



September 16th, 2021 11:00 - 13:00

PARALLEL SESSION 13 - BRAIN 3

ID 534. Development of an automated real-time sleep-state prediction algorithm in preterm infants: the Sleep Well Baby project

Drs Thom Sentner¹, Drs Lieke van Schaijk¹, Drs Eline de Groot¹, Drs Xiaowan Wang¹, Dr. Richard Bartels¹, Dr. Daniel Vijlbrief¹, Prof. Manon Benders¹, Doctor Jeroen Dudink¹

¹UMCU, Utrecht, Netherlands

Introduction: In the womb, sleep is believed to be the major driver of neural activity, a process that is critical for neuronal survival, axonal guidance, and synapse maturation. However, in the NICU, preterm infants are exposed to a myriad of extrinsic stimuli that radically alter their sleep-wake states. To improve sleep in preterm infants, it is essential to co-align elective treatments on sleep and wake states. This is especially challenging because the active sleep states are hard to be distinguished from wake states. We aimed to develop an automated real-time sleep-state prediction algorithm in preterm infants based on vital signs that are routinely collected in neonatal intensive care unit (NICU).

Methods: We designed a novel and robust supervised machine-learning algorithm called SleepWellBaby (SWB) for real-time neonatal sleep-wake classification in the NICU. The SWB algorithm used the vital physiological parameters: heart rate, respiratory rate, and oxygen saturation as input features. The target variable consisted of minute-by-minute sleep states for which ground-truth labels were derived using our in-house behavioral sleep annotation system. The sleep-wake states were annotated as active sleep (AS), quiet sleep (QS), and wake. The random forest model was used as the underlying classifier. The model was trained on 23 unique preterm infants (28wk-32wk PMA; 90% of train data) via k-fold grouped cross-validation and randomized grid search. It was then tested on three independent infants (10% of train data). Bootstrapping was used to estimate 95% confidence intervals (CIs) of the area under the ROC curve (AUC). Model performance was later validated on nine newly observed infants.

Results: The macro-averaged Area Under Curve (AUC) was 0.73 [0.71-0.74], with an AUC of 0.80 [0.78-0.83] for wake (Figure 1). Similar performance was observed in the 9 validation patients (Figure 2), with an averaged AUC of 0.69 [0.67-0.72] and an AUC for wake of 0.77 [0.72-0.81] indicating good generalization performance of the model. Figure 1.

Conclusion: We developed a well performing automated sleep-state prediction algorithm based on bedside vital parameters that generalized well to an independent sample of patients. Currently, we are preparing the next step of validating the model in real-world clinical practice settings.

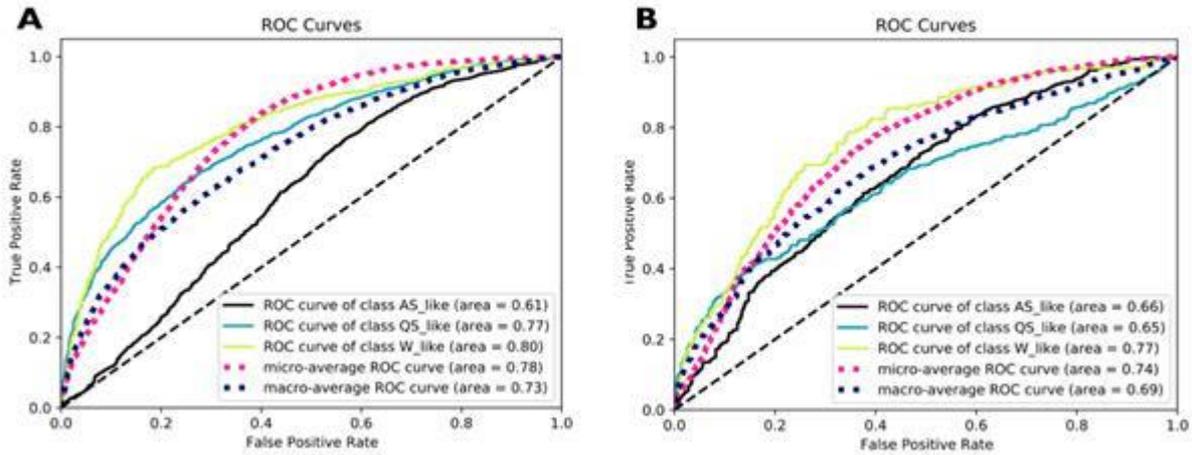


Figure 1. Showing the Receiver operating characteristics curves (ROC), illustrating the predictive ability of the SWB algorithm to distinguish between different sleep/wake states (A) Cross validation train results (B) Pilot results.

Figure 1. Showing the Receiver operating characteristics curves (ROC), illustrating the predictive ability of the SWB algorithm to distinguish between different sleep/wake states (A) Cross validation train results (B) Pilot results.

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the abstract.



ID 277. LEVETIRACETAM OR PHENOBARBITONE AS A FIRST LINE ANTICONVULSANT IN ASPHYXIATED TERM NEWBORNS? - AN OPEN LABEL, SINGLE CENTRE, RANDOMISED CONTROLLED PRAGMATIC TRIAL

Doctor Sukena Susnerwala¹, DR L.S Deshmukh¹

¹Government Medical College Aurangabad, Aurangabad, India

Background: Neonatal seizures are one of the most difficult conundrums for experts across the globe. Although there is no consensus on the 'ideal' treatment of neonatal seizures, phenobarbitone has been the drug of choice for decades. Levetiracetam, though extensively studied in adults and children, lacks rigorous evaluation in the neonatal population, despite its frequent use as an off-label drug.

Methods: The study was designed as an open-label, randomized active control, single-center, pragmatic trial. The objective was to compare the efficacy of levetiracetam to phenobarbitone in term asphyxiated babies as a first-line drug. Inborn term asphyxiated babies with seizures in the first 48 hours of life were included. Babies satisfying the inclusion criteria were randomized to receive levetiracetam (20mg/kg) or phenobarbitone (20mg/kg). Clinical seizure control was noted. Babies who failed to respond to the primary drug were crossed over to receive the other group drug.

Results: Out of 103 eligible babies, 82 were randomized (44 levetiracetam group, 38 phenobarbitone group). Clinical seizure control with the primary drug and maintenance of the same for 24 hours was observed in 29 babies (65.9%) in the levetiracetam group and 13 babies (34.2%) in the phenobarbitone group ($p < 0.05$, RR 0.52, 95% CI 0.32 to 0.84). 57.8% of babies in the phenobarbitone group were controlled after cross over to levetiracetam ($p < 0.05$) (ref table 2)

Conclusion: Levetiracetam can be used with good efficacy as a first and second-line drug in asphyxiated term babies. A larger study on pharmacokinetics and optimal regimen is required.

	Levetiracetam (n=44)	Phenobarbitone (n=38)	Relative Risk	95%CI	Pvalue
Seizure control after primary drug	29(65.9%)	13(34.2%)	0.52	0.34to 0.66	<0.05
Seizures controlled after cross over	14(31.8%)	22(57.8%)	0.54	0.32 to 0.91	<0.05



Abnormal Neurological examination at discharge	6(13.6%)	11(28.9%)	0.47	0.19 to 1.15	>0.05
--	----------	-----------	------	-----------------	-------

Table 2: Outcomes in the two groups
Table 2: Outcomes in the two groups
None declared



ID 235. Whole Exome Sequencing in critically ill neonates and infants: diagnostic yield and predictability of monogenic diagnoses

Tasja Scholz¹, Martin Ernst Blohm², Tatjana Bierhals¹, Fanny Kortüm¹, Dominique Singer², Christian Kubisch¹, Davor Lessel¹, Jonas Denecke³, Jessika Johannsen³, René Santer³, Philipp Deindl², Maja Hempel¹

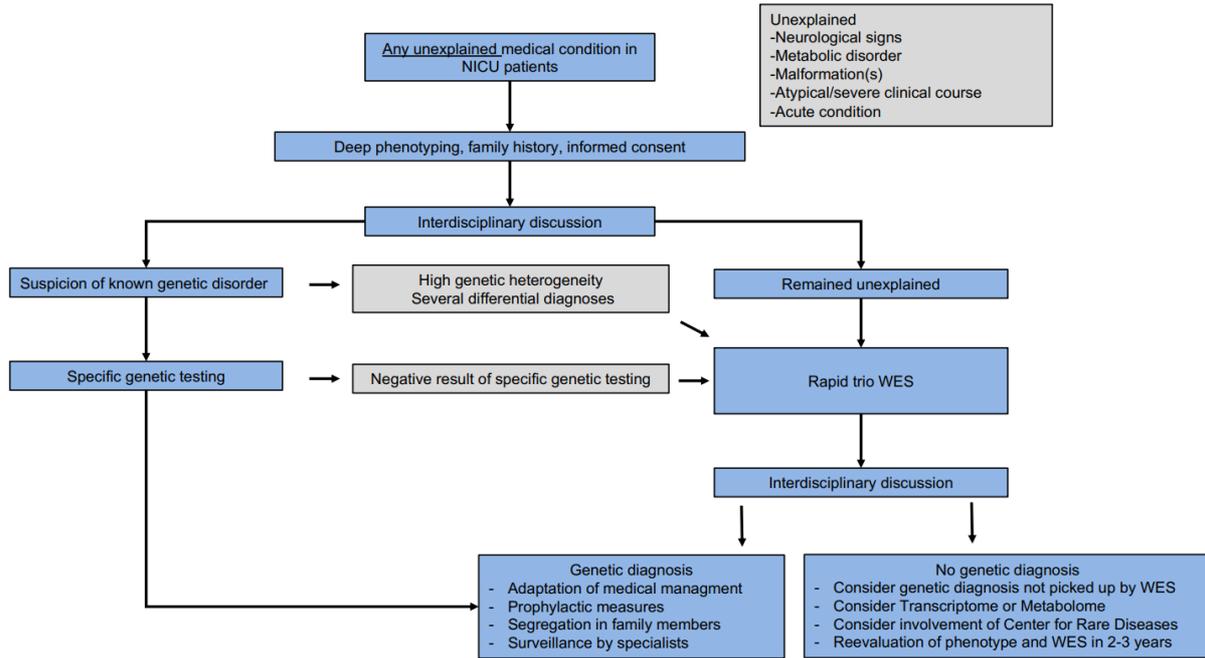
¹University Medical Center Hamburg-Eppendorf, Institute of Human Genetics, Hamburg, Germany, ²University Medical Center Hamburg-Eppendorf, Division of Neonatology and Pediatric Intensive Care, Department of Pediatrics, Hamburg, Germany, ³University Medical Center Hamburg-Eppendorf, Department of Pediatrics, Hamburg, Germany

Background: Monogenic diseases play an important role in critically ill neonates and infants treated in the intensive care unit (ICU). The clinical presentation of monogenic diseases is highly heterogeneous and often unspecific. This is particularly true for critically ill preterm infants and neonates in whom phenotypic features are challenging to interpret, making a targeted approach for genetic testing difficult. This study aims to determine the diagnostic yield of whole-exome sequencing (WES) for monogenic diseases and to identify phenotypes associated with a genetic etiology.

Methods: From March 2017 to March 2020, a comprehensive diagnostic work-up including WES was performed in a single academic center in 61 unrelated, critically ill neonates and infants with an unknown underlying disease. We conducted 59 Trio-WES, 1 Duo-WES, and 1 Single-WES analyses. Symptoms were classified according to the Human Phenotype Ontology (HPO).

Results: The overall molecular genetic diagnostic rate was 46% (28/61), with a genetic diagnosis of 50% (15/30) in preterm neonates. The onset of symptoms leading to admission to the ICU was predominately prenatal (28%) or congenital (59%). Identifying the genetic cause of disease has facilitated an individualized management in the majority of patients. A positive or negative predictive power of specific clinical features or combinations of phenotypes for a genetic diagnosis could not be observed.

Conclusion: WES is a powerful non-invasive diagnostic tool in critically ill neonates and infants with a high diagnostic rate. Importantly, we established monogenetic diagnoses in 50% of preterm infants, emphasizing the usefulness of WES in this patient group. We identified disease-causing variants in 28 genes, illustrating the heterogeneity of underlying diseases in critically ill newborns and infants. We recommend initiating WES as early as possible due to the impact on management and family counseling. Recommendations regarding the clinical utility of WES in critically ill neonates and infants should not be based on phenotype alone. We present a clinical workflow for the application of WES for critically ill neonates and infants in an interdisciplinary setting (Figure 1).



Suggested workflow for the use of WES in NICU. Deep phenotyping includes diagnostic procedures (e.g., metabolic work-up). Specific genetic testing includes chromosome analysis, array CGH and specific molecular genetic testing.

Suggested workflow for the use of WES in NICU. Deep phenotyping includes diagnostic procedures (e.g., metabolic work-up). Specific genetic testing includes chromosome analysis, array CGH and specific molecular genetic testing.

None declared



ID 518. Alterations in circadian genes BMAL1, CRY, CLOCK, and REV-ERB α are associated with inflammatory cytokine profile in neonatal encephalopathy

Doctor Tim Hurley^{1,2,3}, Doctor Lynne Kelly^{1,2,3}, Doctor Eman Isweisi^{1,2,3}, Professor Jan Miletin⁴, Professor Martin White⁴, Professor Naomi McCallion⁵, Professor Adrienne Foran⁵, Professor Afif EL-Khuffash⁵, Doctor Deirdre Sweetman⁶, Doctor Claudine Vavasseur⁶, Professor Eleanor Molloy^{1,2,3,4,7}

¹Paediatrics and Child Health, Trinity College Dublin, Dublin, Ireland, ²Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland, ³Trinity Research in Childhood Centre, Trinity College Dublin, Dublin, Ireland, ⁴Department of Neonatology, Coombe Women and Infant's University Hospital, Dublin, Ireland, ⁵Department of Neonatology, Rotunda Hospital, Dublin, Ireland, ⁶Department of Neonatology, National Maternity Hospital, Dublin, Ireland, ⁷Department of Neonatology, Children's Hospital Ireland at Crumlin and Tallaght, Dublin, Ireland

Background

Circadian genes (CG) Brain and muscle Arnt-like protein-1 (BMAL1), REV-ERB α , and Circadian locomotor output cycles kaput (CLOCK) are present in all immune cells and promote an anti-inflammatory state. Cryptochrome (CRY) negatively regulates the expression of BMAL1. Dysregulated inflammation and delayed sleep-wake cycling onset are both associated with adverse outcome in neonatal encephalopathy (NE). Early randomised trials of melatonin treatment, a chronobiotic agent, as an adjunct to therapeutic hypothermia (HT) has demonstrated improved outcomes. We explored circadian influences on inflammation in NE by investigating the association between CG expression and serum cytokines, and the effect of melatonin treatment on CG expression ex-vivo.

Methods

Blood samples were collected from infants with NE requiring HT during the first week of life and divided into 4 treatment groups – vehicle, lipopolysaccharide (LPS), melatonin, and LPS+melatonin. Serum cytokine concentration was analysed by multiplex ELISA. Cytokines examined were GM-CSF, IFN γ , IL-1 α , IL-1ra, IL-2, IL-1 β , IL6, IL-8, IL-10, IL-18, TNF α , TNF β , Epo, and VEGF. Whole blood RNA was isolated, cDNA was synthesized and analysed by quantitative PCR for the expression of BMAL1, REV-ERB α , CLOCK and CRY. Associations between CG expression and serum cytokine concentrations were examined by Pearson correlation following data log transformation, and differences between treatment groups in CG expression was examined by paired t-tests.

Results

Decreased expression of BMAL1 and CRY (n=36), and increased expression of CLOCK were significantly associated with higher serum concentration of the pro-inflammatory cytokine IFN γ . Decreased expression of REV-ERB α was significantly associated with increased serum concentration of the pro-inflammatory cytokine IL-2. There were no significant differences in CG expression between treatment groups when vehicle vs melatonin, and LPS-stimulated vs LPS+melatonin treatment groups were compared.

Discussion

Factors associated with the entrainment of CG expression in neonates are not fully understood. However, several factors likely to be associated with this entrainment including light exposure and regular feeding are disrupted in the care of patients with NE. While we have demonstrated an association between CG expression and inflammatory cytokines, CG expression does not appear to be influenced by melatonin treatment. Further research into circadian entrainment and the influence on inflammation and outcomes in NE are required.

jENS

Congress of joint
European Neonatal Societies

VIRTUAL
SPACE
TO
BE



European Society
for Paediatric Research



European foundation for
the care of newborn infants



Union of European
Neonatal & Perinatal
Societies



LIVE ONLINE CONGRESS
14-18 September 2021
jenscongress.eu

PRE-CONGRESS COURSES
11-12 September 2021

None declared