A sleep evaluation was requested for a full-term female infant 4 weeks of age. Although there were no perinatal problems, the infant remained in the Neonatal Intensive Care Unit (NICU) because of episodes of cyanosis occurring only during sleep, in which the arterial oxygen saturation by pulse oximetry dropped as low as 60%. During these episodes the infant was noted to breathe shallowly without an increase in respiratory rate until aroused by the caregiver. These episodes were noted daily during the entire stay in the NICU. During wakefulness the infant had a normal oxygen saturation of 96%-98%. No abnormalities in gastrointestinal function or muscle tone were noted by the caregivers.

Physical examination: Normal for age while awake. Labora-

tory evaluation: a chest radiograph, electrocardiogram, echocardiogram, and fluoroscopy of the diaphragm were all normal. A MRI showed no evidence of brainstem abnormalities. Screening studies for inborn errors of metabolism were negative.

Sleep study: Tracings from polysomnography during wakefulness and NREM sleep are shown in Figure 1 while the patient breathed room air.

What is going on with this infant during sleep?
**Answer: Congenital Central Hypoventilation Syndrome**

Congenital Central Hypoventilation Syndrome (CCHS) is a rare disorder affecting approximately 1 per 200,000 live births. CCHS is usually present from birth and is characterized by alveolar hypoventilation without evidence of lung, neuromuscular, or structural brainstem abnormalities. During wakefulness, many patients have normal ventilation although ventilatory responses to hypercapnia or hypoxemia by the rebreathing method are absent or blunted and a perception of dyspnea is absent. The most severely affected CCHS patients also have hypoventilation during wakefulness. Those patients with normal awake ventilation have peripheral chemoreceptor responses to hypoxemia or hypercapnia. It has been hypothesized that the abnormality in CCHS patients is in the central integration of chemoreceptor information rather than defective chemoreceptors.

During sleep, all CCHS patients have worsening of ventilation with profound hypoventilation, exhibited by normal respiratory rates and diminished tidal volumes associated with severe falls in arterial oxygen saturation. The abnormalities are often worse during NREM than REM sleep, as the control of breathing is entirely metabolic during NREM sleep. Of note, one study found that CCHS patients did have intact arousal responses to hypercapnia. However, the arousal response to hypercapnic hypoxemia is impaired as protracted periods of severe arterial oxygen desaturation can occur before arousal from sleep.

Other forms of autonomic dysregulation may be seen in these patients. These abnormalities can include the following: Hirschprung disease (20% of cases), esophageal dysmotility, tumors of neural crest origin (6% of cases), decreased heart rate variability, decreased heart rate response to exercise, decreased pupillary light response, intermittent profuse sweating, and dysregulation of body temperature with decreased baseline body temperature. Hirschprung disease is often suspected when an infant fails to pass meconium by 24-48 hours after birth. Esophageal dysmotility can cause difficulty with feeding. The neural crest tumors include neuroblastoma and ganglioneuroma.

The diagnosis of CCHS should be considered in infants with apneic or cyanotic spells especially during sleep. The infants with the most severe cases do not breathe after birth and require immediate ventilatory support. In others, the abnormalities are noted when the infants sleep. Milder cases may present later with signs of colon malrotation or hypoventilation to central nervous system structures. The diagnosis of CCHS depends on exclusion of other causes of hypoventilation, such as brainstem malformation, inborn errors of metabolism, myopathy, diaphragmatic paralysis, and lung or respiratory pump abnormalities. A suspected diagnosis is confirmed by genetic testing for mutations in the PHOX2b gene. Most persons with CCHS are heterozygous for polyalanine repeat expansion mutations in exon 3 of PHOX2b. The expansion results in lengthening the normal 20-repeat polyalanine tract to 25-33 repeats. Longer expansions are associated with more severe phenotypes. Most mutations occur de novo, but in families with CCHS it is inherited as an autosomal dominant trait.

Treatment includes life-long ventilatory support for all patients during sleep. Some patients will require ventilatory support awake as well. Ventilatory support is usually provided by a volume cycled ventilator via a tracheostomy. In older and milder patients noninvasive mask ventilation may suffice. Diaphragmatic pacing has also been used. Infants with CCHS must be closely monitored as they are at risk for hypoventilation or apnea at sleep onset. Children with CCHS are also at increased risk during chest infections due to their abnormal temperature control, lack of perception of dyspnea, and lack of appearance of respiratory distress.

In the present case, the awake tracing (Figure 1) shows a normal SpO2 and end-tidal PCO2. During NREM sleep, a pattern of reduced tidal volume without an increase in respiratory rate is seen although the end-tidal PCO2 is very increased and the arterial oxygen saturation is severely decreased. A blood sample was sent to a referral laboratory at Rush University. Genetic analysis demonstrated a mutation in the PHOX2b gene consistent with a diagnosis of CCHS. The patient underwent tracheostomy and was started on nocturnal volume cycled ventilation.

**PEARS**

1. Central congenital hypoventilation should be considered as a diagnosis for infants presenting with apneic or cyanotic episodes without other explanation.
2. Some CCHS individuals maintain normal ventilation during wakefulness but all CCHS patients hypoventilate and have severe arterial oxygen desaturation during sleep.
3. The diagnosis of CCHS can be confirmed by genetic testing for mutations in the PHOX2b gene.
4. CCHS is a lifelong disorder requiring ventilatory support at least during periods of sleep.
5. A significant proportion of patients with CCHS have abnormalities of autonomic nervous system function including Hirschsprung disease.
6. The severity of respiratory infections in children with CCHS may be underestimated due to a lack of dyspnea associated with impaired gas exchange and abnormal temperature regulation.

**REFERENCES**