An 8-Year-Old Boy with Intermittent Pain

Robert Listernick, MD

This previously healthy 8-year-old boy was admitted after 10 days of intermittent pain in his upper arms, back, and both lower extremities. There was no inciting event. He was unable to identify the character of the pain, although he couldn’t walk, and the pain had awakened him at night. Review of systems was entirely unremarkable: no history of fever, rashes, viral symptoms, trauma, vomiting, or diarrhea. Past history and family history were unremarkable.

On exam, he was a thin boy who was lying in bed, writhing in pain. He answered questions appropriately, but seemed distracted by his pain. Pulse was 98; respiratory rate 20; blood pressure 112/73. He was in the 75th percentile for weight and 90th percentile for height. There were no rashes. HEENT exam was normal. S1 and S2 were normal without murmurs. Lungs were clear. Abdomen was soft and non-tender without organomegaly. He was Tanner 1. Both testes were descended. He had full range of motion of all his joints, but experienced pain when his knees were touched. There was no swelling, erythema, or edema.

On neurologic exam, he refused to walk. Deep tendon reflexes were 2+ bilaterally. Strength was 5/5 throughout. Cranial nerves two through 12 were normal.

On laboratory evaluation, he had a normal Chem-14; hemoglobin 14 g/dL; white blood cell count of 5,000/mm3 with 48% neutrophils; 43% lymphocytes, 5% monocytes, 3% eosinophils; and platelet count of 260,000/mm3. X-rays of his lower extremities, pelvis, and lumbosacral spine were normal.

Robert Listernick, MD, moderator: In my experience, this type of pain syndrome generally represents one of two conditions.

Robert Liem, MD, pediatric hematologist: Isolated bone pain is an uncommon, but very well-known, presenting sign of acute leukemia in children. These children may not have hepatosplenomegaly or lymphadenopathy. Although the CBC might provide clues, such as thrombocytopenia or abnormal differential count, I’ve definitely seen children with absolutely normal CBCs.

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Dr. Listernick: Have their X-rays been normal as well?

Dr. Liem: You’re referring to “leukemia lines,” which occur in the metaphyses of the long bones. They probably represent a disturbance in endochondral bone formation caused by leukemic cells in the densely packed marrow. I’ve seen them in this clinical scenario, but I can’t say how often they’re present.

Dr. Listernick: So, Robert, you make the call — bone marrow biopsy or no bone marrow biopsy?

Dr. Liem: With no abnormalities on the CBC and normal X-rays, I wouldn’t.

Dr. Listernick: Bone marrow biopsy was performed and was absolutely normal. Now what?

Nancy Kuntz, MD, pediatric neurologist: The second diagnosis to which you were alluding, I assume, is Guillain-Barré syndrome.

Somewhat against this diagnosis in this child are his completely normal deep tendon reflexes and strength. However, as we know, examining children when they’re in a lot of pain can be extremely difficult; assessments of strength and reflexes are notoriously inaccurate.
This definitely could be Guillain-Barré syndrome.

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

**Dr. Kuntz**: He’s had symptoms for long enough that I would expect an elevated CSF protein. I might also perform an electromyogram looking at the nerve conduction velocities.

**Dr. Listernick**: What about magnetic resonance imaging (MRI) looking for contrast-enhancing, inflamed lumbar nerve roots?

**Dr. Kuntz**: I don’t have the data, but I suspect the sensitivity of MRI would be less than either lumbar puncture or nerve conduction velocity testing.

**Dr. Listernick**: What about the possibility that he’s having paresthesias from another cause?

**Dr. Kuntz**: Paresthesias in the hands and feet definitely can be a sign of peripheral neuropathy.

It’s important to remember that there are many different kinds of nerve fibers. Motor fibers and the sensory fibers that give position and vibration sense are large fibers that show abnormalities in nerve conduction studies and cause abnormalities in the deep tendon reflexes. However, abnormalities of selective small fibers may cause sensory and autonomic problems that don’t show any abnormalities on the classic neurologic examination. One clue toward this possibility would be the absence of sweating. I’ve seen children who have autoimmune autonomic neuropathies, occasionally as the result of a paraneoplastic process.

**Dr. Liem**: I’ve seen children who have a peripheral neuropathy on the basis of lead poisoning or sickle cell disease.

**Dr. Kuntz**: In addition, Fabry’s disease is an X-linked multisystem metabolic disorder caused by a deficiency of alpha-galactosidase that may present in childhood with acroparesthesias.

**Dr. Listernick**: So, this child had a normal examination of the bone marrow and a normal MRI scan of the lumbosacral spine looking for evidence of Guillain-Barré syndrome. He remained in the hospital for several days with waxing and waning symptoms.

**On examination, he was extremely irritable, but calmed down when left alone.**

On the third hospital day, his 19-month-old brother came into the emergency room with chief complaints of rash, irritability, and sweating. Over the previous month, he had intermittent intervals of crying, decreased oral intake and, most recently, a 5-day history of rash. He had been seen in the emergency room 1 month earlier for irritability, without any specific symptoms, and was sent home. For several days before this visit, he had been “walking funny,” described by his mother as waddling. The day of admission, he stopped walking. His mother also noted that he sweated frequently despite having a normal rectal temperature. Five days before the visit, he developed a rash on his abdomen that spread to his extremities and palms. Past medical history was unremarkable.

On examination, he was extremely irritable, but calmed when left alone. Temperature 98.96°F; pulse 154; respiratory rate 36; blood pressure 160/96. Weight, height, and head circumference were all in the 25th percentile. HEENT exam was unremarkable. Lungs were clear. S1 and S2 were normal with physiologic splitting. There were no murmurs. Pulses were normal. Abdomen was soft without masses or organomegaly. Both testes were descended. There was full range of motion of all his extremities without edema.

On neurologic exam, deep tendon reflexes were 2+ throughout. Cranial nerves two through 12 were normal. His tone was normal. He had an erythematous maculopapular rash on his torso, back, and legs that was concentrated over his knees. The palms were involved, but there were no lesions on his soles.

Laboratory evaluation revealed normal CBC with differential; Chem 14 including BUN and creatinine; urinalysis; T4; TSH; T3; and chest X-ray. UA had a specific gravity of 1.020.

**Dr. Listernick**: The blood pressure was repeated several times and confirmed as being significantly elevated. Is this malignant hypertension?

**Kavita Hodgkins, MD, pediatric kidney diseases physician**: Malignant hypertension is typically classified as hypertension associated with end organ dysfunction. If the irritability is related to an effect of his elevated blood pressure on his brain, this would certainly be considered malignant hypertension.

**Dr. Listernick**: What would be your approach to managing his elevated blood pressure?

**Dr. Hodgkins**: Since we don’t know how long the blood pressure
has been elevated, we would be careful about dropping it too quickly, so as to preserve cerebral perfusion pressure. The initial goal would be to decrease blood pressure by about 25%. Often, we’ll use a continuous intravenous infusion of nicardipine. However, he was so tachycardic that we chose labetalol, a beta-blocker, as our first-line therapy.

He was admitted to the intensive care unit for close monitoring and titration of the labetalol. Despite increasing the dose of labetalol, his blood pressure was not controlled. Even though we added nicardipine, his elevated pressures persisted.

**Dr. Listernick:** What are the possible causes of his hypertension?

**Richard Cohn, MD, pediatric kidney diseases physician:** First, one should measure lower extremity blood pressures. It’s easy to diagnose coarctation of the aorta without echocardiography. If the gradient between upper and lower extremity blood pressures is greater than 30 mm Hg, you’ve essentially made a diagnosis.

Approximately 60% of the time, hypertension in this age group is caused by renal parenchymal disease, such as one of the many glomerulonephritides or obstructive uropathy. About 10% of such children have renovascular disease. Finally, the remainder have a collection of rarer causes of hypertension such as coarctation of the aorta, hyperthyroidism, neuroblastoma, or Wilms’ tumor. His tachycardia would suggest hyperthyroidism, but we know that the thyroid function tests were normal.

**Dr. Listernick:** How would you have proceeded trying to establish a diagnosis?

**Dr. Cohn:** Once you know the initial laboratory tests are normal, renovascular hypertension becomes a real concern. I would send plasma levels of renin and angiotensin.

As far as imaging, I would start with a renal ultrasound looking for either discrepancy in the sizes of the kidneys, suggestive of renal artery stenosis, or a renal or suprarenal mass, suggesting either Wilms’ tumor, adrenal tumor, or neuroblastoma. Echocardiography could identify a coarctation. Also, significant left ventricular hypertrophy would suggest longstanding hypertension.

**Dr. Listernick:** These were done and were all normal.

**Dr. Cohn:** If I still thought renovascular hypertension was high on the list, I would perform magnetic resonance or computerized tomography angiography. You will get excellent pictures of the main and first branches of the renal arteries. Distal obstructions are identified mainly by conventional selective renal angiography.

**Dr. Listernick:** The problem is, we shouldn’t look at this case in isolation; certainly, there must be a way of linking the two brothers’ disparate symptoms.

**Mike Christian, MD, toxicologist:** An environmental toxin is clearly high on the list. I would obtain a lead level immediately. Initially, we want to ask about their living quarters, occupations, hobbies, drug use, potential exposures in the house, and illnesses among other family members. We’d try to get a sense of the environment.

**Dr. Listernick:** Do you visit the home?

**Dr. Christian:** On rare occasions. If we do, it’s looking for something specific; it’s hard to just go into an environment without having an idea what you’re looking for.

**Dr. Listernick:** The combination of symptoms of these two children was quite suggestive of a particular exposure, which led to further history being obtained.

**Nima Desai, MD, pediatric resident:** After further discussion, we decided to investigate the environment, specifically any heavy metal exposures. I was particularly interested in mercury exposure.

The mother said that the father worked in construction and that a few months earlier he had brought home mercury from an old thermostat and had placed it in a glass jar. All the children had played with it, and it had been stored in an area to which they had had access.

Several weeks ago, she had found the container empty, but she had not investigated further. Ultimately, it was determined that the older brother had spilled it on a rug in a common area, a rug on which the younger brother frequently plays.

**Dr. Christian:** It’s certainly a tough diagnosis to make, but when you look at both cases together,
there are many features of mercury poisoning that stand out.

There are several different kinds of mercury poisoning. Acute exposure to elemental mercury vapors, for instance, if the mother had vacuumed the rug, can lead to acute respiratory symptoms. Swallowed mercury from a glass thermometer is non-toxic.

These children had chronic exposure to elemental mercury either through aerosolization, dermal contact, or both, leading to acrodynia. Chronic exposure to inorganic mercury (acrodynia) may lead to neuropsychiatric symptoms, such as tremors, peripheral neuropathy, or personality changes.

I suspect the older boy’s pain symptoms were caused by acroparesthesias from a peripheral neuropathy. Excessive sweating with normal body temperature is also a classic symptom. Erythema and edema of the palms and soles with a desquamating rash also is seen classically in acrodynia, also called Pink disease. Finally, there have been numerous case reports of hypertension in children caused by chronic inorganic mercury poisoning.

Dr. Cohn: The enzyme catechol-o-methyl transferase degrades all catecholamines and is inhibited specifically by mercury and several other heavy metals. This may lead to elevated levels of circulating catecholamines, and explains hypertension and sweating seen in some children with mercury poisoning.

Dr. Listernick: What about organic mercury poisoning?

Dr. Christian: Chronic organic mercury poisoning through ingestion of contaminated foods may lead to neurologic disorders, such as vision loss, ataxia, and mental deterioration. Methylmercury passes readily through the placenta and may lead to fetal toxicity, such as in classic Minimata disease from ingestion of contaminated fish in Japan.

Trevonne Thompson, MD, toxicologist: There are theoretical reasons that may explain the difference in symptoms between the two children. The younger one might have had more exposure from crawling around on the rug and inhaling of the aerosolized mercury. He’s also around the home all day while his brother is at school.

Dr. Listernick: How do we confirm these diagnoses?

Dr. Christian: The best test is a 24-hour urine collection for mercury; we also asked for a serum mercury level.

Dr. Listernick: Both children had significantly elevated levels of mercury measured in the 24-hour urine collections.

Dr. Thompson: Without going too deeply into the values, we had some heated discussions in our consortium about whether the older brother’s symptoms were truly secondary to mercury poisoning. Regardless, they both had elevated levels and required chelation therapy with succimer.
**Dr. Listernick**: How long does mercury stay in the system if untreated?

**Dr. Thompson**: We know that lead stays in the body for years, but mercury has a much shorter half-life. It’s certainly conceivable that these boys’ levels were much higher on admission and waned before they were measured. The best treatment is removal from the source of the mercury poisoning, but succimer chelation therapy will help speed up the process.

**Dr. Kuntz**: Mercury has a direct effect on dorsal root ganglia, and the neuropathy that develops may take a while to recover because of the damage to the dorsal root ganglia and the axons.

**Dr. Listernick**: How would you perform the chelation therapy?

**Dr. Thompson**: I would administer succimer 10 mg/kg three times orally daily for 3 weeks, wait 1 week then check another 24-hour urine level. The decision to repeat chelation should be based on the urine level and the patient’s symptoms. If he’s been removed from the source and is clinically well, I might not repeat chelation even if the level is still somewhat elevated.

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

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**Key Learning Points**

1. Limb pain and refusal to walk are common presentations of Guillain-Barré syndrome.
2. Paresthesias in the hands and feet can be a sign of peripheral neuropathy. One clue toward this possibility would be the absence of sweating.
3. Fabry’s disease is an X-linked multisystem metabolic disorder caused by a deficiency of alpha-galactosidase that may present in childhood with acroparesthesias.
4. Approximately 60% of the time, hypertension in toddlers is caused by renal parenchymal disease, such as glomerulonephritis or obstructive uropathy. Ten percent have renovascular disease. The remainder have a collection of rarer causes of hypertension, such as coarctation of the aorta, hyperthyroidism, neuroblastoma, or Wilms’ tumor.
5. The best test for the identification of heavy metal poisoning other than lead is a 24-hour urine collection.