



September 15th, 2021 15:00 - 17:00

PARALLEL SESSION 8 - BRAIN 2

ID 159. Regulatory T cells contribute to sexual dimorphism in neonatal hypoxic-ischemic brain injury

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Background:

Neonatal encephalopathy caused by hypoxia-ischemia (HI) is a major cause of death and disability in newborns. Clinical and experimental studies suggest a sexual dimorphism in HI induced brain injury and therapy responses. A major hallmark of HI pathophysiology is the infiltration of peripheral immune cells into the injured brain. However, the specific role of regulatory T cells (Tregs) is still unknown.

Methods:

Nine-day-old mice were exposed to HI by ligation of the right common carotid artery followed by 1 h hypoxia (10% oxygen). Using immunohistochemistry, flow cytometry and microarray analyses, Tregs were investigated in the brain, spleen and blood 24 h post HI. The functional role of Tregs was evaluated by acute Treg depletion in DEREK mice. Brain injury, neuroinflammatory responses and vascular injury were analyzed via immunohistochemistry and western blot 48 h and 7 days after HI.

Results:

Females revealed an increased cerebral Treg infiltration, coinciding with elevated chemokine receptor expression. Treg depletion in females aggravated HI-induced brain tissue injury, associated with enhanced microglia and endothelial activation and leukocyte infiltration. Treg depletion in males resulted in neuroprotection, associated with reduced astrogliosis and vascular injury. Ex vivo isolated female Tregs displayed an increased immunosuppressive activity associated with an altered transcriptional profile compared to male Tregs.

Conclusion:

The present findings demonstrate that Tregs from female mice provide endogenous neuroprotection, whereas Tregs from male mice enhance secondary neurodegeneration. As potential mechanisms, we identified intrinsic transcriptional differences associated with enhanced anti-inflammatory activity of female Tregs and non-immunological detrimental effects of male Tregs, related to vascular damage. Our study emphasizes the urgent need for sex-stratified clinical and pre-clinical analyses.

None declared



ID 12. Predictive performance and metabolite dynamics of proton MR spectroscopy in neonatal hypoxic-ischemic encephalopathy

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Background: Prognostic value of proton MR spectroscopy (H-MRS) in hypoxic-ischemic encephalopathy (HIE) is acknowledged, however, effects of gestational age (GA) and postnatal age (PA) on prediction and metabolite levels are unknown.

Methods: 169 consecutive newborns with moderate-to-severe HIE were studied, having ≥ 1 H-MRS scan during postnatal days 0-14, and known neurodevelopmental outcome (Bayley-II score/cerebral palsy/death). Initial scans were categorized by PA (day 1-3/4-6/ ≥ 7), and metabolite ratios were compared by predictive value. Metabolite dynamics were assessed in a total of 214 scans performed in the study population, using regression modelling, with predictors GA, PA and outcome.

Results: N-acetyl-aspartate (NAA)/creatinine (Cr) and myo-inositol (ml)/NAA height ratios were consistently associated with outcome throughout the first 14 days, with highest predictive value in the late (≥ 7 days) period (AUC=0.963 and 0.816, respectively). Neither GA, nor PA had an overall effect on these metabolite ratios, which showed strongest association with outcome ($p < 0.001$). Assessed separately in patients with good outcome, GA became a significant covariate for metabolite ratios ($p = 0.0058$ and 0.0002 , respectively). However, this association disappeared in the poor outcome group.

Conclusion: In HIE, NAA/Cr and ml/NAA gives most accurate outcome prediction throughout postnatal days 0-14. GA only affected metabolite levels in the good outcome group.

H.B. was supported by the ÚNKP-20-4-I New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund (ÚNKP-20-4-I-SE-8).

None declared



ID 424. A COMPARISON OF FOUR BRAIN MRI SCORING SYSTEMS IN NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: INTERRATER RELIABILITY AND PREDICTION OF OUTCOME

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Background: Brain MRI scan results are main predictors for the outcome of neonates with hypoxic-ischemic encephalopathy (HIE). There is currently no uniform method to assess these brain MRI scans. The aim was to determine which MRI-score demonstrates the highest interrater reliability and most accurately predicts the outcome at 2 years of age.

Methods: Four MRI scoring systems for neonates with HIE were selected: (1) Weeke score; (2) NICHD score; (3) Rutherford score and (4) Trivedi score (the adapted Bednarek). All scores (except the Rutherford score) included assessments of diffusion weighted imaging. Two blinded raters retrospectively assessed and scored the brain MRI images of 161 neonates with HIE, born between 2010 and 2014, treated with hypothermia. Results of all four scoring systems were compared and interrater reliability was assessed. Outcome was assessed by standardized neurodevelopmental testing at the age of 2 years. Neurodevelopmental impairment (NDI) was defined as a motor or cognitive composite score of at least 1 standard deviation below the reference mean on the Bayley Scales of Infant and Toddler Development Third Edition (i.e. a score < 85 points), diagnosis of cerebral palsy (Gross Motor Function Classification System of ≥ 2), hearing loss requiring hearing aids or severe visual loss. The combined outcome was defined as death or NDI.

Results: Interrater reliability analyses demonstrated good reliability of the Weeke score (Intraclass correlation coefficient (ICC) 0.740) and the Trivedi score (ICC 0.759), a reasonable reliability of NICHD (weighted Kappa 0.646) and an insufficient reliability of the Rutherford score (ICC 0.526). The reliability improved when analyzing only high quality scans.

All four different scoring systems performed well in distinguishing between a normal or NDI: Weeke score AUC 0.71(0.60-0.82), NICHD score AUC 0.69(0.59-0.79), Trivedi score AUC 0.67(0.56-0.78) and Rutherford score AUC 0.66(0.55-0.77). This was also true for predicting the combined outcome: Weeke score AUC 0.88(0.82-0.94), NICHD score AUC 0.86(0.79-0.93), Trivedi score AUC 0.85(0.79-0.92) and Rutherford score AUC 0.79(0.71-0.87).

Conclusion: Trivedi score and Weeke score performed best on interrater reliability which possibly can be attributed to the use of DWI. All four MRI brain-scores proved to be usable predictors for the outcome at 2 years of age.

None declared



ID 443. Metabolic and haemodynamic reactivity indices of cerebral auto-regulation provide an early assessment of injury severity and predict neurological outcome following neonatal encephalopathy

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Background:

Neonatal encephalopathy (NE) resulting from intrapartum events remains a significant global health problem. An urgent need exists for a cot-side biomarker for early stratification of injury severity and prediction of neurological outcome. Broadband near-infrared spectroscopy (BNIRS) monitors real-time changes in mitochondrial metabolism (oxCCO) and cerebral oxygenation (HbD). Wavelet semblance (reactivity index of phase difference) of BNIRS variables can measure cerebral autoregulatory disturbance at 48h of life during therapeutic hypothermia and predict neurodevelopmental outcome. A novel dual monitoring platform with BNIRS and diffuse correlation spectroscopy (DCS) directly monitors microvascular cerebral blood flow (BFI) along with mitochondrial metabolism and oxygenation. We hypothesised that optical wavelet reactivity indices early after a hypoxic ischaemic (HI) injury in a preclinical model of NE will relate to outcome.

Methods:

Combined BNIRS-DCS monitoring was performed in 18 newborn piglets during and after induced HI injury. Insult severity was graded to simulate moderate HI in 7 piglets and severe HI in 6 piglets. Five piglets did not have HI insult (control). Reactivity indices were calculated as mean oxCCO-HbD and BFI-HbD semblance over one hour of monitoring at one-hour post-insult using wavelet analysis. All animals had MR imaging and proton MR spectroscopy in a 3T scanner 6hrs post-insult. Thalamic Lac/NAA 0.39 was used as cut-off threshold for neurological outcome along with TUNEL+ cell count in thalamic region on brain histology.

Results:

Both oxCCO-HbD (metabolic reactivity) and BFI-HbD semblance (vascular reactivity) correlated with thalamic Lac/NAA ($p=0.009$, $r^2=0.353$ and $p=0.057$, $r^2=0.234$ respectively). Both oxCCO-HbD and BFI-HbD semblance correlated with thalamic TUNEL+ histology ($p=0.056$ and 0.020). Both oxCCO-HbD and BFI-HbD semblance were significantly different between groups based on insult severity ($p=0.046$ and 0.002) and between groups of animals with good and poor neurological outcome based on thalamic Lac/NAA ($p=0.002$ and 0.025) (Figure 1).

Conclusions:

Early optical markers of metabolic and vascular reactivity (indicating mitochondrial injury and cerebrovascular autoregulatory impairment) following HI insult can assess injury severity and predict neurological outcome in an animal model of NE. These translational findings can be important for clinical decisions and needs to be investigated further in a clinical study.

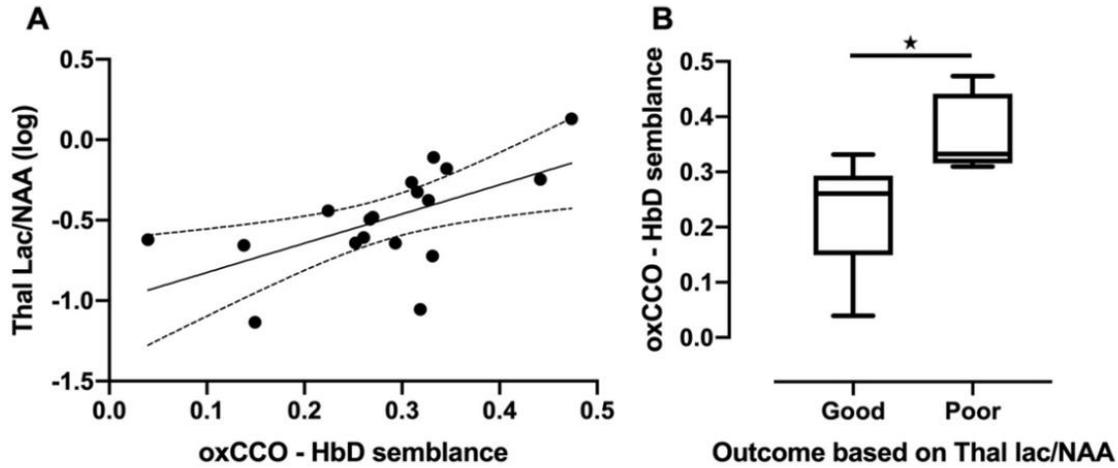


Figure 1. Linear regression analysis between oxCCO-HbD semblance and thalamic lac/NM, $p=0.009$ (A), ox-CCO-HbD semblance was significantly different between outcome groups based on thalamic lac/NM cut off threshold 0.39 (B).

Figure 1. Linear regression analysis between oxCCO-HbD semblance and thalamic lac/NM, $p=0.009$ (A), ox-CCO-HbD semblance was significantly different between outcome groups based on thalamic lac/NM cut off threshold 0.39 (B).

None declared