A 14-Year-Old Boy with Vomiting

Robert Listernick, MD

A 14-year-old boy was transferred from an outside hospital for evaluation of vomiting. He had been well until he traveled to India 3 weeks earlier. Upon return, he developed abdominal pain and recurrent episodes of nonbilious, nonbloody emesis. The day of admission, he ate a slice of pizza and then experienced numerous episodes of vomiting every 15 to 30 minutes. There had been minimal diarrhea at the beginning of the illness, but none over the following 3 weeks. Review of systems was otherwise unremarkable.

The patient’s medical history was remarkable for poor weight gain and linear growth without any evaluation. He is in an eighth-grade classroom, but functions at a first-grade level. His parents are aware that his IQ is low, but they can’t describe the extent of his cognitive impairment. All we know of his developmental/intellectual history is that he walked at 2 years of age and spoke his first words at 3 years. The family follows a traditional Jain vegetarian diet (in this case, essentially vegan). They had given him Ensure in the past because of his poor weight gain. The family history is unremarkable. He has one healthy brother of normal stature. There is no known history of consanguinity. Birth history was unremarkable.

On exam, the patient was a small, thin, malnourished boy. He was afebrile, pulse 82, respiratory rate 20, and blood pressure 112/70. His height was 50th percentile at age 5 years and the 50th percentile at age 9 years. Head circumference was below the fifth percentile. He was not dysmorphic. Head, eye, ear, nose, and throat (HEENT) exam was normal. Cardiac exam was normal. Abdomen was soft and nontender without masses or organomegaly. He had Tanner 2 genitalia. Both testes were descended. His extremities appeared normal and neurologic exam was normal.

On initial laboratory evaluation, serum chemistries were normal save for BUN 30 mg/dL and creatinine 0.7 mg/dL. Complete blood count (CBC), C-reactive protein, and erythrocyte sedimentation rate were normal. Computerized tomography (CT) scan at the outside hospital showed a dilated stomach and tapering of the third portion of the duodenum. Superior mesenteric artery syndrome (SMAS) was diagnosed; continuous nasojejunal feedings were started.

Robert Listernick, MD, moderator: May we look at the radiology?

Delilah Burrowes, MD, pediatric neuroradiologist: The CT scan shows a markedly dilated stomach and first portion of the duodenum with narrowing of the second portion of the duodenum between the aorta and the SMA. There’s a lack of visualization of barium in the second and third portion of the duodenum. All of these findings together are diagnostic of SMAS.

Dr. Listernick: Tell us about SMAS.

Lee Bass, MD, pediatric gastroenterologist: SMAS occurs when there is a narrowing of the angle that is between the SMA and the aorta. SMAS occurs when there is a narrowing of the angle that is between the SMA and the aorta. SMAS occurs when there is a narrowing of the angle that is between the SMA and the aorta. SMAS occurs when there is a narrowing of the angle that is between the SMA and the aorta. SMAS occurs when there is a narrowing of the angle that is between the SMA and the aorta. SMAS occurs when there is a narrowing of the angle that is between the SMA and the aorta.

Robert Tanz, MD, general academic pediatrician: I believe SMAS
was first described in concentration camp survivors while they were being re-fed. It certainly can be seen in adolescents who have eating disorders.

**Dr. Listernick:** How do we treat the patient?

**Dr. Bass:** It’s best to try to feed the patient enterally, so we try to place a nasojejunal tube to bypass the obstruction. Refeeding syndrome is a real consideration. Chronically malnourished patients are total body–phosphate depleted. When they are re-fed and switch from a catabolic to an anabolic state, a large increase in circulating insulin drives more phosphorus into the cells. In addition, there is fluid retention with increases in both extracellular and intracellular fluid. Life-threatening hypophosphatemia, congestive heart failure, arrhythmias, and multiorgan dysfunction may ensue.

**Dr. Listernick:** How do you approach the possibility of refeeding syndrome?

**Dr. Bass:** Refeeding syndrome may not occur until several weeks following the reintroduction of food. I generally start refeeding very slowly with careful monitoring of serum electrolytes, calcium, magnesium, and phosphorus.

**Dr. Listernick:** Here’s a philosophical question — does this child have a weight problem or a growth problem?

**Reema Habiby, MD, pediatric endocrinologist:** Without previous growth records, it’s impossible to distinguish. I’d like to have much more information, such as his dietary intake. Whatever is going on is clearly severe; his weight, height, and head circumference presumably all have been affected.

I also doubt that there was an endocrine cause of his short stature given the significant microcephaly. With that said, I admit that I would have evaluated him for endocrine dysfunction nonetheless. I would have checked thyroid function, IGF-1, IGFBP-3, and serum growth hormone. Children with severe malnutrition have acquired growth-hormone resistance; they may have low levels of IGF-1 and IGFBP-3 but elevated levels of growth hormone.

**Barbara Burton, MD, pediatric geneticist:** Without more information, it’s also possible that the child is not malnourished or stunted, but instead constitutionally small, such as from a chromosomal abnormality or skeletal dysplasia. I would suggest performing whole-genome microarray, as well as a skeletal survey.

**Dr. Listernick:** Does this child have inflammatory bowel disease (IBD) or another malabsorption disorder?

**Dr. Bass:** I think IBD is very unlikely without a history of symptoms such as chronic diarrhea and with normal hemoglobin, albumen, and inflammatory markers. Celiac disease is still within the realm of possibility. This degree of stunting of height would be extremely unlikely in celiac disease.

**Dr. Burton:** You’ll find that geneticists tend to be split as to how to diagnostically approach a child with a nonspecific presentation such as developmental or cognitive delay. Even in this child, you have growth failure and microcephaly but no obvious starting point for a diagnostic approach other than what has been described. Does one simply peel off the first layer of the onion, performing tests that are most likely to yield an abnormality, or does one test for every conceivable possibility?

For example, there are a number of very rare metabolic syndromes that may present simply with developmental delay. Probably more importantly, one would want to try and first diagnose treatable conditions, but there are also genetic counseling implications. If a couple plans on having future children, our first-line approach also

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**Panelists**

- **Robert Listernick, MD**
  Moderator, general academic pediatrician
- **Delilah Burrowes, MD**
  Pediatric neuroradiologist
- **Lee Bass, MD**
  Pediatric gastroenterologist
- **Robert Tanz, MD**
  Moderator, general academic pediatrician
- **Reema Habiby, MD**
  Pediatric endocrinologist
- **Barbara Burton, MD**
  Pediatric neurologist
- **Douglas Nordli, MD**
  Pediatric neurologist
- **Laura Speltz, MD**
  Pediatric neurologist

All panelists practice at Children’s Memorial Hospital, Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for Pediatric Annals.
would be to try to identify conditions that have a significant recurrence risk. For example, in cases of nonspecific mental retardation, we always recommend fragile X testing.

**Douglas Nordli, MD, pediatric neurologist:** When we evaluate children who have cognitive delays, our first branch point is whether they have static or progressive encephalopathy.

**Dr. Listernick:** Moving on, he had normal free T₄, TSH, and whole-genome microarray. IGF-1 and IGFBP-3 were both low with an elevated growth hormone level, consistent with malnutrition. Skeletal survey showed diffuse demineralization, but no evidence of skeletal dysplasia. There was normal testing for carbohydrate deficient glycoprotein syndrome.

**Dr. Burton:** Congenital disorders of glycosylation are a heterogeneous group of disorders caused by defects in as many as 29 separate genes in the N-linked oligosaccharide pathway. Because the varied phenotypes are being constantly refined and new ones are being identified, I have tended to test for them in a number of circumstances.

I generally recommend testing in children with severe developmental delay, hypotonia, or evidence of multisystem dysfunction. More specific red flags that point to the possible presence of a congenital disorder of glycosylation include failure to thrive, protein-losing enteropathy, cerebellar hypoplasia, and wide-spaced hypoplastic nipples, to name a few. First-line testing would be isoelectric focusing of serum transferrin glycoforms.

**Dr. Listernick:** One test that clearly stood out was the serum lactic acid level. He had several levels repeated that were all greater than 6 mg/dL. Plasma lactate:pyruvate ratio was 30, which is elevated and indicates impairment of oxidative metabolism. Plasma amino acids had an elevated alanine, suggesting primary lactic acidosis.

**Dr. Burton:** We are often consulted for children who have mildly elevated lactic acid levels — either because they were drawn during an episode of sepsis or shock or the blood was mishandled — who almost always have no metabolic disease. This seems to be the real thing.

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“If all the above are negative and you still have a high suspicion for a mitochondrial disorder, what next?”

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There are basically two subsets of disorders that cause primary lactic acidosis. Defects in pyruvate metabolism would lead to an elevated pyruvate and the ratio of the lactate to pyruvate would be normal. In this child, the more likely reason for an elevated lactic acid is a defect in oxidative phosphorylation, which includes mitochondrial disorders.

**Dr. Listernick:** What would be your diagnostic approach in this patient?

**Dr. Burton:** I would first look for the common mitochondrial DNA mutations or deletions that may be identifiable in white blood cells.

**Dr. Listernick:** What is a mitochondrial depletion syndrome?

**Dr. Burton:** There are approximately 10 nuclear genes responsible for mitochondrial development. Mutations in these genes lead to fewer functional mitochondria per cell than normal. Most mitochondrial disorders diagnosed in childhood are not the result of genetic changes in the mitochondrial DNA, but rather of mutations in these or one of the many other nuclear genes that affect mitochondrial function. These disorders are inherited as autosomal recessive traits. There’s now a commercially available gene “chip” that sequences 24 of these known nuclear genes. He doesn’t have a phenotype that suggests mitochondrial depletion syndrome, such as liver failure.

**Dr. Listernick:** If all the above are negative and you still have a high suspicion for a mitochondrial disorder, what next?

**Dr. Burton:** Because of the phenomenon termed heteroplasmy, different cells may have different mixtures of normal and abnormal mitochondria. If no mutations or deletions are detected in white blood cells, we can perform a muscle biopsy looking for these abnormalities.

**Dr. Listernick:** What is the clinical course of these patients?

**Dr. Burton:** It varies. Although eventually they all exhibit some form of organ dysfunction and deterioration, they may remain static for many years without any signs of progression. Ultimately, the body loses the ability to keep up with the necessary energy production.

**Dr. Listernick:** He was discharged home awaiting the results of numerous laboratory tests. One month later, he experienced two left-sided clonic seizures simultaneously involving the left leg and arm, and was transferred back here from an outside hospital. Several hours later, he developed two right-sided clonic seizures.

**Dr. Burrowes:** Magnetic resonance imaging (MRI) shows global cerebral volume loss. In addition, there is a large area of restricted diffusion on the right. MR spectroscopy reveals a large lactic peak in the same area. These findings are consistent with an
Key Learning Points

1. Superior mesenteric artery syndrome (SMAS) occurs because of a loss of a visceral fat pad that normally separates the superior mesenteric artery and the aorta, leading to compression of the third part of the duodenum. Treatment is best performed by enteral feeding through a nasojejunal tube bypassing the obstruction.

2. Children with severe malnutrition have acquired growth-hormone resistance and may have low levels of IGF-1 and IGFBP-3 but elevated levels of growth hormone.

3. Primary lactic acidosis may be caused by defects in pyruvate metabolism, which lead to an elevated serum pyruvic acid or disorders of oxidative phosphorylation.

4. Heteroplasmy is a phenomenon in which different cells may have different mixtures of normal and abnormal mitochondria. This may lead to variable phenotypes within family members who have the same mitochondrial mutation or deletion syndrome.

ischemic stroke; the elevated level of lactate also suggests metabolic disease, but is still nonspecific. If we had placed a voxel over the ventricle and found an elevated lactate peak, this would be extremely specific for a primary metabolic disorder.

Laura Speltz, MD, pediatric neurologist: When I first saw him, he had a mild left hemiparesis that disappeared the next day. Given the exam, previous history, and initial neuroradiologic findings, we treated him as if he had a metabolic stroke. This includes careful control of his core body temperature and blood pressure, as well as maintenance of euglycemia and normal serum electrolytes.

We also started an intravenous infusion of 10% dextrose with electrolytes because children with metabolic strokes may have high energy needs. Aspirin can act as a mitochondrial toxin; its use is contraindicated in children with presumed mitochondrial disease or metabolic strokes.

Dr. Nordli: Clonic seizures are excellent localizers of pathology. There’s a higher than 90% chance that if a clonic seizure is associated with pathology, it will correlate to the contralateral area. The fact that we’re seeing multifocal seizures suggests that these are not typical vascular strokes.

Dr. Listernick: During this admission, results showed that he had a mitochondrial mutation at the 3243 position of the mitochondrial genome typical of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke syndrome (MELAS). There are several mutations in the mitochondrial DNA that correlate with the clinical syndrome we call MELAS. Results also indicated that the sample had 88% mutant load, meaning that 88% of the mitochondrial DNAs in the circulating white blood cells had mutant DNA.

Dr. Burton: Just to be clear, this does not mean that other body tissues, such as the brain or muscle, have similar mutant loads; any organ may be involved. This mutation displays maternal inheritance and clinical phenotypes may vary dramatically within families; this particular mutation has also been associated with diabetes and deafness.

Dr. Listernick: Is there any treatment available?

Dr. Burton: There are at least a couple of papers that suggest some benefit of coenzyme Q10 in patients with MELAS; a few suggest that intravenous arginine at the time of the stroke-like episodes may be beneficial; and some authorities suggest chronic arginine might be beneficial. However, this is purely anecdotal. We do ask the patients to take carnitine and multivitamin supplements.

Dr. Listernick: Thank you, everyone.