Robert Listernick, MD, and colleagues discuss hard-to-diagnose cases.

A 16-Year-Old Boy with Leg Swelling

Robert Listernick, MD

This 16-year-old boy with autism and type 2 diabetes mellitus is transferred for evaluation of right lower leg swelling. His sister first noted the swelling 5 days before admission. Since the patient is not very communicative, it is unclear whether he had been in any pain. He went to his physician because of worsening swelling and was transferred here. In all other respects, he has been acting like his normal self. There is no history of fever, dyspnea, chest pain, abdominal pain, or vomiting.

His past history is remarkable for what had been called autism. However, he appears to have a significant degree of mental retardation. He has been followed by a psychiatrist for behavior problems and has been receiving risperdal, cogentin, and lithium. He had aseptic necrosis of the left hip several years ago. Around the same time, he was diagnosed with type 2 diabetes and has been receiving metformin 500 mg twice daily. Family history is unremarkable. There is no history of early strokes, pulmonary emboli, or clotting problems.

On exam, he is an obese boy and cooperates with the examination, but is not communicative. Pulse is 108, respiratory rate 28, blood pressure 118/53. He weighs 136 kg. HEENT exam is unremarkable. There are no dysmorphic features. His neck is supple without adenopathy. Lungs are clear. Cardiac examination is normal. Pulses were 2+ and equal throughout.

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Abdomen is soft and non-tender without hepatosplenomegaly. He has full range of motion of all four extremities. His right thigh, calf, and foot are swollen with overlying erythema. This entire area is sensitive to the touch. There is calf pain on dorsiflexion of the right ankle (Homan’s sign). Superficial leg veins are palpable like a cord. Neurologic examination is unremarkable.

On laboratory evaluation, hemoglobin is 11.3 g/dL with MCV 72 and RDW 15. White blood cell count is 3,400/mm³ with 40% neutrophils, 50% lymphocytes, and 3% eosinophils; platelet count 63,000/mm³. Prothrombin time 14.6 seconds; PTT 27 seconds; fibrinogen 349 mg/dL; D dimer 1.9 mcg/mL (slightly elevated). Serum chemistries are normal save for uric acid 10 mg/dL (markedly elevated).

Robert Listernick, MD, moderator: How should one approach the possible etiology of his autism and mental retardation?

Barbara Burton, MD, geneticist: Diagnostic evaluation initially depends on whether there are dysmorphic features that point to a specific diagnosis and whether he is macrocephalic or microcephalic. Assuming none of these are present, I would start by looking at a whole-genome microarray, searching for small deletions or insertions of genetic material, as well as Fragile X syndrome testing. Since this patient was born before we were performing newborn screening for inborn errors of metabolism, I also would probably order plasma amino acid and urine organic acid testing. Finally, if the family history suggested similarly affected males, there are panels that test for a wide array of genes that cause X-linked mental retardation.

Dr. Listernick: He was receiving metformin for type 2 diabetes.

Don Zimmerman, MD, pediatric endocrinologist: Metformin is an insulin sensitizer most commonly used in a person who’s insensitive to insulin because of excessive weight gain. We used to believe that metformin’s utility was limited to its ability to increase the liver’s sensitivity to insulin.
However, we now understand that insulin is one of the signals that helps a person sense fullness at the level of the hypothalamus, and that metformin also acts at the hypothalamus by making it more sensitive to that “fullness signal.” So metformin actually may attenuate the patient’s appetite.

**Dr. Listernick:** What about the hyperuricemia?

**Dr. Zimmerman:** Hyperuricemia may be a consequence of metabolic syndrome. Look at all the illustrations from Victorian literature of obese men with gout. It was actually felt to be a “prized” consequence of wealth and obesity.

**Dr. Burton:** He doesn’t have hyperuricemia related to Lesch-Nyhan syndrome because there is no history of self-mutilation. I doubt that he has Prader-Willi syndrome. You didn’t mention a history of neonatal hypotonia nor of cryptorchidism, which is almost universally present in males with that syndrome.

**Dr. Listernick:** Moving to the present, it appears as if he has a deep venous thrombosis (DVT).

**Ellen Benya, MD, pediatric radiologist:** Using color Doppler imaging, there’s a large clot in the superficial femoral vein. We generally can identify DVT using Doppler imaging when they occur between the common iliac vein through the popliteal vein. Calf veins are difficult to see using this technique.

**Anjali Sharathkumar, MD, pediatric hematologist:** This child is a clear setup for thrombosis given his obesity, sedentary lifestyle, and metabolic syndrome. Individuals with metabolic syndrome may have compromised fibrinolysis, since they have low levels of plasminogen. Fibrinolysis is critical to prevent extension of clot and resolution of clot. It is critical to obtain a careful family history of DVT in first-degree relatives to consider a possibility of familial thrombophilia. It is also helpful to obtain a history of miscarriages or cerebrovascular events at a young age. His mother actually had a history of five second-trimester miscarriages.

**Dr. Listernick:** Could you clarify why you performed a thrombophilia evaluation when he had multiple risk factors for DVT?

**Dr. Sharathkumar:** Children usually require an acute trigger event for development of DVT, such as presence of central venous catheters, dehydration, use of estrogen containing birth control pills, or local trauma. Since we were not convinced of any acute trigger, we opted to perform a thrombophilia evaluation.

**Dr. Burton:** He should also have a homocysteine level measured. Individuals with homocystinuria are at increased risk for thrombosis. He does not have a marfanoid habitus, as one would see in homocystinuria. I would also test for carbohydrate-deficient glycoprotein syndrome, in which individuals may have mental retardation and thromboses.

**Dr. Listernick:** Protein C, protein S, homocysteine, and antithrombin-3 activity were normal. However, he was heterozygous for both Factor V Leiden and the prothrombin gene polymorphism G20210A. Do these results contribute to his acute management?

**Dr. Sharathkumar:** They do. This patient is at increased risk for development of recurrent thrombotic events. There’s growing evidence in pediatrics that we should be more aggressive in trying to dissolve these clots using a systemic or catheter-directed thrombolysis with tissue plasminogen activator. It is important to underscore that thrombolysis is associated with serious risk of bleeding.

**Dr. Sharathkumar:** Before we had these abnormal results, I placed him...
He has pancytopenia and a prothrombotic predisposition. It wouldn’t be much of a leap to consider possible clots elsewhere, such as in the portal vein, leading to hypersplenism. It wouldn’t surprise me if he had splenomegaly that couldn’t be appreciated because of his morbid obesity.

Dr. Listernick: What about Budd-Chiari syndrome?

Dr. Alonso: Hepatic vein thrombosis leads to a large, painful liver, which he clearly doesn’t have. Portal vein thrombosis can be extremely indolent. It would be paramount to order an abdominal ultrasound with Doppler imaging of portal vein blood flow to establish the diagnosis.

Dr. Benya: Surprisingly, abdominal ultrasonography revealed an 11 cm x 14 cm cystic lesion in the mid-upper abdomen. There was no portal vein clot and the blood flow was in the correct direction. The next study performed was computed tomography of the abdomen. There is a large, complex cystic lesion with peripheral calcifications that is compressing the splenic veins. It looks most like a pancreatic pseudocyst. The spleen is quite large and there are numerous gastric varices.

Dr. Alonso: So he doesn’t have portal hypertension, but he does have hypersplenism as a result of the splenic vein obstruction, just as if he had had splenic vein thrombosis. Clearly, he had one or more unrecognized episodes of pancreatitis in the past.

Dr. Burton: I know there are multiple etiologies of pancreatitis, but recurrent pancreatitis is a typical, although relatively uncommon, manifestation of a number of organic acidemias, including propionic acidemia, methylmalonic acidemia, and isovaleric acidemia.

Dr. Alonso: There is an extensive list of potential etiologies of pancreatitis in children, including infections (mumps, enteroviruses, CMV); cholelithiasis; congenital anatomic abnormalities (pancreas divisum, choledochal cysts); medications (most notably valproic acid, L-asparaginase, corticosteroids); metabolic causes (hypertriglyceridemia, hypercalcemia); and single gene disorders caused by mutations in PRSS1, SPINK1, and CFTR (cystic fibrosis gene).

Dr. Listernick: What do we do now?

Dr. Alonso: Even though he’s “asymptomatic,” he could have a signifi-
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significant bleeding diathesis because of the gastric varices. One option would be to percutaneously drain the pseudocyst.

**Dr. Listernick**: That’s exactly what was done and 1 L of fluid was removed that had an extremely high amylase level, proving its pancreatic origin. A drain was left in place that is draining 20 to 30 cc of fluid daily. Now the concern is for the development of a chronic fistula that won’t close. Some of the surgeons feel nothing should have been done since he was “asymptomatic.”

**Dr. Alonso**: I disagree. It might take several weeks for the drainage to stop. I certainly wouldn’t consider this a “chronic fistula” right now. After several weeks have passed, I would perform magnetic resonance cholangiopancreatography (MRCP) to assess the ductal anatomy. If a ductal problem is identified, I would perform endoscopic retrograde cholangiopancreatography to stent the duct open and prevent backflow of pancreatic fluid and reaccumulation within the pseudocyst.

**Dr. Benya**: I would perform the MRCP early before fluid re-accumulates in the pseudocyst, distorting the anatomy.

**Dr. Sharathkumar**: Because pancreatitis is a prothrombotic condition, I plan to recommend lifelong anticoagulation. We can transition him to Coumadin in the future.

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

*Editor’s note*: No anatomic etiology was found for the patient’s pancreatic pseudocyst. The cutaneous drainage ultimately stopped.