A 3-Year-Old Boy with Acute Respiratory Failure, Sleep Apnea, and Rapid Weight Gain

Robert Listernick, MD

A 3-year-old boy was transferred from an outside hospital for evaluation of three episodes of acute respiratory failure requiring endotracheal intubation. He was well until 3 months prior to admission, when he developed a persistent upper respiratory tract infection. His father noted that he had not been acting like his normal self. Due to increasing lethargy and cyanosis, he was hospitalized. A diagnosis of pneumonia due to *Mycoplasma pneumoniae* was made. Following that admission, his father stated that “he never returned to baseline.” He became progressively more lethargic and had more difficulty walking, dragging his left leg.

Six weeks later, he had another episode of respiratory failure that was treated with intravenous corticosteroids, bronchodilators, and antibiotics. A chest X-ray at that time demonstrated no infiltrates, and the respiratory cultures were negative. He had a normal echocardiogram, and an MRI of the brain showed mild ventriculomegaly and a small, nonspecific white matter lesion of the right frontal lobe. There was no evidence of increased intracranial pressure. He did not require mechanical ventilation at that time, and he was discharged on Flovent (GlaxoSmithKline, London, UK) Singulair (Merck & Co., Whitehouse Station, NJ), albuterol, antibiotics, and tapering doses of corticosteroids. He had been hospitalized for 5 days and did not require mechanical ventilation.

Four days later, he awoke with a cough after which he developed increasing tachypnea and cyanosis. On return to the emergency room, chest X-ray showed interstitial airspace opacities bilaterally. A sleep study showed obstructive and central apneic episodes. He was noted to have unexplained episodes of sinus tachycardia, usually in the morning and afternoon. He was given nightly bilevel positive airway pressure and subsequently transferred here.

Review of systems is remarkable for a 17-lb weight gain over the past several months with markedly increased appetite. His father states that when the child is tired he “dragged his left leg a little more.”

The child’s history is remarkable for asthma. He was a 27-week premature infant who had an uncomplicated neonatal course without significant lung disease. He never required mechanical ventilation. Family history is unremarkable.

His development was normal prior to the start of this series of illnesses. He speaks in full sentences, knows colors, and can count to 20. Gross motor development was normal.

On exam at the time of transfer he was sedated and being mechanically ventilated. His weight was greater than the 95th percentile, length was in the 5th percentile, and head circumference was in the 80th percentile. Blood pressure was 109/72 mm Hg. He was not dysmorphic. There were no neurocutaneous lesions. Lungs were clear. Cardiac examination was normal. Abdomen was soft without masses or organomegaly. On neurologic examination, the pupils were 2+ bilaterally and equal but minimally reactive. There was impaired upward and downward gaze. He tracked in the horizontal plane with end-gaze nystagmus. There were roving eye movements. He was able to open and close his eyes spontaneously but with diminished strength. Fundoscopic examination was normal. He had normal tone. Reflexes were 1+ bilaterally. The toes were upgoing. Strength was difficult to assess because he was sedated.

The following laboratory tests were normal: complete blood count with differential, Chem-14, creatine...
phosphokininase, ammonia. Results of lumbar puncture were normal. Plasma lactic acid was minimally elevated.

**Robert Listernick, MD, moderator:** Is it common for somebody to have a first episode of pneumonia that leads to endotracheal intubation and mechanical ventilation?

**Stanford T. Shulman, MD, pediatric infectious disease physician:** Obviously it’s hard to generalize, but this story is very odd. In addition, it’s quite unlikely that *Mycoplasma pneumoniae* would lead to such a severe pneumonitis.

**Dr. Listernick:** Is the diagnosis of infection caused by *Mycoplasma pneumoniae* easy to make?

**Dr. Shulman:** Traditionally, mycoplasmal infections have been difficult diagnoses to substantiate because serologic testing is not very good. With the advent of polymerase chain reaction tests, we have been able to improve our sensitivity and specificity substantially.

**Dr. Listernick:** So what the heck is going on? He’s had three episodes of moderate-severe respiratory disease, two of which required mechanical ventilation.

**Mary Nevin, MD, pediatric pulmonologist:** First, let’s remember that children who are born prematurely, even mildly prematurely, can have significant airway reactivity much worse than their normal gestational age counterparts. However, once we see a child who has had three severe episodes that do not respond to conventional therapy, we should start thinking about immunologic disorders or the possibility of muscular weakness in a neurologically abnormal child.

**Dr. Listernick:** What about the fact that he has had several normal chest X-rays?

**Dr. Nevin:** Chest X-rays may not be particularly sensitive markers of chronic lung disease, particularly interstitial disease. I wouldn’t put much stock in that history, and I’d certainly want to review them personally.

**Dr. Listernick:** Moving forward, this child was transferred here to be evaluated for the possibility of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD).

**Debra Weese-Mayer, MD, neonatologist:** The acronym suggests the order in which the symptoms unfold. Classically, these children are seemingly normal until between 2 and 7 years of age, at which time they develop a voracious appetite and rapidly gain as much as 30 lbs in 6 months. Following this, the children often have a respiratory arrest following a minor viral illness, and it’s noticed in the hospital that they have hypoventilation, which leads to suspicion of the diagnosis. In addition, these children have symptoms of autonomic dysregulation, such as ice-cold hands and feet, low body temperatures, altered circadian rhythm of temperature, and large dilated pupils that are minimally reactive to light.

**Dr. Listernick:** When I was an intern, a 6-year-old girl was transferred who had had a respiratory arrest. She had recently developed massive obesity and ultimately the diagnosis of congenital central hypoventilation syndrome (CCHS) was made prior to description of ROHHAD. She was on a ventilator for several weeks; her first words following extubation were: “I want a hot dog.”

**Dr. Weese-Mayer:** I didn’t think this child had ROHHAD due to the lack of autonomic symptoms. The referring physicians were also concerned about the possibility of CCHS. This child exhibited respiratory distress, which suggests that he doesn’t have a control-of-breathing deficit. Children with CCHS don’t have a sense of shortness of breath.

**Dr. Listernick:** Can the diagnosis of CCHS and ROHHAD be confirmed?

**Dr. Weese-Mayer:** Mutations in the homeobox gene *PHOX2B* are responsible for CCHS. We are actively looking for the genetic abnormality behind ROHHAD.

**Dr. Listernick:** Are there other clinical scenarios in which we should suspect CCHS or ROHHAD?

**Dr. Weese-Mayer:** Consider these diagnoses in anyone who has unexplained hypoventilation, hypercarbia, or neurocognitive delay. In addition, it’s been described in infants who have repeated apparent life-threatening events and in children who are “amazing” underwater swimmers who aren’t short of breath when they get pulled out of the water.

**Dr. Listernick:** Testing for *PHOX2B* was negative. What was his neurologic status when he arrived here?

**Mark Wainwright, MD, PhD, pediatric neurologist:** One approach would be to think about this boy in the context of his prematurity. As a former 27-week premature infant, he was clearly developmentally normal, although the MRI was abnormal in the right frontal area, which would be consistent with the recent history of

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dragging of the left leg. Perhaps there had been some white matter injury due to the prematurity, and left leg weakness was brought out now by his chronic illness. However, despite his sedation at the time of transfer, he had upper motor neuron findings and abnormal extraocular movements. So the combination of the history and physical exam suggests that the underlying disease process, whatever it is, probably involves both the cortex and the brain stem. He underwent repeat MRI.

Corey Bregman, MD, pediatric neuroradiologist: The diffusion-weighted imaging (DWI) result is the most striking. DWI looks for diffusion restriction, which is most often seen in the setting of ischemia (tissue that is being deprived of oxygen). It can also be seen in cases of cytotoxic edema from other causes. The DWI images in this child show marked diffusion restriction in the cerebellar peduncles, the cerebellum itself, and the entire medulla all the way to the cervico-medullary junction. There’s also sub-cortical white matter involvement in the cerebellum. Magnetic resonance spectroscopy was performed sampling the left basal ganglia, posterior left deep white matter, and the frontal horns. The sample over the frontal horns, which is largely sampling cerebrospinal fluid (CSF), demonstrates peaks highly suggestive of lactate. The distribution of all the findings is extremely symmetric.

**Dr. Listernick:** And putting this all together?

**Dr. Bregman:** The findings considered together are highly suggestive of a mitochondrial or metabolic process.

**Dr. Wainwright:** The term “Leigh syndrome” is actually a catchall phrase used to describe children who have elevated serum or CSF lactate levels, neurologic regression, and characteristic MRI findings involving the deep gray matter and brainstem in a symmetric pattern. Although mutations in the gene for cytochrome c oxidase are probably most commonly found, Leigh syndrome can be due to mutations in one of more than 30 different nuclear or mitochondrial genes involved in mitochondrial energy production.

**Dr. Listernick:** In 2014, what’s the best way to confirm the diagnosis?

**Dr. Wainwright:** Most importantly, the physician should have a high index of suspicion for mitochondrial disease, considering it in such diverse presentations as children who have unexplained multiorgan disease to recurrent intractable migraine. Many, but not all, of these children have elevated plasma lactic acid. We try to do focused testing depending upon symptoms and type of organ involvement. For instance, if a child has recurrent stroke-like episodes and elevated lactate, we’ll order the specific test for MELAS (mitochondrial encephalomyopathy, lactic acid, and stroke like episodes) mutation. Or if a child has myoclonic seizures and evidence of a peripheral neuropathy, we’ll look for the MERRF (myoclonic epilepsy with ragged-red fibers) mutation. If we’re really stuck, we have the availability of ordering a panel that includes testing for the entire mitochondrial genome as well as all the nuclear genes that control mitochondrial function. This is a last resort because it’s quite expensive.

**Dr. Listernick:** Assuming the diagnosis is confirmed, is there any available treatment?

**Dr. Wainwright:** The mainstay of therapy for mitochondrial disorders is...
avoidance of metabolic crises, which essentially translates into the maintenance of good nutrition. We often use a cocktail of supplements that targets multiple aspects of mitochondrial function, including thiamine, lipoic acids, and antioxidants like vitamin E. Their efficacy has not been validated in clinical trials.

Dr. Listernick: Assuming the diagnosis is correct, one would anticipate a steady downhill course of progressive respiratory and neurologic decline. Now what?

Joel Frader, MD, pediatric ethicist and palliative care physician: We can certainly try to moderate the course of the disease. The literature suggests that roughly 50% of patients with Leigh syndrome die within 1 year following diagnosis. However, it’s inappropriate to be absolutely definitive with parents about long-term consequences because the phenotype varies widely. They need to be prepared for the possibility of death but with an understanding of the uncertainty of the time course. Clinicians often talk about “giving” or “taking away” hope. However, the literature suggests that hope is a complex phenomenon over which physicians have little control. This family, for example, is extremely invested in the possibility that their son may have significant neurologic recovery, so much so that if they have to take him home on a ventilator, that’s what they want to do. Our role as palliative care physicians is to support them and help them come to terms with the diagnosis, not tell them what to do.

Ranna Rozenfeld, MD, pediatric critical care physician: I agree wholeheartedly with Joel. The parents understand that he might have less than 1 year to live but they absolutely wanted to proceed on the assumption that he might improve and that they can take him home to be with his family, even if it meant chronic home ventilation. I explained that it is generally a 3-month process before that can be arranged. They agreed so we proceeded with tracheostomy and gastrostomy tube placement.

Dr. Listernick: Thank you, everyone.

Key Learning Points

1. Polymerase chain reaction testing is currently the best way to establish the diagnosis of Mycoplasma infections.

2. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) should be suspected in children who are seemingly normal until between 2 and 7 years of age who then develop a voracious appetite and rapidly gain as much as 30 lbs in 6 months. They often have a respiratory arrest following a minor viral illness. In addition, these children have symptoms of autonomic dysregulation, such as ice-cold hands and feet, low body temperatures, altered circadian rhythm of temperature, and large dilated pupils that are minimally reactive to light.

3. Diffusion-weighted imaging on MRI scans looks for areas of diffusion restriction, most often seen in the setting of ischemia (ie, tissue that is being oxygen-deprived).

4. The mitochondrial disease, Leigh syndrome, is a catchall phrase used to describe children who have elevated serum or cerebrospinal fluid lactate levels, neurologic regression, and characteristic MRI findings involving the deep gray matter and brainstem in a symmetric pattern.