Case: A 7-day-old male presented to the emergency department of our hospital with a history of lethargy and poor feeding for 1 day. He had no fever, no vomiting, no difficulty breathing, and no other complaints. He was born at 37 weeks’ gestation by normal spontaneous vaginal delivery, and his birth weight was 4 kg. The mother was colonized with group B streptococcus infection and received penicillin while in labor. She reported no medical history of herpes simplex virus (HSV) or any other infections. Rupture of membranes occurred 18 hours before delivery. In the newborn nursery, the mother reported that the infant had a low body temperature at 24 hours of life and required placement under an overhead warmer. His temperature stabilized and he was discharged to home at 48 hours of life. His total bilirubin level was 14 mg/dL on day of life 3, and he received home phototherapy on days 3 and 4. He did well on days 5 and 6, until day of life 7, when he presented to the emergency department.

On examination, the patient was minimally responsive to pain, appeared lethargic, and was cool to touch. His temperature was 30.7 °C, pulse was 94 beats/min, respiratory rate was 49 breaths/min, blood pressure was 89/61 mm Hg, and pulse oximeter was 100% on room air. His weight was 3.8 kg (50th percentile for age); height, 47 cm (25th percentile for age); and head circumference, 38 cm (75th percentile for age). Results of his head, eyes, ears, nose, throat, heart, and lung examinations were within normal limits. His abdomen was soft and non-distended, with no hepatosplenomegaly. Genitourinary examination was normal male. His skin examination showed mild jaundice at the head and trunk with no other rashes or lesions. The extremities had 2+ pulses, but capillary refill was delayed at 4 seconds. Results of the neurologic examination revealed lethargy and diffuse hypotonia with little spontaneous movement. He had intact gag and suck reflexes; deep tendon reflexes were 2+; and toes were upgoing.

The infant was placed under an overhead warmer and on a warm mattress, and he was given warm intravenous fluids. After 1 hour, he became more active, and his temperature was 34.9 °C. His initial evaluation in the emergency department revealed a white blood cell count of 4900/µL with 52% neutrophils, 1% bands, 38% lymphocytes, 4% monocytes, and 3% atypical lymphocytes. His hemoglobin level was 19 g/dL, hematocrit was 53%, and platelet count was 124 000/µL. A complete metabolic panel revealed the following: sodium, 141 mmol/L; potassium, 6 mmol/L; chloride, 107 mmol/L; bicarbonate, 24 mmol/L; blood urea nitrogen, 11 mg/dL; creatinine, 0.6 mg/dL; glucose, 72 mg/dL; total bilirubin, 11 mg/dL; direct bilirubin, 0.2 mg/dL; alanine aminotransferase, 35 U/L; aspartate aminotransferase, 35 U/L; albumin, 3.0 g/dL; and calcium, 9.5 mg/dL. The urinalysis
showed specific gravity of 1.010 and a pH of 5.5 but was otherwise negative. His ammonia level was 30 µmol/L, thyroid-stimulating hormone levels were 7.4 mIU/L, and free thyroxine was 1.89 ng/dL. Assessment of cerebrospinal fluid (CSF) revealed a white blood cell count of 3/µL, red blood cell count of 18/µL, protein of 144 mg/dL, and glucose of 44 mg/dL. Ampicillin, cefotaxime, and acyclovir were administered. The chest radiograph and echocardiogram results were within normal limits. A brain MRI revealed a mild subdural hemorrhage at the posterior aspect of the falx cerebri, which was thought to be related to birth trauma; the brain otherwise appeared normal. Urine organic acids, serum amino acids, total and free carnitine, and an acylcarnitine profile were sent for analysis. He was then admitted to the PICU.

In the PICU, the infant was continued on antibiotics and IV fluids. Over his 4-day stay, his energy level and feeding slowly improved, and the hypotonia resolved. His body temperature was maintained in the range of 35.8°C to 37°C with bundling. The infant was transferred to the general care floor on hospital day 5. Results of the CSF HSV polymerase chain reaction (PCR) analysis were negative. Blood HSV PCR and HSV surface cultures were not obtained. Results of the bacterial cultures were negative, and results of the urine organic acids, serum amino acids, carnitine level, and acylcarnitine tests were all within normal limits. His newborn metabolic screen also returned and was within normal limits. He was discharged to home on hospital day 10. On the day of discharge (at 17 days of life), he was able to take 2 ounces of formula per feeding, although his weight on this day was only 3.84 kg (still not back to his original birth weight).

On the day after discharge, the parents noted a temperature of 35.5°C at home, which was slightly below our normal limit of 36°C for temperature. The infant also was not feeding well, and they returned to the emergency department. He appeared stable with a temperature of 35.9°C, and results of laboratory testing revealed normal blood cell count, glucose, electrolytes, renal, and hepatic function. The infant was admitted to the general care floor for further evaluation.

**Question:** Although this neonate has had an extensive evaluation already, what other disease could explain these persistent symptoms, and are any other diagnostic tests necessary?

**Discussion:** This neonate presented initially with lethargy, poor feeding, hypotonia, and severe hypothermia with a temperature of 30.7°C. Test results were negative for infection, central nervous system (CNS) malformation, cardiorespiratory abnormality, hepatic failure, renal failure, anemia, hypothyroidism, organic acidurias, amino acid disorders, fatty acid oxidation disorders, and urea cycle defects. Although the brain MRI revealed a small subdural hematoma, we believed such a small hematoma would be unlikely to cause his symptoms. In addition, because the infant’s initial hypotonia appeared to show some improvement, we reasoned that he did not have a neuromuscular disorder such as spinal muscular atrophy, hereditary motor neuropathy, infant botulism, myasthenia gravis, or myotonic dystrophy.

Because of the nature and persistence of the infant’s symptoms, however, we believed that further testing for neurologic and metabolic diseases was warranted. In particular, we considered chromosomal abnormalities such as Prader-Willi syndrome. We also considered disorders of neurotransmitters, lysosomes, peroxisomes, mitochondria, metal metabolism, purine metabolism, creatine metabolism, and congenital disorders of glycosylation. Examples of these disorders, which can sometimes present in the neonatal period, are listed in Table 1.

Additional testing that would be needed to make these diagnoses would include CSF neurotransmitter levels, plasma lysosomal enzymes, plasma very long chain fatty acids and plasmalogen levels, plasma and CSF catecholamine levels, urine for succinyl purines, creatine and creatinine levels in urine and plasma, mitochondrial DNA testing, muscle biopsy, and plasma transferrin isoforms. After consultation with the neurology and genetics services, we began the evaluation by ordering a DNA microarray, rather than ordering all of the aforementioned metabolic studies. Ten days later, the result of this DNA microarray, with confirmatory PCR analysis, returned and showed a deletion of 124 kb at the long arm of chromosome X at band g21.1, the known locus of the gene for a copper-transporting ATPase. Deletions at this locus have been shown to cause Menkes disease.

**Question:** What is Menkes disease, and is it treatable?

**Discussion:** Menkes disease is an X-linked recessive disorder with an incidence of 1 in 90 000 to 254 000. The defective copper transporter in this disease leads to trapping of copper at
the intestinal mucosa and kidney and failure of delivery to the CNS and connective tissues. The lack of copper at the CNS then leads to demyelination, reactive gliosis, and eventual neuron loss.

This disease most commonly presents in early infancy with the symptoms of lethargy, poor feeding, failure to thrive, hypothermia, and myoclonic seizures. The face is sometimes described as cherubic, and the hair is often steely and depigmented. Skeletal changes that can develop include wormian bones in the lamboid and sagittal sutures, anterior rib flaring and cupping, lateral or medial spur formation at the proximal and distal metaphyses of the femur and humerus, and osteoporosis, often by 6 months of age. Brain MRI frequently reveals subdural hemorrhage in early infancy, and intracranial vascular tortuosity and white matter loss later. Urinary bladder diverticula and diaphragmatic hiatal hernia have been described in some patients. Milder phenotypes of this disease have been reported, and some heterozygous female subjects may also exhibit some mild manifestations and require treatment.

Plasma and CSF catecholamine levels are distinctively abnormal in patients with Menkes disease. Elevations in the levels of dihydroxyphenylalanine and dihydroxyphenylacetic acid, with low levels of norepinephrine metabolites, are characteristic. Beyond the first 6 weeks of life, serum copper and ceruloplasmin levels are often low, and hepatic copper levels are typically low as well. Because most gene mutations are unique to each patient, clinical molecular diagnosis and mutation identification can sometimes be problematic.

Early diagnosis is critical for patient outcomes. Treatment with subcutaneous copper injections must be initiated as early as possible. Significant improvement in neurologic function can occur with early treatment, and even normal neurologic development is possible. In the largest reported case series of Menkes patients, 12 patients who were diagnosed in the neonatal period received daily subcutaneous copper injections until 3 years of age. Eleven of these patients survived. Two of the original 12 patients had normal neurologic development at a median follow-up of 4.6 years. The authors of the study postulated that these 2 children with normal development likely had mild mutations and some residual copper-transporting ATPase activity.

Follow-up: Our patient was referred for treatment with copper injections at the National Institutes of Health. He received his first injection at 7 weeks of age and continued daily injections until he was 3 years old. At 10 months of age, a repeat brain MRI showed that he had developed tortuosity of the intracranial cerebral arteries (particularly the middle cerebral arteries). This tortuosity remained stable on a repeat MRI at 2 years of age. His brain otherwise appears normal on MRI examinations. He was also found to have a right diaphragmatic hernia, a small urinary bladder diverticulum, and grade 4 left vesicoureteral reflux during his first year of life. Developmentally, he began walking at 18 months but continues to have some hypotonia. He speaks in sentences but has some mild speech delay. He is now 5 years old and preparing to start kindergarten.

Summary: This case highlights the challenge and importance of diagnosing metabolic diseases in early infancy. Our patient’s vomiting, poor feeding, and failure to thrive were nonspecific and could have been indicative of many disorders. After ruling out the most common disorders, however, his physicians were obligated to investigate other causes through extensive literature searching and further

---

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Class</th>
<th>Early Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic L-amino acid decarboxylase deficiency</td>
<td>Neurotransmitter disorder</td>
<td>Lethargy, hypothermia, hypotonia, seizures</td>
</tr>
<tr>
<td>GM1 gangliosidosis, early infantile form</td>
<td>Lysosomal storage disorder</td>
<td>Hypotonia, feeding difficulty, mild dysmorphic features, hepatosplenomegaly</td>
</tr>
<tr>
<td>Neonatal adrenoleukodystrophy</td>
<td>Peroxisomal disorder</td>
<td>Hypotonia, feeding difficulty, mild dysmorphic features</td>
</tr>
<tr>
<td>Menkes disease</td>
<td>Metal metabolism</td>
<td>Lethargy, hypothermia, myoclonic seizures</td>
</tr>
<tr>
<td>Adenylosuccinate lyase deficiency</td>
<td>Purine biosynthesis disorder</td>
<td>Hypotonia, seizures, mild dysmorphic features</td>
</tr>
<tr>
<td>CDG type 1n</td>
<td>Congenital disorder of glycosylation</td>
<td>Hypotonia, feeding difficulty, seizures, deafness</td>
</tr>
<tr>
<td>Coenzyme Q10 deficiency</td>
<td>Mitochondrial disorder</td>
<td>Feeding difficulty, seizures, acidosis, hypothermia</td>
</tr>
</tbody>
</table>
laboratory testing. His hypothermia was characteristic of Menkes disease, and it should have helped to guide our test selection toward this disorder of metal metabolism. In fact, Menkes disease is the first disease listed as a possible cause for neonatal hypothermia at Online Mendelian Inheritance in Man (www.omim.org). We were fortunate that our patient had a gene deletion large enough to be detected by using DNA microarray; a smaller abnormality such as a deletion or point mutation would have been undetectable. His neurologic outcome would have been much worse had the diagnosis and treatment been delayed.

An exceedingly large number of various metabolic disorders have now been identified, and testing for all of them in a cost-effective manner is extremely difficult. Evidence-based guidelines for the testing of such uncommon diseases are lacking. Many of these disorders now have effective therapies if diagnosed early. Examples include bone marrow transplant for some lysosomal storage disorders, coenzyme Q10 for coenzyme Q10 deficiency, and copper injections for Menkes disease.2 Physicians should have a high index of suspicion and consider more extensive investigation and metabolic testing in the appropriate clinical scenarios.

REFERENCES