Male Infant with Shallow Respirations

Robert Listernick, MD

This is the story of a 3,522-g full-term male delivered vaginally to a 24-year-old G1P1 female. Apgar scores were six at 1 minute and seven at 5 minutes. There was a single nuchal cord at delivery. During the first day of life in the hospital, it was noticed that he had “shallow respirations.” He had a cyanotic event with subsequent unresponsiveness, which led to his transfer to the neonatal intensive care unit. After a second cyanotic event, he underwent endotracheal intubation and was transferred to a children’s hospital. Examination at the time was unremarkable, save for mild micrognathia. Metabolic laboratory evaluation was unremarkable.

Robert Listernick, MD, moderator: Comments?

Karna Murthy, MD, neonatologist: On presentation, we should think about common causes of apnea in term neonates. Did the mother receive opiates or magnesium before delivery that could cause neonatal respiratory suppression? Is the child septic or did he sustain head injury during delivery leading to intracranial hemorrhage? The nuchal cord raises the potential concern of significant acidemia, and certainly, a significant degree of micrognathia could lead to upper airway obstruction such as in infants who have Pierre-Robin sequence.

Dr. Listernick: What would have been your initial approach?

Dr. Murthy: There’s a good deal of experience that continuous positive airway pressure may allow the patient to avoid intubation by both providing airway distending pressure to prevent collapse and as a general stimulus to breathing. However, without a clear etiology for apnea, in the face of recurring apnea events, mechanical ventilation is warranted.

Dr. Listernick: Over the next several weeks, he failed multiple attempts of extubation. Each time, he was noted to be hypotonic following the extubation and had frequent episodes of apnea and oxygen desaturation requiring reintubation. Endoscopic evaluation of his airway showed bilateral choanal patency with possible left choanal stenosis, moderate obstruction at the level of the base of the tongue and mild laryngomalacia; vocal cords were functioning normally.

Dr. Murthy: Obviously, this is far beyond any of the “routine” causes of neonatal apnea.

Dr. Listernick: Although the initial focus was on micrognathia, this turned out to be insignificant. Ultimately, a sleep study revealed that the child had multiple episodes of central hypoventilation. After identifying that the cause of his recurrent hypoventilation/apnea was on a central basis, paired-like homeobox 2B (PHOX2B) testing was performed, which was abnormal, confirming the diagnosis of congenital central hypoventilation syndrome (CCHS). While awaiting the results of PHOX2B testing, were there other causes of central hypoventilation which needed to be investigated?

Pallavi Patwari, MD, critical care and autonomic medicine physician: Primarily, we want to evaluate for the presence of brainstem abnormalities, which were ruled out by his normal brain magnetic imaging. Of course, you would want to make sure that any child with recurrent apnea had a normal cardiopulmonary system as well as normal neuromuscular function.

Dr. Listernick: What is the clinical syndrome of CCHS?

Dr. Patwari: Children with CCHS generally have adequate...
ventilation when awake, but lack normal ventilatory and arousal responses to hypercarbia when asleep. More severely affected children also have abnormal respiration when awake. Most of these children present in the newborn period, although less severely affected individuals may present later in childhood or even in adulthood. In addition, when evaluated they have various abnormalities of the autonomic nervous system, which most commonly include decreased beat-to-beat heart rate variability, attenuated heart rate and ventilatory response to exercise, pupillary abnormalities, esophageal dysmotility, low basal body temperature, abnormal sweat production, altered pain perception, and more. Depending upon the specific PHOX2B mutation found, some children with CCHS are at risk for the development of Hirschsprung’s disease (HD), tumors of neural crest origin (ganglioneuroma, ganglioneuroblastoma, and neuroblastoma), and cardiac asystoles.

**Dr. Listerick:** Let’s talk about the genetics of CCHS and the PHOX2B gene.

**Debra Weese-Mayer, MD, specialist in diseases of the autonomic nervous system:** By definition, all children who have CCHS have an abnormality of the gene responsible for CCHS, PHOX2B, which encodes a homeodomain transcription factor important in the development of murine autonomic nervous system reflex circuits. The inheritance pattern is autosomal dominant fashion from somatic mosaic parents or from an affected individual, though most cases occur as a de novo mutation. Over 90% of children with CCHS have a polyalanine repeat expansion mutation (PARM) on the third exon of the gene. The remaining 10% of children with CCHS have a non-polyalanine repeat expansion mutation (NPARM), a missense, nonsense, or frameshift mutation, in the PHOX2B gene.

**Dr. Listerick:** Is there a difference in the phenotype between the CCHS children who have PARMs versus those with NPARMs?

**Dr. Weese-Mayer:** Most children with NPARMs have 24-hour ventilator dependence. In addition, over 90% of them will develop HD and, for those who survive past 1 year of age, about 50% will develop neuroblastoma (NBL). This speaks to the neural crest origin of this disease. Of the PARMs, the risk for HD and tumors of neural crest origin will depend upon the specific PHOX2B genotype. Overall, approximately 20% of these children develop HD and very few (about 1%) develop the relatively benign tumors of neural crest origin that are ganglioneuromas or ganglioneuroblastoma.

**Dr. Listerick:** The diagnosis of CCHS was confirmed by PHOX2B testing at the end of the first month of life. Also during the first month, he began having difficulty passing stools and had progressive abdominal distension. At 28 days of age, the diagnosis of HD was established. A diverting colostomy was performed and he remained on the ventilator. Over the next several months, he underwent several operations for small bowel obstruction and lysis of adhesions. At 10 months of age, he had a Soave pull-through procedure. At that time, approximately 38 cm of descending colon was removed. The biopsy report confirmed that no ganglion cells were present at the proximal end of the resected bowel.

Family history was unremarkable. At 15 months of age, he sat without assistance, but he was unable to stand independently. He did not have a pincer grasp. He babble but did not make single syllable sounds. He was able to gesture toward objects.

On exam, his weight was in the 70th percentile, height in the 90th percentile, and head circumference greater than 95th percentile. HEENT exam was remarkable for an over-turned lateral one-third of the upper vermilion border and a boxy-shaped face with flattened profile. He had anisocoria. Lungs were clear. S1 and S2 were normal without murmurs. Gastrostomy tube was in place. Abdomen was soft and non-tender without masses.

**Dr. Listerick:** Forgetting about CCHS for the moment, what’s the general approach to an infant once the diagnosis of HD is made?

**Kathy Barsness, MD, pediatric surgeon:** Most importantly, we generally won’t perform a definitive pull-through procedure in a child with HD who has a complex problem such as CCHS until their other medical issues are well-controlled. Instead, we perform an initial leveling procedure, during which we do multiple biopsies moving up the colon looking for the level at which ganglion cells are present. Typically in approximately 85% of patients with HD, this level is in the rectum or sigmoid colon, and we have a short segment of aganglionic colon. Once we’ve determined that point, we resect most of the aganglionic
colon from the proximal end and create an ostomy with a piece of proximal colon that has normal ganglion cells. We create a Hartmann’s pouch, which is a mucous fistula connecting the distal colon to the abdominal wall. The anus remains open and patent.

**Dr. Listernick**: What happened in this child?

**Dr. Barsness**: This child has a longer diseased segment with a much higher level. During this child’s original surgery, the surgeon created a loop colostomy, which placed the proximal and distal stomas next to each other. Stool was leaking over into the retained segment of aganglionic colon, and the child was having repeated bouts of enterocolitis in the aganglionic segment that were interpreted as small bowel obstructions.

**Dr. Listernick**: Given that this child wasn’t doing well, what other problems should be considered?

**Dr. Barsness**: First and foremost, there should be concern that there is retained aganglionic colon in the proximal segment.

**Dr. Listernick**: Should the fact that this child has a *PHOX2B* mutation enter into the thought process?

**Dr. Weese-Mayer**: Children with the more severe NPARMs often have total colonic HD. Those with PARMs usually have much shorter segment disease.

**Dr. Barsness**: Still, I’m not going to rely on genetics to define the level of aganglionic colon. He needed to have another leveling procedure. When we perform the definitive pull-through procedure, we always determine a level to make sure that there isn’t any retained aganglionic colon. Once the pull-through is performed, any subsequent operations create a high risk of injuring the anal sphincters leading to incontinence. We did find retained aganglionic colon, which was resected.

**Dr. Listernick**: What are the surgical options now?

**Dr. Barsness**: The Soave procedure is considered a potentially safer operation in which the surgeon performs a submucosal plane of dissection 3 or 4 cm above the sphincters, followed by a full thickness dissection for the remainder of the rectum. The Swenson procedure is a full-thickness dissection all the way until just above the sphincter. If the Soave was the initial procedure, there is still sufficient tissue remaining to allow the surgeon to return to perform a Swenson procedure if the child doesn’t do well for some reason. Right now he has enterocolitis because of retained stool from the aganglionic bowel. Eventually when his enterocolitis has resolved using antibiotics and high volume rectal irrigations, we will perform a leveling procedure and Swenson pull-through.

**Dr. Listernick**: Unfortunately, there’s more to talk about. At 13 months of age he had a 25-minute generalized seizure while at home.

**Dr. Patwari**: Idiopathic seizures are not typical in children with CCHS; he may have had an episode of hypercarbia or hypoxemia. His EEG was normal. The local hospital performed neuroimaging. However, given his *PHOX2B* genotype, this infant was at risk for the development of ganglioneuroma or ganglioneuroblastoma. Since he required general anesthesia in order to...
perform the MRI scan of the head, his mother asked that he have imaging of his chest and abdomen at the same time “just to be sure.”

Frank Prendergast, MD, pediatric radiologist: There’s a large right suprarenal mass with calcifications within it. The mass extends caudally and there’s compression of the inferior vena cava as well as erosion of the L2 vertebral body. In addition, there are several intraparenchymal nodules at the right lung base. Iodine-123 meta-iodobenzylguanidine (MIBG) nuclear imaging was performed. There’s evidence of multiple bony metastases in the proximal right humerus, proximal right femur, distal femurs, lower spine, and the pelvis.

Dr. Listernick: Can you give a brief description of the MIBG scan?

Dr. Prendergast: MIBG is specifically taken up by the norepinephrine transporter of neuroblastoma cells, which are found in approximately 90% of NBL tumors. It’s both highly sensitive and specific for both diagnosing and staging NBL.

Dr. Listernick: So how should we proceed now?

Elaine Morgan, MD, pediatric oncologist: He has stage IV disease, although I wonder whether he truly has pulmonary metastatic disease, as it is extremely unusual in neuroblastoma. Until 18 months of age, the risk categories are based on a combination of histology, stage, N-myc amplification, and DNA index. After 18 months, everyone with stage IV disease is considered high risk. Our standard approach to high risk neuroblastoma is extremely aggressive combination of treatments given successively: 1) intensive chemotherapy; 2) surgical resection; 3) one to three autologous stem cell transplants; 4) radiation therapy; 5) cis-retinoic acid; and 6) treatment with a specific antibody against neuroblastoma.

Dr. Listernick: What is your success rate with this approach?

Dr. Morgan: We achieve approximately 40% disease-free survival, although that combination is clearly extending lives. However, given this child’s underlying illness, it’s doubtful that he would survive this intensive approach. After much discussion, it was recommended to the family that he be treated as an intermediate-risk patient with the hope that he would respond well.

Dr. Barsness: We decided not to perform a definitive pull-through procedure, given the therapy he will be receiving over the next year. Instead, we performed a leveling procedure. As expected, he has total colon HD. We performed a colectomy and created an ileostomy. For the moment, treatment of the neuroblastoma takes priority.

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Key Learning Points

1. Common causes of apnea in full-term neonates include maternal medications administered, such as magnesium sulfate or opiates, before delivery; sepsis; or head injury during delivery.

2. Congenital central hypoventilation syndrome (CCHS) is diagnosed based on the clinical presence of central alveolar hypoventilation in the absence of primary cardiac, pulmonary, neuromuscular, or brainstem abnormality, that can account for the entire phenotype (including the autonomic nervous system [ANS] dysregulation); and genetically by mutations in the PHOX2B homeobox gene.

Children with CCHS have generalized ANS dysfunction as characterized by abnormal ventilatory and arousal responses to hypercarbia and hypoxemia; decreased heart rate beat-to-beat variability; attenuated heart rate and ventilatory response to exercise; pupillary abnormalities; esophageal dysmotility; low body temperature; and abnormal distribution and amount of diaphoresis.

3. Most children with CCHS present in the newborn period with recurrent episodes of alveolar hypoventilation that are often interpreted as apnea.

4. Associated morbidities may develop in some children with CCHS depending upon the specific genotype such as Hirschsprung’s disease and tumors of neural crest origin, including ganglioneuroma, ganglioneuromablastoma, and neuroblastoma.