Chapter: 12

SLEEP in NEONATES

Jacquelyn D. Hrabowski RN, BSN
Kimberly A. Hardin MD, MS, MCR, FAASM

Human fetuses and neonates spend most of their life asleep. Sleep is an essential function and recent data support the biologic role of sleep in brain development. We will review the ontogenesis of sleep-wake states in neonates, sleep deprivation impact on the infant, and how this may impact brain development and further outcome, and the latest data on sleep-related breathing disorders in infancy.

Development of Sleep States

The emergence of sleep states is one of the most significant aspects of central nervous system (CNS) development. Sleep architecture in infants is similar, but opposite to that in adults. In adults, sleep consists of 2 major states: NREM and REM, where NREM predominates and is the entry state into sleep. Healthy newborns exhibit 2 spontaneously discrete and cyclic patterns: active sleep (AS) and quiet sleep (QS). The earliest age where distinct sleep states emerge during fetal development and in preterm infants remains controversial, but may occur as early as 25 weeks (Scher M. Pediatr Res 2005 57 879-882). QS corresponds to NREM sleep in adults and is associated with behavioral characteristics of closed eyes without eye movement, no body movements, regular heart and respiratory rate, and more difficulty in arousal. In contrast, AS is equivalent to adult REM sleep and is the main sleep state and entry state of sleep up to 3-4 months of age. It is characterized by rapid eye movements, suckling, smiling, body movements, irregular heart and respiratory rate, and frequent micro-awakenings. One cycle of sleep is characterized by a complete AS and QS interval. These intervals vary from 40 – 70 minutes and are variable between gestational age and within the same infant. With increasing age, QS becomes a greater proportion of total sleep. By 6 months of age, sleep states resemble adult pattern and cycling.

Sleep and Brain Development

A necessary factor for the maturation of central pathways is stimulus-driven neuronal activity. Deprivation of visual experiences at a specific time (during visual development) permanently alters the response of the brain to visual stimulation. During fetal development and early neonatal period, sleep is the primary activity and therefore leaves the infant devoid of external stimuli. It is hypothesized that AS provides intrinsic stimulation in the neonate (and late prenatal) that creates an increase in functional capacity of neurons before the infant is in need of more complex neurologic activities that are necessary during prolonged periods of wakefulness. Indeed, AS is characterized by intense levels of neuronal activity. Secondly, studies indicate that maturation of QS coincides with thalmacortical and intracortical patterns of innervation and increased synaptogenesis.

In extreme premature infants (GA 24-25 weeks) little has been studied regarding sleep. EEG's are disorganized with periods of electroneutrality and intermittent burst of various rhythms. Rudimentary sleep states, although difficult to identify, have been documented in pre-term infants at 25 weeks gestation who had normal neurologic outcomes followed to the age of 2 yrs. Additionally, Iglowstein and coworkers (4) conducted a longitudinal study comparing 5 different sleep behaviors between preterm infants (<37 wks) and term infants (>37 wks) from birth to 10 years of age and found no difference between groups.

Sleep-Related Disorders Presenting in the Neonatal Period

1. **Congenital Central Hypoventilation Syndrome (CCHS)—**Once consider a rarity and known as "Odine's Curse" is a genetic disorder (PHOX2B) causing autonomic nervous system dysregulation. The infant will have alveolar hypoventilation, central apnea when sleeping with cardiac instability. During wakefulness this does not occur due to the voluntary effort to breathe. There are variants in penetration of the gene expression resulting in various phenotypes that may persist into early adulthood or not present until then. **Congenital central hypoventilation syndrome (CCHS) and sudden infant death syndrome (SIDS): Related disorders of autonomic dysregulation?**
2. **Sudden Infant Death Syndrome (SIDS)—** sudden and unexpected death of an infant <1 year, whose death remains unexplained after post-mortem evaluation. Occurs in families, can be recurrent in the same infant and caused by a multi-factorial, "multi-hit" process. A combination of environmental, maternal, neonatal and genetic factors must be present for SIDS to occur. The most important environmental factors are prone positioning and cigarette smoking. Several genetic defects have also been delineated and include calcium ion channel defect leading to prolonged QT syndrome, PHOX2A/B gene, and polymorphisms in the 5HTT (serotonin) receptor. Serotonin is necessary for cardiovascular, respiratory, and circadian regulation. Active apoptotic mechanisms in the medullary have been identified, which further destroy cells necessary for ANS function and are shown to be associated with age, gender, prone sleeping and cigarette smoke exposure.
3. **Apnea of Prematurity (AOP)**--Pathogenesis and treatment continues to be a major issue in the NICU. AOP reflects immature, but GA appropriate neurologic development of the infant, but results in impaired respiratory function in the extrauterine environment. Auditory evoked responses are impaired in infants with AOP (delay in brainstem conduction time) but improve after treatment with aminophylline/caffeine – suggesting functional rather than anatomical prematurity. No clinical evidence reliably links a ventilatory control abnormality to SIDS. A history of prior hyperbilirubinemia is associated with persistent AOP in preterm infants and poor neurodvelopmental outcome. Nurse reports of severity of apnea may be unreliable and impedence monitoring techniques fail to identify mixed and obstructive events that can be concomitantly present. GERD is not a cause of AOP.

Effect of Sleep Deprivation

There must be a balance between brainstem noradrenergic and serotonergic activity and acetylcholine activity to initiate AS. Drugs that alter these neurotransmitters can result in increased wakefulness, QS and decrease AS. It is well established in animal and humans that increased serotonin suppresses AS. Only increased serotonin is shown to have long-term effects that may affect adult sleep behavior. Animals who are deprived of AS have smaller brain size, hyperactivity and increased anxiety, attention and learning defects, as well as increased voluntary alcohol consumption.

Sleep deprived healthy newborns have shown an impact on cardiac autonomic control consistent with an increase in sympathetic tone. Short term sleep deprivation in infants is shown to be associated a significant increase in arousal threshold and effect on pain perception. Disturbances in sleep may have behavioral and physiological effects in the premature infant that carry on into adulthood.

Interventions that may Promote Sleep and Development in the NICU

Newborns hospitalized in the NICU are exposed to a great deal of stimuli which causes disruptions in their sleep patterns. Promoting normal sleep of the preterm infant in the NICU not only enhances neurologic maturation; it also promotes normal sleep after discharge home. Involving the family in this endeavor improves transition from NICU to home for both baby and parents.

The Neonatal Individualized Developmental Care Program (NIDCAP) for very low birth weight (VLBW) preterm infants has been suggested to improve several medical outcome variables such as time on ventilator, time to nipple feed, the duration of hospital stay, better behavioral performance on Assessment of Preterm Infants' Behavior (APIB), and improved neurodevelopmental outcomes. This becomes even more important today as the survival rate in very preterm infants (GA 26-28 weeks) has doubled in the last 2 decades. Of those who survive, 10% have cerebral palsy.

Instituting the NIDCAP is helping to improve the neurobehavioral outcome of these high risk neonates.

-altering the environment by decreasing excess light and noise in the room and by using covers over incubators and cribs
-use of positioning aids to promote a balance of flexion and extension postures
-modification of direct hands-on caregiving to maximize preparation of infants for, tolerance of, and facilitation of recovery from interventions
-promotion of self-regulatory behaviors
-attention to the readiness for, and the ability to take oral feedings
-involving parents in the care of their infants as much as possible.
-Kangaroo Care
-Time out cues
-Identifying infants at risk for sleep-related breathing disorders

References

1. Bertelle V, Sevestre A, Laou-Hap K. Sleep in the neonatal intensive care unit. *J Perinat Neonat Nurs.* 2007;21:140-148.

2. Darnall R, Ariagno R, Kinney H. The late preterm infant and the control of breathing, sleep, and brainstem development: a review. *Clin Perinatol.* 2006;33:883-914.
3. Hunt C, Hauck F. Sudden infant death syndrome. *CMAJ.*2006; 174(13):1861-1869.
4. Iglowstein I, Hajnal B, Molinari L. Sleep behaviour in preterm children from birth to age 10 years: a longitudinal study. *Child Development Center, Department of Pediatrics, University of Children's Hospital Zurich, Zurich, Switzerland.*
5. Leiter JC, Bohm I. Mechanism of pathogenesis in the sudden infant death syndrome. *Respiratory Physiology & Neurobiology.* 2007; 159: 127-138.
6. Malloy M. Size for gestational age at birth: impact on risk for sudden infant death and other causes of death, USA 2002. *Arch Dis Child Fetal Neonatal Ed*. 2007;92:F473-F478.
7. Malloy M. Sudden infant death syndrome among extremely preterm infants: United States 1997-1999. *Journal of Perinatology.* 2004; 24: 181-187.
8. Peirano P, Algarin C, Uauy R. Sleep-wake states and their regulatory mechanisms throughout early human development. *J Pediatr. 2003*; 143:S70-S79.
9. Peirano P, Algarin C. Sleep in brain development. *Biol Res.* 2007; 40: 471-478.
10. Vecchierini M, Allest A, Verpillat P. EEG patterns in 10 extreme premature neonates with normal neurological outcome: qualitative and quantitative data. *Brain & Development.* 2003; 25: 330-337.
11. Abu-Shaweesh J and Martin RJ. Neonatal apnea: what's new? *Pediatric Pulmonology* 2008; 43: 937-944.
12. McGrath JM. Implementation of interventions that support sleep in the nicu. *Journal of Perinatal and Neonatal Nursing* 2007; April-June: 83-85.