A 10-Year-Old Boy with Muscle Cramps
Robert Listernick, MD

A 10-year-old boy was evaluated for a 4-month history of muscle cramps. Initially, the cramps occurred twice weekly, usually in his calves. More recently, he had been having cramps in both arms and hands which lasted for up to 5 minutes. On occasion, his fingers would get "stuck" for several minutes before he could straighten them. Although he still participates in gym class, his mother reported he had become more cautious about physical activity.

There was no history of fever, chills, night sweats, weight loss, visual problems, nausea, vomiting, or diarrhea, although in the past year, he also has noted "dark spots" on his ankles and lower extremities. His past history was unremarkable, although his brother has autism with sensory integration problems.

On exam, the patient was alert and appeared healthy. Weight and height were in the 50th percentile. Pulse 88, respiratory rate 16, blood pressure 107/61. There were several 2 to 3 cm hyperpigmented patches with irregular borders on his lower extremities. HEENT exam was unremarkable. Lungs were clear. S1 and S2 were normal without murmurs, rubs, or gallops. Abdomen was soft and non-tender without masses or organomegaly. He was Tanner 1. Both testes were descended. Back was straight. Extremities were normal. Muscle mass was normal without tenderness. On neurologic examination, deep tendon reflexes were 2+ bilaterally. Toes were downgoing. Muscle strength was 5/5 throughout. Cranial nerves II through XII were intact.

On initial laboratory evaluation, hemoglobin was 9.7 g/dL, white blood cell count 8,600/mm³ with 45% neutrophils, 41% lymphocytes, 10% monocytes; platelet count 178,000 mm³. MCV was 74, MCH 21, RDW 22 (normal 12.5-16), reticulocyte count 4.5%. Chem14 and ionized calcium were normal save for an albumin of 2 g/dL. GGT was normal. Sedimentation rate and C-reactive protein were normal; CPK was 510 IU/L (normal 27-248 IU/L).

Robert Listernick, MD, moderator: I know this may be a profound metaphysical, philosophical question, but what’s a muscle cramp?

Dr. Listernick: Are there clues on exam to the presence of myotonia rather than simple cramps?

Dr. Kuntz: One clue is the presence of percussion myotonia. You hit a relaxed muscle with a reflex
hammer, which provokes sustained muscle contraction. Action myotonia refers to sustained muscle contraction following muscle activity, such as gripping or hand shaking. In the presence of myotonia, you can observe slowed relaxation of a muscle contraction.

**Dr. Listernick:** What are some of the causes of myotonia?

**Dr. Kuntz:** There’s a long list, including a variety of channelopathies, myotonic dystrophy, and even hypothyroidism.

**Dr. Listernick:** What about our patient?

**Dr. Kuntz:** He had nothing abnormal on examination. His strength was normal. There was no action or percussion myotonia. However, his CPK was elevated, as you pointed out.

**Dr. Listernick:** Even though there was no significant weakness or rash, the possibility of dermatomyositis was raised. He was seen by a rheumatologist who felt that this diagnosis was unlikely given the absence of a rash or elevated inflammatory markers. There was no serologic evidence of a systemic vasculitis. However, the CBC is certainly unusual.

**Robert Liem, MD, pediatric hematologist:** There’s definitely some contradictory information. He has a mild microcytic anemia with a wide RDW and an elevated reticulocyte count. If he didn’t have an elevated reticulocyte count, the most likely cause for the anemia would be iron-restrictive anemia or sideroblastic anemia. In these situations, the reticulocyte count would be low. Soluble transferrin receptor would be very useful in distinguishing between these entities; it’s elevated in iron deficiency but normal in chronic inflammatory states.

**Dr. Listernick:** It was normal in this child. What was the contradictory information?

**Dr. Liem:** Anemia with an elevated reticulocyte count often implies hemolysis. However, most hemolytic anemias are normocytic. Hence, the information is contradictory.

**Dr. Listernick:** How would you have proceeded?

**Dr. Liem:** I would have reviewed the smear for signs of hemolysis, such as spherocytes or schistocytes, and looked for ancillary markers of hemolysis, such as an elevated LDH, total bilirubin, or the presence of hemoglobinuria.

He needs a Coombs test. Serum haptoglobin is a great test for hemolysis, but the results may take several weeks to come back, depending on the institution. Haptoglobin binds plasma-free hemoglobin, so it is low in the presence of acute or chronic hemolysis.

**Peter Whitington, MD, pediatric hepatologist:** You have to have really abrupt and severe hemolysis to increase indirect bilirubin in a child who has normal liver function.

**Dr. Listernick:** Coombs testing was negative; he did have an elevated LDH with a normal bilirubin. However, early in the evaluation, he was referred to genetics because of an elevated CPK and the possibility of a genetic syndrome that causes recurrent rhabdomyolysis.

**Barbara Burton, MD, pediatric geneticist:** Although we see many patients who have episodic rhabdomyolysis with pain from a variety of metabolic causes, muscle cramps are not the usual complaint. It didn’t sound like one of our diseases, but we did proceed with an evaluation.

**Dr. Listernick:** What testing was performed?

**Dr. Burton:** We looked for fatty acid oxidation defects, such as very long chain acyl-coA dehydrogenase deficiency and carnitine palmitoyltransferase-2 deficiency. We also did a plasma acylcarnitine profile and a plasma carnitine level. In 2011, these diseases are screened for on our state’s newborn screening panel, but they weren’t looked for when this 10-year-old boy was born.

In addition, respiratory chain defects can present with rhabdomyolysis. We performed non-invasive testing for mitochondrial function, including plasma lactate, plasma amino acids, and urine organic acids. Muscle biopsy was considered.

**Dr. Kuntz:** Both phosphofructokinase and phosphoglyceromutase deficiencies are muscle diseases that can also lead to hemolytic anemia. These can be diagnosed by testing red blood cell enzyme levels, obviating the need for muscle biopsy. The levels were normal. Chronic pain is not typical of these syndromes; more commonly, these individuals have exercise intolerance or myoglobinuria.

**Dr. Listernick:** Would EMG have been helpful at this point?

**Dr. Kuntz:** EMG would be useful to exclude any myotonic disorder or any disorder of increased hyperexcitability of the muscle membrane. Given the unusual nature of this case, I didn’t think it would be useful. But we did proceed to muscle biopsy.
**Dr. Listernick:** All of the plasma and urine tests were normal. There was no urine myoglobin detected. The muscle biopsy was totally normal, including the routine histology, immunostaining for dystrophin, and the special stains looking for specific muscle enzymes.

Moving forward, sometime during the course of his evaluation, a coagulation profile was obtained that revealed prothrombin time 20.8 seconds, INR 1.7, PTT 35.8 seconds, and fibrinogen 290. He received vitamin K and the prothrombin time did not correct; however, the prothrombin time did correct upon mixing with normal plasma. Interpretation?

**Dr. Liem:** Prothrombin time reflects the extrinsic arm of your coagulation pathway; the only factor of significance that it reflects is factor VII, which has a short half-life. Isolated prothrombin time elevation suggests factor VII deficiency either from an inherited deficiency, early impaired synthetic function caused by liver disease, or early vitamin K deficiency, most commonly from malabsorption. Rarely, one can acquire an inhibitor to factor VII.

**Dr. Listernick:** How do you distinguish among these possibilities?

**Dr. Liem:** If the prothrombin time corrects in vitro when mixed with normal plasma, then the problem is factor VII deficiency, either congenital or acquired. If it doesn’t correct, then a circulating inhibitor is present. If the prothrombin time doesn’t correct in vivo with the administration of vitamin K, liver disease should be suspected.

**Lee Bass, MD, pediatric hepatologist:** We often measure a variety of coagulation factors in a child who appears to have liver dysfunction to distinguish whether a prolonged prothrombin time is caused by either disseminated intravascular coagulation (DIC) or synthetic liver dysfunction. In DIC, factors V, VII, and VIII are all decreased, whereas in the setting of synthetic liver dysfunction, only factors V and VII are decreased.

**Dr. Listernick:** One of the early confounding factors was the lack of recognition that there could be significant liver disease present despite the fact that the transaminases, GGT, bilirubin, and alkaline phosphatase were all normal.

**Dr. Bass:** The elevated prothrombin time that doesn’t correct following the administration of vitamin K reflects liver synthetic dysfunction. Normal transaminases imply that there isn’t significant ongoing hepatocellular damage.

**Dr. Whitington:** In addition, specific diseases may lead to specific profiles of liver dysfunction. For instance, tyrosinemia is a perfect example of a disease in which patients usually have relatively low aminotransferases without jaundice, yet have evidence of significant synthetic dysfunction. This is probably caused by a direct toxic effect of intermediate metabolites on the terminal carboxylation of the prothrombin factors in the liver.

**Dr. Listernick:** At this point, a diagnostic study was performed. The combination of nonimmune hemolytic anemia and liver disease strongly suggested the possibility of Wilson’s disease (WD). Ophthalmolo-
logic examination revealed the presence of Kayser-Fleischer rings.

**Dr. Bass:** As you stated, the key was the recognition that nonimmune hemolytic anemia may be a presenting sign of WD and that this child had significant hepatic synthetic dysfunction. WD has a broad spectrum of presentations, ranging from mild transaminase elevation and asymptomatic hepatomegaly or splenomegaly to fulminant hepatic failure. There are myriad neuropsychiatric presentations of WD, including movement disorders, dystonia, depression, and psychosis. Multiple other organ systems may be involved, including pancreas (recurrent pancreatitis), kidney (nephrolithiasis) and heart (cardiomyopathy). Hemolysis may be the presenting symptom in as many as 10% of patients.

**Dr. Listernick:** What about this child’s muscle cramps?

**Dr. Kuntz:** This was a learning experience for me; muscle cramping has not been a reported complication of WD. There are two case reports of rhabdomyolysis, but he had only mild elevation of CPK.

**Dr. Bass:** Muscle cramping and dystonia are mentioned as possible symptoms in published WD guidelines, but they are not referenced. I couldn’t find any specific case reports.

**Dr. Listernick:** How do you confirm the diagnosis?

**Dr. Bass:** The normal screening test that we perform is a serum ceruloplasmin, but the positive predictive value is low. The presence of Kayser-Fleischer rings is very helpful. Most helpful is an elevated 24-hour urine copper level.

**Dr. Listernick:** This child’s ceruloplasmin was very low. Is liver biopsy necessary?

**Dr. Whittington:** It’s not necessary for diagnosis, but it’s necessary for treatment. Chelation needs to be continued until there’s no measurable liver copper. Wilson’s disease is a perfect example of a toxic hepatopathy in which protein synthesis may be the only abnormality evident on initial testing.

**Dr. Kuntz:** What about his autistic brother?

**Dr. Bass:** “Autism” has been a reported presenting feature of WD. The sibling’s testing was normal.

**Dr. Listernick:** What did his biopsy show?

**Hector Melin-Aldana, MD, pediatric pathologist:** The liver has extensive areas of cirrhosis and scarring. There was interface hepatitis demonstrating inflammatory cells invading the portal tracts. These findings can be seen in a number of chronic liver diseases, including autoimmune hepatitis, hepatitis B or C, and WD. However, the “copper stain” of the hepatocytes was positive. This stain actually detects deposition of a complex protein bound with copper. Finally, the measured copper content of the liver was significantly elevated.

**Dr. Listernick:** Will he need a liver transplant?

**Dr. Bass:** That remains to be seen. Chelation is the first-line therapy for WD and has been since the mid-1950s. The primary chelators we use are penicillamine and trientine. Penicillamine has a high incidence of side effects that can cause up to 20% to 30% of people to discontinue their therapy, so we started with trientine. Time will tell, but he very well may recover and lead a healthy life without the need of transplantation.

**Dr. Listernick:** Thank you, everyone.

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**Key Learning Points**

1. Myotonia, the sensation of “getting stuck” in which there’s delay in relaxation of the muscles, may be caused by diverse etiologies, including channelopathies, myotonic dystrophy, and hypothyroidism.

2. Myokymia, localized involuntary muscle quivering, may be caused by drugs or to a paraneoplastic process.

3. Measurement of soluble transferrin receptor is helpful in distinguishing between iron deficiency anemia (low) and the anemia of chronic inflammatory conditions (normal).

4. Isolated prothrombin time elevation suggests either an inherited factor VII deficiency, synthetic function caused by liver disease or vitamin K deficiency, most commonly from malabsorption.

5. The presence of both nonimmune hemolytic anemia and liver dysfunction is highly suggestive of Wilson’s disease.