7 (results are presented as mean ± standard error). Patients with IVH+CBH association had a mean gestational age of 26 ± 0.3 and tDQ of 84.27 ± 3.8. Detailed results for total and subscale scores in two groups can be found in **Tab. 1**. Difference between two groups was present only as a trend for total DQ ($p = 0.149$), but have reached statistical significance for subscale A ($p < 0.05$). Mean gestational age was lower for babies with IVH+CBH association (28 ± 0.4) compared to those with IVH only ($p < 0.001$).

CONCLUSIONS

Presence of CBH in addition to IVH has ambiguous effects at 2 years. We cannot exclude further detrimental influence on longer outcome, as a significant reduction on scale A can conceal additional deficits. In fact, locomotor skills can be reliably distinguished from cognitive abilities only in older children, while at this stage scale A relates to mental energy and concentration as well. Our findings seem not to be independent form GA at birth.

ABS 116

INCIDENCE AND CHARACTERISTICS OF INFANTS WITH RETINOPATHY OF PREMATURITY IN CROATIA

M. Vucinovic[1], L.J. Znaor[2], A. Vucinovic[2]

[1]*Neonatal Intensive Care Unit, University Hospital Split, Split, Croatia*
[2]*Ophthalmology Department, University Hospital Split, Split, Croatia*

INTRODUCTION

The purpose of this research was to study the incidence of retinopathy of prematurity (ROP) in a neonatal intensive care unit in Croatia and obtain information on risk factors associated with ROP. There have been limited studies on ROP in Croatia where the screening for ROP and its treatment is still insufficient and not introduced in many intensive care units.

METHODS

This retrospective study included 247 premature infants admitted to the neonatal intensive care unit of University Hospital Split, over a 5-year period between January 2012, and December 2016. In this paper the relationship between clinical risk factors and the development of ROP was analyzed.

Table 1 (ABS 116). Table Univariate analysis of risk factors (no retinopathy of prematurity [ROP] v. any ROP).

		Total (n = 247)	ROP		p	OR (95% CI)	p[b]
			No (n = 188)	Yes (n = 59)			
Multiple births		78 (32)	59 (31)	19 (32)	0.906		
Cesarean section		162 (66)	127 (68)	35 (59)	0.315		
Chorioamnionitis		116 (47)	88 (47)	28 (47)	1.0		
Preeclampsia		52 (21)	38 (20)	14 (24)	0.693		
Antenatal steroids		117 (47)	92 (49)	25 (42)	0.378		
Gender	**Male**	141 (57)	103 (55)	38 (64)	0.249[a]		
	Female	106 (43)	85 (45)	21 (36)			
Birth weight (g)	**< 1,000**	37 (15)	19 (10.1)	18 (30.5)	< 0.001[a]	1.7 (1.3-2.2)	< 0.001
	1,001-1,250	43 (17.4)	30 (16)	13 (22)			
	1,251-1,500	60 (24.3)	49 (26.1)	11 (18.6)			
	> = 1,500[c]	107 (43.3)	90 (47.9)	17 (28.8)			
Gestational age (weeks)	**< 31**	121 (49)	81 (43)	40 (68)	0.002[a]	2.8 (1.5-5.1)	0.001
	≥ 31[c]	126 (51)	107 (57)	19 (32)			
SGA		62 (25)	49 (26)	13 (22)	0.652[a]		
APGAR 1 min,	**< 6**	106 (43)	72 (38)	34 (58)	0.014[a]	2.2 (1.2-4)	0.010
	≥ 6[c]	141 (57)	116 (62)	25 (42)			
Severe Apnoea		94 (38)	61 (32)	33 (56)	0.002[a]	2.6 (1.4-4.8)	0.001
CLD		28 (11)	17 (9)	11 (19)	0.073[a]	2.5 (?)	
IVH ≥ grade 2		52 (21)	39 (21)	13 (22)	0.977[a]		
PDA		27 (11)	16 (8.5)	11 (18.6)	0.053[a]	2.5 (1.1-5.6)	0.034
Sepsis		109 (44)	85 (45)	24 (41)	0.644		
Blood transfusion		223 (90)	169 (90)	54 (91)	0.907[a]		
NCPAP (days)	**≤ 2[c]**	156 (63)	131 (70)	25 (43)	< 0.001	3 (1.6-5.6)	< 0.001
	> 2	90 (37)	57 (30)	33 (57)			
SIPPV (days)	**≤ 1.5[c]**	124 (50)	104 (56)	20 (34)	0.006[a]	2.4 (1.3-4.5)	0.004
	> 1.5	122 (50)	83 (44)	39 (66)			
Duration of oxygen (days)	**≤ 14[c]**	129 (52)	111 (59)	18 (31)	< 0.001[a]	3.2 (1.7-6)	< 0.001
	> 14	117 (48)	77 (41)	40 (69)			

Data are presented as n (%).
ROP: retinopathy of prematurity; SGA: Small for gestational age; CLD: chronic lung disease; IVH: Intraventricular haemorrhage; PDA: patent ductus arteriosus; NCPAP: nasal continuous positive airway pressure; SIPPV: synchronised intermittent positive pressure ventilation; OR : odds ratio; CI : confidence interval.
[a]χ^2 test; [b]logistic regression; [c]$p < 0.05$, significant level of reference.

RESULTS

The overall incidence for ROP was 23.9% (59 infants), for Type 1 ROP was 9.3% (23 infants); for Type 2 ROP was 14.6% (36 infants). Median gestational age (GA) and birth weight (BW) were significantly lower among infants with ROP versus those without ROP (29: 23-34 vs. 31: 23-34, $p < 0.001$ and 1,180:630-2,000 vs. 1,485:590-2,000, $p < 0.001$ respectively). Multivariate analysis showed that only BW ($p = 0.029$) and small for gestational age (SGA) ($p = 0.045$) predicted the development of ROP (**Tab. 1**).

CONCLUSIONS

Birth weight and small for gestational age were the most significant risk factors for developing ROP. In comparison with studies from highly developed countries, infants in Croatia are developing Type 1 ROP with a much wider range of gestational age and birth weights.

ABS 117

SYSTEMIC ALTERATIONS IN HYPOXIA-INDUCIBLE FACTOR 1α EXPRESSION AND THE NLRP3 INFLAMMASOME IN POST NEONATAL ENCEPHALOPATHY IN SCHOOL AGE CHILDREN AND RESPONSE TO MELATONIN *IN VITRO*

L. Russo[1], V. Mc Eneaney[2], Z. Zareen[3], L.A. Kelly[4], E.J. Molloy[5]

[1]Paediatrics, Trinity College Dublin, Dublin, Ireland
[2]National Children's Hospital, Tallaght, Dublin, Ireland
[3]National Maternity Hospital, Holles Street, Dublin, Ireland
[4]Trinity Translational Medicine Institute (TTMI), Trinity College Dublin, Dublin, Ireland
[5]School of Biochemistry and Immunology, Trinity College Dublin, Dublin, Ireland

INTRODUCTION

Inflammasome and Hypoxia inducible factor 1α (HIF1α) pathways are important in chronic diseases. We aimed to examine the differences in the systemic expression of these genes between school-age children post NE, age-matched controls and children with severe cerebral palsy (CP).

METHODS

We measured the mRNA expression of HIF1α and NLRP3 inflammasome in whole blood, before and after treatment, *in vitro* with Lipopolysaccharide (LPS) (10 ng/ml) and Melatonin (42μM) using reverse transcription polymerase chain reaction (RT-PCR) following previous analysis of the NLRP3 inflammasome. Samples were analysed using Graphpad Prism V5. Results were analysed using the 2-ΔΔCT method.

RESULTS

HIF1α was increased within the CP group compared with the controls upon treatment with LPS and was decreased by a melatonin. There was also a statistically significant difference in the expression of HIF1α following melatonin treatment alone in the NE group versus the controls ($p < 0.03$). Expression of NLRP3 gene was significantly increased in children with NE ($p = 0.04$) after LPS stimulation in comparison to children in CP and control groups and was reduced with *in vitro* treatment with melatonin.

CONCLUSIONS

HIF1α and NLRP3 inflammasome expression were elevated in school age children with CP and also children post-NE. Targeting specific immune pathways maybe a therapeutic option in persistent inflammation in children with brain injury.

ABS 118

BRAIN GROWTH AND RELATIONSHIPS WITH ILLNESSES AND NEURODEVELOPMENT OUTCOME

R. D'Ascenzo[1], B. Pieroni[1], A. Pianesi[1], A. Peretti[1], L. Regnicolo[2], G. Polonara[2], M.J. Benders[3], V.P. Carnielli[1]

[1]Division of Neonatology, Salesi Children's Hospital, Polytechnic University of Marche, Ancona, Italy
[2]Department of Neuroradiology, University Hospital, Ancona, Italy
[3]Department of Neonatology, Wilhelmina Children Hospital, University Medical Center Utrecht, Utrecht, the Netherlands

INTRODUCTION

MRI of the preterm brain has been considered as a tool for predicting neurodevelopmental outcome since several years. Regional volumes and qualitative measures have been reported and related to outcomes, but are not yet clinically accessible. More recently, simple brain metrics (BM) have been identified as a measure of brain growth.

METHODS

We conducted a retrospective study on premature babies consecutively admitted from 1st January 2009 to 31st December 2016 to the Ancona Salesi Children's Hospital, with gestational age (GA) less than 30 weeks or birth weight (BW) less than 1,250 g and who underwent magnetic resonance imaging at term equivalent age (TEA-MRI). BM measures were undertaken according to Kidokoro brain growth measurements. Prospectively collected clinical data and Bayley scores were related to BM with regression analysis.

RESULTS

206 preterm infants with BW 886 ± 217 g and GA 27.5 ± 2.0 weeks underwent a TEA-MRI. On multivariable analysis including the major perinatal and postnatal factors, higher BW z-score and postmenstrual age at magnetic resonance imaging (PMAi) were independently associated with bi-parietal diameter, transverse cerebellar diameter (TCD) and basal ganglia surface (BGS), while male sex was associated with bi-parietal diameter and BGS (data not shown). **Tab. 1** shows the relationships between BM and postnatal diagnosis after adjustment of perinatal variables and PMAi.

Bayley III test was available in 80 infants and after adjustment for perinatal variables, TCD and sepsis were predictive of cognitive outcome (mean differences of 1.2 [CI 0.1-2.29] for each mm in change of the TCD, $p < 0.05$), while no BM were predictive of the motor ones (only sepsis).

CONCLUSIONS

This study provides further evidence that altered brain growth in preterm infants is associated with growth restriction and severity of illness. In our cohort among all the BM measurements only cerebellum diameter was significantly associated with cognitive outcome.

Table 1 (ABS 118). Relationships between brain metrics (BM) and postnatal diagnosis, after adjustment of perinatal variables and postmenstrual age at magnetic resonance imaging (PMAi).

Multivariable analysis Differences in brain diameters (Beta unstandardized coefficient), mean (95% CI), mm			
	Bi-parietal diameter	**TCD**	**BGS**
Sepsis[c]	NA	NA	-4.23 (-8.11 to -0.36)[a]
NEC II-III	NA	-3.63 (-6.02 to -1.24)[a]	-12.15 (-19.3 to -4.97)[b]
IVH III-IV	-2.49 (-4.42 to -0.56)[a]	-3.50 (-5.16 to -1.84)[a]	NA
BPD	NA	-2.37 (-3.69 to -1.04)[a]	NA

CI: confidence interval; TCD: transverse cerebellar diameter; BGS: basal ganglia surface.
[a]p .05. ; [b]p .01. ; [c]culture-proven sepsis.