PREDICTION OF NEURODEVELOPMENTAL OUTCOME IN PRETERM NEONATES

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ABSTRACT

Very low birth weight preterm infants are at increased risk for neurodevelopmental impairment. In this prospective study we hypothesized that using a combination of neuroimaging (serial head ultrasounds), neurophysiologic measurement (amplitude integrated EEG), and clinical neurobehavioral examination (NICU Network Neurobehavioral Scale) can predict neurodevelopmental outcome of very low birth weight infants < 1500 grams. One hundred infants with gestational age of 27.9 ± 2.6 weeks and birth weight of 997 ± 299 gram admitted to the George Washington University Hospital were enrolled. Controlling for other confounders, early predictors of adverse short term outcomes (death or severe developmental delay at 4 months corrected age) were intubation in the delivery room, and grade III-IV intraventricular hemorrhage. The head ultrasound had poor sensitivity for predicting adverse outcome. Dysmature aEEG in the first 1 week of life increased the sensitivity of ultrasound in detecting adverse outcome from 27% to 58%. The NICU Network Neurobehavioral Scale could predict the mental development at 4 months corrected age. We conclude that amplitude integrated EEG and NICU Network Neurobehavioral Scale at term are feasible tools that can be used to predict the outcome of very low birth weight infants.

(**Key words**: very low birth weight- premature- neurodevelopmental – outcome – aEEG- NNNS- Head Ultrasound)

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LIST OF ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
ADHD	Attention Deficit Hyperactivity Disorder
aEEG	Amplitude Integrated Electroencephalography
APIB	The Assessment of Preterm Infant's Behavior
ATNAT	Amiel Tison Neurological Assessment at Term
BPD	Bronchopulmonary Dysplasia
BRS	Behavioral Rating Scale
BSID-II	Bayley Scales of Infant Development- Second Edition
c-PVL	Cystic Periventricular Leukomalacia
CA	Corrected Age
CC	Corpus Callosum
CNMC	Children's National Medical Center
CP	Cerebral Palsy
CPAP	Continuous Positive Airway Pressure
CT	Computerized Tomography
DEHSI	Diffuse Excessive High Signal Intensity
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalography
ELBW	Extremely Low Birth Weight
ETT	Endotracheal Tube
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
FS	Frontal Sharp Waves
GMH	Germinal Matrix Hemorrhage
GM-IVH	Germinal Matrix- Intraventricular Hemorrhage
GMs	General Movements
GWUH	George Washington University Hospital

HUS	Head Ultrasound
IQ	Intelligence Quotient
IVH	Intraventricular Hemorrhage
MDI	Mental Developmental Index
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-Acetyl Aspartate
NAPI	Neurobehavioral Assessment of the Preterm Infants
NBAS	The Neonatal Behavioral Assessment Scale
NDI	Neurodevelopmental Impairment
NDO	Neurodevelopmental Outcome
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NNNS	The Neonatal Intensive Care Unit Network Neurobehavioral Scale
NREM	Non- Rapid Eye Movement
OS	Occipital Sharp Waves
PDA	Patent Ductus Arteriosus
PDI	Psychomotor Developmental Index
PLIC	Posterior Limb of the Internal Capsule
PMA	Postmenstrual Age
PRS	Positive Rolandic Sharp Waves
PTS	Positive Temporal Sharp Waves
PVHI	Periventricular Hemorrhagic Infarction
PVL	Periventricular Leukomalacia
PVWM	Periventricular White Matter Injury
REM	Rapid Eye Movement
SD	Standard Deviation

SWC	Sleep Wake Cycling
VLBW	Very low Birth Weight
VM	Ventriculomegaly
WMI	White Matter Injury

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INTRODUCTION AND AIM OF THE WORK

Whereas early preterm outcome studies were mainly concerned about their survival, subsequent studies demonstrated increased incidences of cerebral palsy, mental retardation, sensory impairments, minor neuromotor dysfunction, language delays, visual-perceptual disorders, learning disabilities and behavior problems as compared to full term controls (Allen 2002). Perinatal factors associated with poor neurodevelopmental outcome include serious abnormalities of the sonographic appearance of the brain, chronic lung disease (CLD), decreasing birth weight, sepsis, chorioamnionitis, necrotizing enterocolitis, use of postnatal steroids, and important demographic characteristics such as gender and socioeconomic status (Laptook, O'Shea et al. 2005).

The main tools available in the NICU bedside to evaluate the clinical status of these babies include head ultrasounds, neurophysiologic measures as EEG and neurobehavioral examination.

For head ultrasounds, abnormal readings as a result of major lesions such as a large intraventricular hemorrhage, periventricular leukomalacia, and ventriculomegaly are associated with poor outcome, such as cerebral palsy and delayed mental development. Although head ultrasound was helpful in correlating major cranial anomalies with major developmental delay (Aziz, Vickar et al. 1995; Ment, Vohr et al. 1999; Vollmer, Roth et al. 2003) nearly 30% of extremely low birth weight infants with a normal HUS had either CP or a low MDI (Laptook, O'Shea et al. 2005).

The clinical, diagnostic, and predictive value of the neonatal EEG has been studied in term and preterm infants. Major changes as burst suppression pattern (Grigg-Damberger, Coker et al. 1989), isoelectric EEG (Holmes and Lombroso 1993) , and electrographic seizures (McBride, Laroia et al. 2000) were those noted to correlate

with poor neurological outcome. However, technical difficulty and difficulty in interpretation prevented EEG to be used routinely for premature babies. Recently, aEEG, a limited-channel, time-compressed EEG monitor, has gained widespread popularity and was correlated with conventional EEG (Toet, van der Meij et al. 2002). aEEG can solve most of the problems of conventional EEG in this age group by the generation of a compressed curve allowing continuous monitoring for hours and a relative ease of application and interpretation. The aEEG has been used in a number of clinical and experimental neonatal settings including routine clinical monitoring of brain activity, detection of epileptic seizure activity, and as a research tool (Hellstrom-Westas, Blennow et al. 2002; Olischar, Klebermass et al. 2004; ter Horst, Sommer et al. 2004) Although a potential scoring system was reported by Burdajalov et al. (Burdjalov, Baumgart et al. 2003) and was proposed as a measure of neurological maturity for the preterm neonate, such score was not studied in correlation with long-term outcome.

Neurological examination and behavior assessment should be a part of standard care. The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) was developed for the NIH study on prenatal drug exposure and child outcome in preterm and term infants (Maternal Lifestyle Study). The NNNS evolved from a rich tradition of previous infant assessments. It is a comprehensive assessment of both neurologic integrity and behavioral functioning, including general signs of stress (Lester and Tronick 2004; Lester, Tronick et al. 2004). Normative data for NNNS summary scores in term babies have been published (Tronick, Olson et al. 2004). When studied in preterm infants at term corrected age, altered neurobehavior was present in the the majority of scores compared to term infants (Brown, Doyle et al. 2006). The NNNS as a predictor of late neurodevelopmental outcome in premature infants is not yet evaluated.

In this prospective study we hypothesize that using a combination of neuroimaging

(serial head ultrasounds), neurophysiologic measurement (amplitude integrated EEG), and clinical neurobehavioral examination (Neonatal Network Neurobehavioral Scale) will be predictive of neurodevelopmental outcome of premature infants.