



## Week 5: Neonatal Neurology

### Neonatal Neurology: Clinical II

**Thursday, July 30 2:30-4:00 pm EDT**

#### **Moderators**

Susan Cohen

Fernando Gonzalez

EDT	Abstract	Title	Presenting Author
2:30 pm		Introduction & General Information	
2:35 pm	3376425	The BIMP study: Brain imaging findings in Moderate-late Preterm infants	Vivian Boswinkel
2:45 pm	3364946	An integrated study of placenta, blood and brain MRI implicates IL-8 dysregulation in preterm brain injury.	Gemma Sullivan
2:55 pm	3377908	Post Hemorrhagic Hydrocephalus Management Among NICUs and Associated Comorbidities and Complications	Erwin Cabacungan
3:05 pm	3376637	Association of longitudinal brainstem development with neurodevelopmental outcomes in children born very preterm: from the neonatal period to 8 years	Mireille Guillot
3:15 pm	3369456	Maturation of functional connectivity for language networks from 30 weeks GA to age 3 years	Dustin Scheinost
3:25 pm	3378126	Whole transcriptome analyses and risk for cerebral palsy (CP) in extremely low gestational age neonates (ELGAN)	An Massaro
3:35 pm	3375779	The epigenetic clock: At the crossroads of preterm birth and brain injury	Noha Gomaa
3:45 pm	3373114	Impact of maternal dietary supplementation with pomegranate juice on brain injury in infants with IUGR: a randomized controlled trial	Madeline Ross
3:55 pm		Wrap Up	

Note: Schedule subject to change based on presenter availability.

**CONTROL ID:** 3376425

**TITLE:** The BIMP study: Brain imaging findings in Moderate-late Preterm infants

**PRESENTER:** Vivian Boswinkel

**AUTHORS (LAST NAME, FIRST NAME):** Boswinkel, Vivian<sup>1</sup>; Nijboer-Oosterveld, Jacqueline<sup>3</sup>; Krüse-Ruijter, Martine<sup>1</sup>; Smit-Wu, Mei-Nga<sup>1</sup>; Mulder - de Tollenaer, Susanne<sup>1</sup>; Boomsma, Martijn<sup>3</sup>; de Vries, Linda S.<sup>2</sup>; van Wezel - Meijler, Gerda<sup>1</sup>

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neurology: Clinical

**KEYWORDS:** moderate-late preterm , brain abnormalities, incidence.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Moderate-late preterm (MLPT) infants, born at 32 – 36 weeks' gestation, do not routinely undergo neuro-imaging. Therefore, little is known about the incidence of brain abnormalities.

**Objective:** To describe findings on cranial ultrasound (CUS) and magnetic resonance imaging (MRI) and to investigate perinatal factors associated with brain abnormalities in MLPT infants.

**Design/Methods:** Prospective cohort study of unselected MLPT infants born at Isala Women and Children's hospital. Data were collected at three time points. Early CUS was performed at day 3-4 and before discharge. At term equivalent age (TEA) CUS was repeated and MRI was additionally performed. CUS and MRI were scored using a scoring system for abnormalities in the ventricles, white matter (WM) and basal ganglia, including minor changes. The association of several perinatal factors with brain abnormalities was investigated using logistic regression.

**Results:** In total, 167 infants were included. All underwent early CUS. At TEA 149 infants underwent CUS and 127 infants MRI. Early CUS showed non-physiological periventricular echogenicity (PVE) in 47/167(28%) infants. At TEA this was still seen in nineteen, corresponding with WM signal intensity changes on MRI in four. In eight additional infants without PVE, WM changes were seen on MRI. Grade I and II intraventricular hemorrhage (IVH) was seen on early CUS in fifteen infants. In one case IVH was complicated by a periventricular hemorrhagic infarction. In eight infants IVH was still recognized at TEA CUS. Three infants with IVH had no MRI. In four of the remaining five infants, IVH was also seen on MRI. Watershed infarction was only seen on MRI in one infant. Other abnormalities not seen on CUS (i.e. delayed maturation, small cerebellar hemorrhages and punctate hemorrhages in the ventricular wall) were seen on MRI in 14 infants. No subdural hemorrhages were noted. In total, neuro-imaging abnormalities (CUS and/or MRI) were present in 50/149(34%) infants around TEA. Respiratory failure needing respiratory support was significantly associated with brain abnormalities around TEA (OR 2.82 95%CI 1.34 – 5.96; p=0.006).

**Conclusion(s):** Non-physiological PVE and low grade IVH were frequent findings on early CUS in MLPT infants. The incidences of WM changes and IVH were lower on TEA MRI. Respiratory failure was associated with brain imaging abnormalities. Follow up is needed to investigate the clinical consequences of these abnormalities and thus to consider whether routine neuro-imaging is indicated in (selected) MLPT infants.

(No Image Selected)

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**CONTROL ID:** 3364946

**TITLE:** An integrated study of placenta, blood and brain MRI implicates IL-8 dysregulation in preterm brain injury.

**PRESENTER:** Gemma Sullivan

**AUTHORS (LAST NAME, FIRST NAME):** Sullivan, Gemma<sup>1</sup>; Galdi, Paola<sup>1</sup>; Blesa Cabez, Manuel<sup>2</sup>; Borbye-Lorenzen, Nis<sup>6</sup>; Stoye, David<sup>3</sup>; Lamb, Gillian<sup>2</sup>; Evans, Margaret J.<sup>4</sup>; Quigley, Alan<sup>5</sup>; Thrippleton, Michael J.<sup>2</sup>; Skogstrand, Kristin<sup>6</sup>; Chandran, Siddharthan<sup>1</sup>; Bastin, Mark<sup>2</sup>; Boardman, James<sup>2</sup>

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neurology: Clinical

**KEYWORDS:** Preterm, MRI brain, Inflammation.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

#### **ABSTRACT BODY:**

**Background:** Systemic inflammation during perinatal life contributes to white matter disease in preterm infants. Histologic chorioamnionitis (HCA) is associated with white matter disease and cerebral palsy but the mediators that drive this association are poorly understood, which limits development of neuroprotective strategies.

**Objective:** To identify specific inflammatory mediators associated with HCA and white matter disease in preterm infants, using multi-scale data from placenta, blood and brain MRI.

**Design/Methods:** *Participants:* 102 preterm infants (mean postmenstrual age [PMA] 29<sup>+2</sup> weeks, range 23<sup>+3</sup>-32<sup>+0</sup>). *Inflammatory profile:* Customised immunoassay of 24 inflammatory markers and trophic proteins from umbilical cord and postnatal day 5 blood. *Placental histopathology:* Reaction patterns indicative of HCA. *MRI:* Structural and diffusion MRI were acquired at mean PMA 41<sup>+0</sup> weeks (range 38<sup>+0</sup>-44<sup>+4</sup>) using a 3T system. Peak width skeletonised mean diffusivity (PSMD) and neurite density index (PSNDI) were calculated as the difference between the 95th and 5th percentiles of water diffusion tensor maps and neurite orientation dispersion density imaging (NODDI) metrics. *Analysis:* Cord blood analytes differentially expressed in infants exposed to HCA were identified using Mann Whitney, and their relationship to HCA was investigated using logistic regression and ROC statistics. Principal component analysis identified day 5 analytes contributing >70% of variability in the data, and these were used in multiple regression models to predict PSMD and PSNDI, with adjustment for PMA at birth and PMA at scan.

**Results:** 44% of infants were exposed to HCA and had higher cord blood levels of C3, C5a, C9, CRP, IL-1 $\beta$ , IL-6, IL-8, MIP-1 $\beta$  and MCP-1. In logistic regression models IL-8 was the strongest predictor of HCA ( $\chi^2$  (2)=40.963 p<0.001). ROC curve analysis showed IL-8 AUC=0.917 (SE .039), 95% CI=0.841-0.993, p<0.001). In multivariable regression using day 5 analytes to predict PSNDI, the model explained a significant amount of variance (F(16,54)=5.09, p<0.001, R<sup>2</sup>=0.60, R<sup>2</sup>adjusted=0.48) and IL-8 was the only analyte identified as a predictor ( $\beta$ =0.221, p=0.037). There were no significant predictors of PSMD.

**Conclusion(s):** IL-8 is a sensitive predictor of HCA in preterm infants and is negatively associated with white matter maturity at term-equivalent age. These findings suggest that IL-8 dysregulation provides a link between systemic inflammation during perinatal life and atypical white matter development in preterm infants.

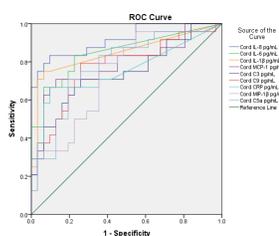


Figure 1. ROC curve analysis of cord blood markers for the prediction of HCA.

**IMAGE CAPTION:**

Figure 1. ROC curve analysis of cord blood markers for the prediction of HCA.

**CONTROL ID:** 3377908

**TITLE:** Post Hemorrhagic Hydrocephalus Management Among NICUs and Associated Comorbidities and Complications

**PRESENTER:** Erwin T. Cabacungan

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**CURRENT CATEGORY:** Neurology

**CURRENT SUBCATEGORY:** Neonatal Neurology: Clinical

**KEYWORDS:** Post-Hemorrhagic Hydrocephalus, National database, Outcomes.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Post-hemorrhagic hydrocephalus (PHH) remains a major morbidity of premature birth resulting from intraventricular hemorrhage (IVH). National consensus guidelines to direct timing of surgical interventions are lacking and leads to considerable variation in management among NICUs. Early intervention has been shown to improve outcomes, but we hypothesized that timing to intervene affects the comorbidities and complications associated with PHH.

**Objective:** To characterize comorbidities and complications associated with PHH management in a large national inpatient care dataset.

**Design/Methods:** We conducted a retrospective cohort study of hospital discharge data for premature infants (<1500g) with PHH using 2006-2016 Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID). Our primary outcome was timing of PHH intervention (early (EI) ≤28 days vs late (LI) >28 days). Hospital stay data included hospital region, gestational age (GA), birth weight (BW), length of stay (LOS), PHH treatment procedures, comorbidities, surgical complications, and death. Statistical analysis included Chi-square, Fisher exact, and Poisson or logistic regression. Analysis was adjusted for demographics, comorbidities and complications.

**Results:** Of the 1394 infants diagnosed with PHH, 357 (25%) had documented timing of surgical interventions during their hospital stay. More infants had LI compared to EI (76.4%). LI group infants were younger GA, lower BW, and more likely on public insurance. There was a regional difference in timing of treatment: hospitals in the West performed EI, whereas hospitals in the Midwest performed LI (Table 1). The LI group was associated with longer median LOS compared to the EI group (107 vs. 77 days, Figure 1.). More temporary reservoir/drains were placed in the EI group, whereas more permanent shunts were placed in the LI group. In those infants who required conversion to shunts in the EI group, replacement occurred earlier in the EI group than the LI group (median 74 vs 84 days). Shunt/device removal and complications did not differ between the two groups (Table 2). The LI group had 3-fold higher odds of sepsis (p<0.01) and a ¼ -fold lower odds of death (p<0.05) compared to the EI group (Table 3).

**Conclusion(s):** Timing of PHH intervention has regional differences suggesting the importance of national consensus guidelines. Development of these guidelines can be informed by the results of large national datasets which provide insights to comorbidities and complications of PHH interventions.

Characteristic	Early Intervention (EI)	Late Intervention (LI)	p-value
Region			<.001
West	10	1	
Midwest	1	10	
South	1	1	
North	1	1	
Other	1	1	
Insurance			<.001
Medicaid	10	10	
Medicare	1	1	
Private	1	1	
Other	1	1	
None	1	1	
GA (mean)	28.5	27.5	<.001
BW (kg)	1.2	1.0	<.001
LOS (days)	77	107	<.001
PHH treatment			<.001
Reservoir/Drain	10	1	
Shunt	1	10	
Conversion	1	1	
Replacement	1	1	
Removal	1	1	
Complication	1	1	
Death	1	1	

Table1: Significant Differences in Demographics between the 2 Groups with PHH [Early

Intervention (EI) group, ≤ 28 Days vs. Late Intervention (LI) group, > 29 Days]†

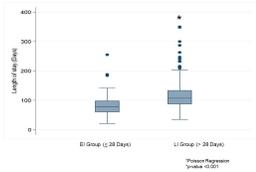


Figure 1: Significant Differences of Length of Stay between the 2 groups with PHH [Early Intervention (EI) group, ≤ 28 days vs. Late Intervention (LI) group > 28 days]†

Significant Differences	Number of Subscribers/Procedures (%)		p-value
	≤ 28 Days (EI)	> 29 Days (LI)	
Age	100	100	0.000
Gender	100	100	0.000
Insurance	100	100	0.000
Comorbidities and Complications	100	100	0.000
Procedure	100	100	0.000

Table 2: Significant Differences in the Treatment Procedures and its Complications between the 2 Groups with PHH [Early Intervention (EI) Group, ≤ 28 Days vs. Late Intervention (LI) Group, > 28 Days]†

Table 3: Significant Adjusted Odds Ratio [OR(95%CI)] for Comorbidities and Complications†

Comorbidity/Complication	Number of Subscribers/Procedures (%)		OR (95%CI)
	≤ 28 Days (EI)	> 29 Days (LI)	
Age	100	100	1.000
Gender	100	100	1.000
Insurance	100	100	1.000
Procedure	100	100	1.000

Table 3: Significant Adjusted Odds Ratio [OR(95%CI)] for Post-Hemorrhagic Hydrocephalus Comorbidities and Complications†

**IMAGE CAPTION:**

Table1: Significant Differences in Demographics between the 2 Groups with PHH [Early Intervention (EI) group, ≤ 28 Days vs. Late Intervention (LI) group, > 29 Days]†

Figure 1: Significant Differences of Length of Stay between the 2 groups with PHH [Early Intervention (EI) group, ≤ 28 days vs. Late Intervention (LI) group > 28 days]†

Table 2: Significant Differences in the Treatment Procedures and its Complications between the 2 Groups with PHH [Early Intervention (EI) Group, ≤ 28 Days vs. Late Intervention (LI) Group, > 28 Days]†

Table 3: Significant Adjusted Odds Ratio [OR(95%CI)] for Post-Hemorrhagic Hydrocephalus Comorbidities and Complications†

CONTROL ID: 3376637

TITLE: Association of longitudinal brainstem development with neurodevelopmental outcomes in children born very preterm: from the neonatal period to 8 years

PRESENTER: Mireille Guillot

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**CURRENT CATEGORY:** Neurology

**CURRENT SUBCATEGORY:** Neonatal Neurology: Clinical

**KEYWORDS:** preterm, brainstem, neurodevelopment.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

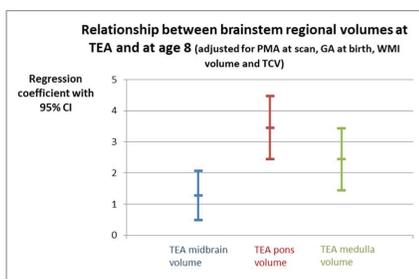
**Background:** The brainstem is critical to vital body functions. However, brainstem development from the neonatal period to school age and its relationship with neurodevelopmental outcome in children born very preterm are largely unknown.

**Objective:** In children born very preterm, determine (1) the trajectory of brainstem development from the neonatal period to school age; (2) the relationship between brainstem regional volumes (midbrain, pons and medulla) at term-equivalent age (TEA) and age 8 years with longitudinal neurodevelopmental outcomes.

**Design/Methods:** A prospective cohort of 120 children born very preterm (mean gestational age [GA] 27.9 weeks, SD 2.4), underwent brain MRI at early in life, TEA and 8 years (mean post menstrual age [PMA] 32.4 weeks, 40.5 weeks and 8.1 years, respectively). Brainstem regional and total volumes were obtained at TEA and at 8 years with MAGeT-Brain pipeline, and white matter injury (WMI) volumes at early in life were quantified. Neurodevelopmental outcomes were assessed in 111 children. Cognitive outcomes were assessed with Bayley-III (cognitive composite) at 18 and 36 months, WPPSI-III (full-scale IQ [FSIQ]) at 4.5 years, and WASI-II (FSIQ, vocabulary and matrix reasoning scores) at age 8. Motor outcomes were assessed with Bayley-III (motor composite) at 18 and 36 months, and MABC-2 at 4.5 and 8 years. Multivariable regression models adjusting for PMA at scan, GA at birth, WMI volume and total cerebral volume (TCV) were used.

**Results:** Brainstem regional volumes at 8 years were predicted by regional TEA volumes (Figure). Motor and cognitive outcomes at 18 months, 36 months and 4.5 years were predicted by brainstem total volumes at TEA with a stronger effect size than TCV and/or WMI volume. At age 8, the volume of the pons was associated with WASI-II FSIQ ( $\beta=0.003$ ,  $p=0.013$ ) and vocabulary scores ( $\beta=0.002$ ,  $p=0.006$ ), but not motor skills. Neither midbrain nor medulla volumes were independently associated with neurodevelopmental outcome at school age.

**Conclusion(s):** In children born very preterm, a smaller brainstem at TEA predicts adverse neurodevelopmental outcomes up to preschool age. The pons volume at age 8, which is strongly predicted by its volume at TEA, is associated with adverse cognitive outcomes. Further research is needed to identify the neural mechanisms implicated in the association between pontine development and long-term cognition.



**IMAGE CAPTION:**

**CONTROL ID:** 3369456

**TITLE:** Maturation of functional connectivity for language networks from 30 weeks GA to age 3 years

**PRESENTER:** Dustin Scheinost

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**CURRENT CATEGORY:** Neurology

**CURRENT SUBCATEGORY:** Pediatric Neurology

**KEYWORDS:** neural networks, language , developing brain.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** The acquisition of language is a hallmark of human development. Although the neural scaffolding for language acquisition is putatively present in neonates, the maturation of the functional connectivity (FC, or the temporal correlation of activity) between the key language regions, Broca's and Wernicke's regions, is unknown.

**Objective:** Employing cross-sectional data, we examine functional connectivity between Broca's and Wernicke's regions from 30 weeks of gestation through 3 years of age.

**Design/Methods:**

Resting-state FC MRI data were acquired in 9 fetuses at 30-32 weeks GA (31.8±1.2 weeks), 8 fetuses at 34-46 weeks GA (35.0±.72 weeks), 49 one-month-old infants (1.0±.35 months), 52 nine-month-old infants (9.1±.24 months), and 19 toddlers between 16-36 mos (26.6±6.7 months). Standard seed connectivity analyses from seeds placed in Broca's and Wernicke's regions in the L hemisphere and their R hemisphere homologues were performed. For each subject, we calculated the FC (i.e., correlation of time-courses) between pairs of regions. T-tests were used to compare the Fisher transformed correlations across subjects to 0. Significance was assessed at p<0.05.

**Results:** In fetuses, FC between L and R homologues and between L Broca's and L Wernicke's region was not significantly different than 0 (**Table 1**). After birth, significant FC between L and R homologues of Broca's and Wernicke's regions was observed for all ages. Significant FC between L Broca's and L Wernicke's regions was only observed in toddlers. Correlation between L Broca's and L Wernicke's region connectivity and R Broca's and R Wernicke's region connectivity in the neonatal period was  $r(26)=.469$ ,  $p=.012$ , suggesting parallel development of these critical regions.

**Conclusion(s):**

While not connected in the 3<sup>rd</sup> trimester, the homologues of Broca's and Wernicke's regions are already connected at birth. In contrast, neural connectivity between L Broca's and Wernicke's regions does not develop until years 2-3 of life. Connectivity between these key regions for language develops in parallel in early life, suggesting an early lack of lateralization for language.

Table 1. Mean(SD) FC between Broca's and Wernicke's in fetuses, neonates, infants, and toddlers and their statistics comparing strength of FC to 0.

	L-R Broca's	L-R Wernicke's	L Broca's-L Wernicke's
30-32 wks GA	M=-.15(SD=.39)  t(8)=1.1, p=.29	M=-.29(SD=.15)  t(8)=1.5, p=.16	M=-.096(SD=.29)  t(8)=.95, p=.36
34-46 wks GA	M=-.11(SD=.38)  t(7)=.85, p=.42	M=-.08(SD=.55)  t(7)=1.1, p=.32	M=-.17(SD=.46)  t(7)=1.1, p=.32
1 mo	M=-.40(SD=.16)  t(51)=20.5, p<.001	M=-.40(SD=.25)  t(51)=11.2, p<.001	M=-.04(SD=.16)  t(51)=1.1, p=.44
9 mos	M=-.29(SD=.27)  t(47)=7.4, p<.01	M=-.35(SD=.27)  t(47)=9.2, p<.001	M=-.02(SD=.22)  t(47)=.66, p=.51
Toddlers	M=-.32(SD=.28)  t(18)=6.0, p<.001	M=-.39(SD=.24)  t(18)=6.9, p<.001	M=-.20(SD=.23)  t(18)=3.5, p=.002

## IMAGE CAPTION:

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**CONTROL ID:** 3378126

**TITLE:** Whole transcriptome analyses and risk for cerebral palsy (CP) in extremely low gestational age neonates (ELGAN)

**PRESENTER:** An N. Massaro

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neurology: Translational

**KEYWORDS:** cerebral palsy, prematurity, transcriptomics.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

### ABSTRACT BODY:

**Background:** Extremely Low Gestational Age Neonates (ELGANs) experience high rates of neurodevelopmental impairment, including cerebral palsy in up to 10%. Whole transcriptome analysis is a promising avenue for discovery of biomarkers that can elucidate causal pathways and provide potential novel therapeutic targets for CP in this high risk population.

**Objective:** To identify individual differentially expressed genes and relevant gene pathways which distinguish ELGANs with and without CP.

**Design/Methods:** We evaluated PBC specimens collected in the context of a randomized controlled trial evaluating erythropoietin for neuroprotection in the ELGAN (Preterm Epo Neuroprotection Trial– PENUT, NCT# 01378273). RNA was isolated (Qiagen, Inc., Valencia, CA) from stored PBC pellets collected on day 1 and 14. Whole transcriptome data were generated from subjects with adequate RNA (RIN>5) using the Human Clariom S Array (Affymetrix, ThermoFisher Scientific, Waltham, MA). Gene expression data were analyzed using Bioconductor packages in R software (r-project.org). Bayesian models were used to compare a) CP vs Control at day 1 and 14, b) the interaction (day 1 to 14 change) between CP vs Control, and c) the day 1 to 14 change for each diagnosis. A false discovery ratio (FDR) threshold of <0.05 was considered statistically significant. Secondly, impact analyses (iPathwayGuide) were performed to identify relevant pathways that were unique to each diagnosis.

**Results:** Gene expression data were generated from 56 subjects (n=29 CP vs n=27 Control) on day 1 and 23 subjects (n=12 CP vs n=11 Control) on day 14. While there was evidence for numerous differentially expressed genes for the between day comparisons within each diagnosis (Control Day 1 vs 14 n=841 significant genes; CP Day 1 vs 14 n=579; Figure 1), there were no significant differentially expressed genes between CP vs Control at day 1, day 14 nor the change between day 1 to 14 (Bayesian model FDR>0.05). However, iPathwayGuide analysis of differentially expressed genes between day 1 and 14 that were unique to each diagnosis (Figure 1, Control=blue, CP=yellow) identified several top pathways of potential clinical relevance (Table 1).

**Conclusion(s):** Whole transcriptome analyses identified a profile of genes that are uniquely differentially expressed between day 1 and 14 in patients who later developed CP. Several genes are involved in neurodegenerative pathways that warrant further investigation.

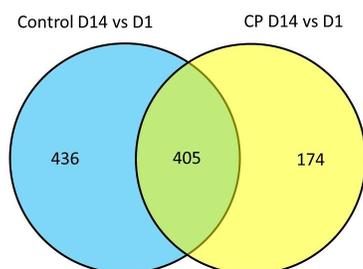


Figure 1. Venn diagram of differentially expressed genes between day 1 and 14 in CP compared to control ELGANs

	Pathway Name	p-value	FDR	Perturbed Genes	Notes
UNIQUE TO CP	Huntington Disease	4.593e-5	0.008	Upregulated: VDAC2, COX5A, POLR2E Downregulated: GPX1, NDUFB3, NDUFA13, UQCRC10, TGM2, COX7C	Interference with BDNF transcription/transport, destabilization of neuronal mitochondria
	Thermogenesis	2.889e-4	0.026	Upregulated: COX5A, ADCY7 Downregulated: GNAS, NDUFB3, NDUFA13, UQCRC10, DPFB3, COX7C, ADRB3, ADCY1-6, ADCY8-10	Process triggered by hypothermia whereby chemical energy is converted to heat in adipose tissue to ensure normal cellular processes
	Parkinson Disease	5.085e-4	0.030	Upregulated: CYCS, VDAC2, CASP9, CASP3, COX5A Downregulated: NDUFB3, NDUFA13, UQCRC10, COX7C	Proteasome dysfunction, mitochondrial impairment and oxidative stress leading to loss of dopaminergic neurons
	Ferropitosis	7.290e-4	0.032	Upregulated: VDAC2, CYBB Downregulated: SLC11A2, GCLC	Regulated cell death characterized by production of reactive oxygen species from iron and lipid peroxidation; involved in neurodegenerative disease
UNIQUE TO CONTROL	Ribosome	2.035e-8	5.188e-6	Upregulated (in Control): RPL7A, RPL11, RPL19, RPL23A, RPL30, RPL37, RPL38, RPS5, RPS8, RPS11, RPS15A, RPS20, RPS29, MRPL20 Downregulated (in Control): UBA52, MRPL1	Developmental increase in ribosomal biogenesis observed in controls but not CP subjects is consistent with prior reports of impaired ribosomal activity in CP

Table 1. Top pathways based on differentially expressed genes between day 1 and 14 in CP vs Control cases

**IMAGE CAPTION:**

Figure 1. Venn diagram of differentially expressed genes between day 1 and 14 in CP compared to control ELGANs

Table 1. Top pathways based on differentially expressed genes between day 1 and 14 in CP vs Control cases

**CONTROL ID:** 3375779

**TITLE:** The epigenetic clock: At the crossroads of preterm birth and brain injury

**PRESENTER:** Noha AE Gomaa

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**CURRENT CATEGORY:** Neurology

**CURRENT SUBCATEGORY:** Neonatal Neurology: Clinical

**KEYWORDS:** epigenetic clock, preterm birth, early brain injury.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

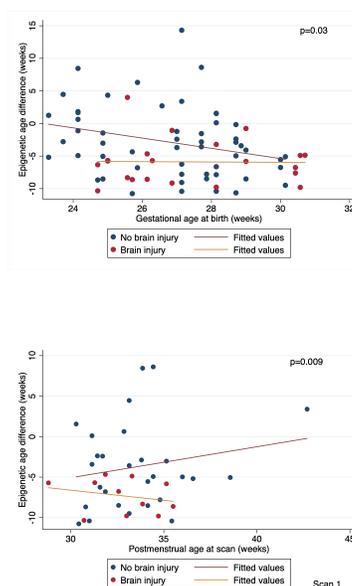
**Background:** Epigenome-wide association studies show epigenetic alterations to associate with several health conditions. More recently, the epigenetic clock was introduced to assess age-specific epigenetic changes in relation to developmental milestones. The relationship between epigenetic age and preterm birth and its link to neonatal brain health has not been investigated.

**Objective:** To determine the association between preterm birth and epigenetic age, and whether this relationship is modified by postnatal brain injury.

**Design/Methods:** In this prospective cohort of 39 very preterm neonates (gestational age (GA)= 23.2-30.7w), MRI scans were obtained: i) early in life (median postmenstrual age (PMA)=33.1w, IQR=31.5-34.8), and ii) at term-equivalent age (PMA=43.0w, IQR=40.6-45.9w). Severe intraventricular haemorrhage (IVH) and moderate to severe white matter injury (WMI) were concordant in this cohort. Severe brain injury (BI) was thus categorized as severe IVH (Grade 3 or 4) and/or moderate to severe WMI (Grade 2 or 3). Buccal swabs were collected at each scan and samples were run on Illumina Infinium EPIC arrays. The Pediatric-Buccal-Epigenetic Clock calculated epigenetic age from DNA methylation at 94 age-informative CpG sites, based on a recent method in a normative pediatric population. Epigenetic age difference (dDNAMAge) was calculated by subtracting epigenetic age from PMA. Neonates were dichotomized into extremely preterm (< 28weeks) and very preterm ( $\geq 28$  weeks GA). Generalized estimating equations were used to assess the association between dDNAMAge and GA, and dDNAMAge and PMA at 1<sup>st</sup> scan, and whether severe BI modified these relationships.

**Results:** GA was inversely associated with dDNAMAge, with extremely preterm neonates showing an accelerated epigenetic age compared to very preterm neonates ( $\beta=-2.2$ ,  $p=0.03$ ). Severe BI modified the GA and dDNAMAge relationship, where extremely preterm neonates with severe BI showed a significantly decelerated epigenetic age ( $p=0.01$ ) (Fig. 1). Within the first two weeks of life, epigenetic age accelerates for all neonates, except for extremely preterm ones with severe BI who continue to be epigenetically decelerated (Fig. 2).

**Conclusion(s):** Epigenetic age may be more sensitive to BI in extremely preterm neonates, compared to their older GA counterparts. The epigenetic clock may be a tool to understand the relationship between early brain health and development in the preterm neonate. Ongoing research assesses the relationship between epigenetic age, brain injury and neurodevelopmental outcomes .



**IMAGE CAPTION:**

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**CONTROL ID:** 3373114

**TITLE:** Impact of maternal dietary supplementation with pomegranate juice on brain injury in infants with IUGR: a randomized controlled trial

**PRESENTER:** Madeline Ross

**AUTHORS (LAST NAME, FIRST NAME):** Ross, Madeline<sup>2</sup>; Turner, Daria<sup>1</sup>; Mikulis, Nicole D.<sup>3</sup>; Cherkerzian, Sara<sup>1</sup>; Matthews, Lillian G.<sup>1</sup>; Inder, Terrie<sup>1</sup>

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neurology: Clinical

**KEYWORDS:** IUGR, antioxidant, MRI.

**SESSION TITLE:** Neonatal Neurology: Clinical II |Neonatal Neurology: Clinical II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

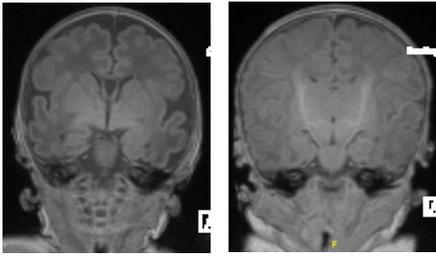
**Background:** Previous studies in animal models have demonstrated that polyphenol-rich pomegranate juice can act as a neuroprotectant against hypoxic-ischemic injury (HIE). We have recently reported differences in brain structure and function in a randomized controlled trial of maternal pomegranate juice consumption in pregnancies with intrauterine growth restriction (IUGR), namely reduced diffusivity within the anterior (ALIC) and posterior (PLIC) limbs of the internal capsule, as well as reduced functional connectivity within visual resting state networks.

**Objective:** The objective of this double-blind randomized controlled trial was to further investigate the impact of maternal dietary supplementation with pomegranate juice on brain injury in a second cohort of newborns with IUGR.

**Design/Methods:** Mothers with a fetal diagnosis of IUGR less than the 5th percentile on the Doublilet fetal growth curve at 24-34 weeks' gestation were recruited and randomly assigned to either treatment (pomegranate juice) or placebo (polyphenol-free juice). Participants drank 8 ounces of either treatment or placebo juice each day from enrollment until delivery. Infants underwent magnetic resonance imaging (MRI) at term equivalent age. The MRIs were assessed for brain injury score according to established criteria. Associations between juice arm and brain injury were adjusted for potential confounding by sex, gestational age at birth, and postmenstrual age at MRI.

**Results:** 96 mothers were randomized to drink placebo (n=45) or pomegranate juice (n=51). To date, of those participants randomized, 55 infants underwent MRI (n=29 in placebo group, n=26 in treatment group). Infants randomized to pomegranate juice were 3.9 (95% CI 2.4-6.6) times less likely to demonstrate any abnormality on scoring of the MRI. Infants whose mothers drank pomegranate juice were 5.8 (95% CI 4.2-8.2) times less likely to demonstrate impaired myelination, 2.4 (95% CI 1.8-3.2) times less likely to demonstrate delays in gyral maturation, 2.8 (95% CI 1.6-5.0) times less likely to demonstrate enlarged lateral ventricles, and 1.5 (95% CI 1.1-2.1) times less likely to demonstrate brain volume reduction compared to infants whose mothers drank placebo juice.

**Conclusion(s):** Preliminary analyses demonstrate reduced brain injury among infants whose mothers were randomly assigned pomegranate juice compared to infants of mothers who drank placebo juice, suggesting a neuroprotectant effect of pomegranate juice on the neonatal brain.



**Figure 1. Representative T1 coronal MRI images from IUGR infants imaged at term equivalent age.** A) Left: infant of mother who drank placebo juice. This scan demonstrates delayed gyral maturation, and delayed myelination. Total injury score = 7 (3 for white matter delays, 3 for cortical gray matter delays, 1 for small cerebellum). B) Right: infant of mother who drank pomegranate juice. This scan demonstrates tertiary cortical folding and distinct myelination. Total injury score= 0.

**IMAGE CAPTION:**

**Figure 1. Representative T1 coronal MRI images from IUGR infants imaged at term equivalent age.** A) Left: infant of mother who drank placebo juice. This scan demonstrates delayed gyral maturation, and delayed myelination. Total injury score = 7 (3 for white matter delays, 3 for cortical gray matter delays, 1 for small cerebellum). B) Right: infant of mother who drank pomegranate juice. This scan demonstrates tertiary cortical folding and distinct myelination. Total injury score= 0.

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