An 11-Year-Old Boy with Seizures and Fatigue

Robert Listernick, MD

This 11-year-old male was admitted to the intensive care unit following three seizures over the previous 12 hours. For the previous 3 weeks he has had fatigue, weakness, and sluggishness. Several nights before admission, he felt dizzy and had a headache with two episodes of non-bilious emesis. His headache became progressively worse over the next several days, but it was relieved by over-the-counter medicines. His mother had noticed that the area around his face and eyes seemed somewhat puffy.

The night of admission, he had generalized clonic movements lasting 60 seconds followed by a 15-minute period of sleepiness. He was admitted to an outside hospital; there he was noted to be hypotensive and received intravenous fluids, following which he had another 15-second episode of staring and unresponsiveness. He was noted to be anemic and thrombocytopenic, received a transfusion of packed red blood cells, and was transferred here.

During transport, he had an episode of right eye and head deviation with stiffening lasting approximately 15 seconds.

Review of systems is only remarkable for two formed “coal-like stools” over the last 2 weeks. His past history is remarkable in that he had an episode of cerebral malaria in 2005 at age 4 years in Nigeria. He was born in Nigeria and moved to the US in 2006. Otherwise, his history is unremarkable. He lives with both parents and has not traveled outside the US since 2006. There is no history of camping, swimming in fresh water lakes, or animal exposures. The family history is unremarkable in detail.

On physical examination, he was an alert, healthy-appearing boy. Weight was in the 80th percentile and height greater than 95th percentile. Pulse was 111, respiratory rate was 21, blood pressure was 105/52 mm Hg. HEENT exam was unremarkable save for pale conjunctivae and mild bilateral periorbital edema. Pupils were equal, round, and reactive to light. Extraocular movements were intact. Discs were flat bilaterally. Neck was supple without significant adenopathy. Lungs were clear.

He had a soft II/VI midsystolic ejection type murmur heard best at the left upper sternal border. Abdomen was mildly tender to palpation diffusely without rebound or guarding. There were no masses or organomegaly. There was a small reducible umbilical hernia. He had Tanner 1 genitalia and both testes were descended. There was no peripheral edema or rashes. Neurologic exam was entirely normal.

Initial laboratory evaluation showed hemoglobin 4.5 g/dL, white blood cell count 10,000/mm³ with 83% neutrophils, 17% lymphocytes; platelet count 81,000/mm³. MCV (mean corpuscular volume) was 88 and reticulocyte count was 4.5%. CRP (C-reactive protein) was < 0.5. Serum chemistries were unremarkable save for albumin 1.8 mg/dL. Urinalysis was normal.

Robert Listernick, MD, moderator: Gestalt?

Doug Nordli, MD, pediatric neurologist: Viewing the elephant from my limited perspective, a presenting complaint of seizures in a previously healthy child, three categories of etiology come to mind: idiopathic, acute symptomatic (seizures occurring as a result of a new insult such as sepsis), and remote symptomatic (new seizures due to a past event/insult). Given that he seems sick and has had a flurry of seizures, these sound like acute symptomatic seizures related to a condition yet to be elucidated.

Dr. Listernick: Can you localize from where they are originating, other than “the brain”?

These sound like acute symptomatic seizures related to a condition yet to be elucidated.
Dr. Nordli: Based on the third event during which his head turned to the right, one might speculate that he’s having focal seizures, some of which have generalized. There are two possibilities as to the exact location of the seizures based on the history. It could be from the left frontotemporal region because his eyes deviated to the right; however, when that occurs you usually see associated nystagmus. Alternately, they may be arising from the right parietal-occipital region. Since his neurologic exam is normal, I would bet the latter because it’s easier to hide a lesion there to the untrained eye.

Dr. Listernick: Any other theories?

Robert Tanz, MD, general academic pediatrician: Given anemia, thrombocytopenia, hypoalbuminemia, and seizures, I’d like to think that he has a chronic inflammatory disease such as lupus. However his normal CRP mitigates against this. Another fleeting thought might be hemolytic uremic syndrome, except his urinalysis and creatinine are normal. The normal bilirubin goes against acute hemolysis. There’s certainly a suggestion of gastrointestinal bleeding based on the “coal-like” stools but that doesn’t explain everything else. We need more information.

Dr. Listernick: Let’s parse this out a bit. Tell us about cerebral malaria.

Julie Kim Stamos, MD, pediatric infectious disease physician: Cerebral malaria in African children is probably its most severe complication. A high proportion of deaths due to malaria are a result of cerebral malaria. Although its onset is generally gradual in adults over days, children may develop encephalopathy, including delirium or psychosis, after only a short duration of fever. More than 50% of children with cerebral malaria develop seizures, which may be either focal or generalized. Cerebral malaria is a clinical diagnosis and is almost exclusively associated with infection by *Plasmodium falciparum*.

Dr. Listernick: From what we know, he was encephalopathic for several days but never had clear seizures until very recently. What are the neurologic sequelae of cerebral malaria?

Dr. Stamos: Although neurologic sequelae are very rare in adults, approximately 10% of surviving children will have gross neurologic handicaps at the time of discharge from the hospital. Those who have seizures during their course may develop a subsequent seizure disorder.

Dr. Listernick: Treatment of cerebral malaria?

Dr. Stamos: Careful infusion of IV (intravenous) quinidine while monitoring for QRS or QT prolongation. If the trophozoite burden is very high, one would consider exchange transfusion.

Dr. Listernick: Given that he’s severely anemic and has seizures, could his presentation today have anything to do with acute malaria?

Dr. Stamos: It’s possible, but unlikely, that his seizures are related to his past malaria given a lack of symptoms for 7 years. In addition, *P. falciparum* malaria does not relapse after such a long quiescent period. Conceivably that could occur with *Plasmodium vivax* or *Plasmodium ovale*, but they do not cause cerebral malaria.

Dr. Listernick: OK, let’s move forward and discuss the severe anemia and the possible hematochezia. Is he having significant gastrointestinal hemorrhage?

Maria Greene, MD, pediatric gastroenterologist: Quite possibly, especially given a history of melena. Potential causes could include esophageal or gastric varices, an ulcer, polyps or, less commonly at this age, Meckel’s diverticulum. I couldn’t explain thrombocytopenia unless he had associated hypersplenism; however, there is no

Panelists

Robert Listernick, MD
Moderator

Doug Nordli, MD
Pediatric neurologist

Robert Tanz, MD
General academic pediatrician

Julie Kim Stamos, MD
Pediatric infectious disease physician

(Not pictured: Maria Greene, MD, Pediatric gastroenterologist; Robert Liem, MD, Pediatric hematologist; and Yana Kiesau, pediatric ophthalmologist.)

All panelists practice at The Ann and Robert H. Lurie Children’s Hospital of Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for *Pediatric Annals*. 
spleenomegaly noted on the physical examination.

**Dr. Listerick:** What about the hypoproteinemia?

**Dr. Greene:** Conceivably he could have significant synthetic liver disease or a protein-losing enteropathy. There’s certainly no evidence for the former, such as hepatomegaly, spleenomegaly, or elevated serum transaminases. Causes of protein-losing enteropathy include *Helicobacter pylori* infection, intestinal lymphangiectasia, inflammatory bowel disease, celiac disease, etc. The list is quite extensive.

**Robert Liem, MD, pediatric hematologist:** From a hematologist’s point of view, there are very few conditions that can cause such a severe normocytic anemia: acute blood loss, hemolysis, or sequestration. From this list, you can decide where the thrombocytopenia fits. Right off the bat, he didn’t have spleenomegaly, which discounts the possibility of hypersplenism. Next, we looked at the smear and there was no evidence of red blood cell destruction (schistocytes, red blood cell fragments) from disseminated intravascular coagulation (DIC). Therefore, given the history of black stools, we felt that gastrointestinal bleeding was the most likely cause of the anemia.

**Dr. Listerick:** What about the thrombocytopenia?

**Dr. Liem:** That was difficult to explain. There appears to be a mythology that severe bleeding can lead to thrombocytopenia, presumed to be from consumption. I can’t find any support for this in the literature. There are reported instances of thrombocytopenia in patients with catastrophic blood loss who are receiving multiple units of blood over a short time period. However, I would guess that this could be explained by concomitant DIC we often see in these catastrophically ill patients.

**Dr. Listerick:** I would have expected the reticulocyte count to be higher with this degree of anemia?

**Dr. Liem:** It’s possible that the bleed was hyperacute and the bone marrow hasn’t had a chance to mount such a vigorous response yet.

**Dr. Listerick:** Moving forward, he underwent abdominal ultrasonography with Doppler evaluation looking at portal blood; there was no spleenomegaly and portal blood flow was normally antegrade. Because of the possibility of gastrointestinal hemorrhage, he underwent upper endoscopy.

**Dr. Greene:** There were no esophageal or gastric varices seen. However, we found two duodenal ulcers that were extremely friable but not actively bleeding. Visually, the ulcers appeared similar to those seen in association with *H. pylori*. Specifically, nodular mucosa in the antrum of the stomach, as seen in this patient, is quite characteristic of *H. pylori* infection. Unfortunately, the rapid urease test was negative for *H. pylori*. However, the patient had received a protein pump inhibitor, which can lead to a falsely negative test. Ultimately, the stool antigen test for *H. pylori* was positive.

**Dr. Listerick:** What are the sensitivity and specificity of the stool antigen test?

**Dr. Greene:** They approach 100%, much better than the urease test.

**Dr. Listerick:** What is the treatment for *H. pylori* infection?

**Dr. Greene:** We generally use a combination of two antibiotics, most commonly amoxicillin and clarithromycin for 2 weeks, in conjunction with a protein pump inhibitor. As for the hypoproteinemia, there have been cases of protein-losing enteropathy in association with *H. pylori* infection, especially in the presence of ulcers.

**Dr. Nordli:** This is all very interesting, but I’m concerned that his neurological presentation isn’t explained by what we know so far.

**Dr. Listerick:** Agreed. Many things were happening simultaneously. He had abnormal neuroimaging, which I’ll show in a minute. He initially received blood transfusions, and his hemoglobin stabilized without evidence of rebleeding. He began treatment for ulcers. Over the next few days, the platelet count and albumin slowly improved. As part of his evaluation, he was seen by an ophthalmologist.

**Yana Kiesau, MD, pediatric ophthalmologist:** We obtained more history from the father. Apparently 3 months earlier, the patient had been experiencing problems with distance vision. At that time, he was seen by an ophthal-

**Key Learning Points**

1. Cerebral malaria is a clinical diagnosis, almost exclusively associated with infection by *Plasmodium falciparum*. Although its onset is generally gradual in adults over days, children may develop encephalopathy, including delirium or psychosis, after only a short duration of fever. More than 50% of children with cerebral malaria develop seizures that may be either focal or generalized.

2. Severe normocytic anemia may be due to blood loss, hemolysis, or splenic sequestration.

3. Congenital hyperypertrophy of the retinal pigment epithelium (CHRPE) consists of flat pigmented areas in the retina that are generally asymptomatic, incidental findings. When CHRPEs are bilateral and in multiple locations, one should consider the possibility of familial adenomatous polyposis (FAP).

4. FAP is an autosomal dominant cancer predisposition syndrome characterized by the development of hundreds to thousands of precancerous colonic polyps. Additional gastrointestinal features may include precancerous adenomatous polyps of the stomach and duodenum, pancreatic cancer, and hepatoblastoma.

5. Extraintestinal manifestations of FAP include osteomas, thyroid cancer, dental abnormalities, CHRPEs, and desmoid tumors.
mologist who noted “funny looking spots in the back of his eyes.” On our exam, we observed multiple chorioretinal scars of various sizes and shapes. Our first consideration was that these were scars related to old toxoplasmosis, but they didn’t quite fit this. They also bore a resemblance to the “sunburst” lesions that we see in the retinopathy associated with sickle cell disease. However, they looked most like congenital hypertrophy of the retinal pigment epithelium (CHRPE).

**Dr. Listernick:** CHRPE?

**Dr. Kiesau:** They are flat pigmented areas in the retina that are generally asymptomatic, incidental findings. They may grow over time. As long as the growth is slow and the lesions remain flat, they are of no concern. Rapid, three-dimensional growth may point to the development of a malignant adenocarcinoma of the retinal pigment epithelium. However, multiple bilateral CHRPEs suggest the possibility of familial adenomatous polyposis (FAP).

**Dr. Greene:** FAP is an autosomal dominant cancer predisposition syndrome characterized by the development of hundreds to thousands of precancerous colonic adenomatous polyps. Additional gastrointestinal features may include precancerous adenomatous polyps of the stomach and duodenum, pancreatic cancer, and hepatoblastoma.

**Dr. Listernick:** There are numerous extraintestinal manifestations, including osteomas, thyroid cancer, dental abnormalities, and desmoid tumors. Other epiphenomena in the literature include Gardner syndrome (classic FAP with osteomas and soft tissue tumors) and Turcot syndrome (classic FAP with brain tumors, particularly medulloblastoma). CHRPEs are commonly seen in all of these variants.

**Dr. Kiesau:** Our retina specialist felt that these lesions looked most like CHRPEs but that all the conditions I mentioned were still possibilities. They definitely were not the result of cerebral malaria as some physicians had questioned.

**Dr. Liem:** When I first heard the story I was worried that he had sickle cell anemia that was never diagnosed in Africa. However, his hemoglobin electrophoresis was normal.

**Dr. Listernick:** Bringing it full circle, he had an MRI scan of the brain that showed numerous supratentorial T2, hyperintense, predominantly subcortical white matter lesions. Their appearance was nonspecific and lacked contrast enhancement or diffusion restriction. They were felt to most likely represent sequelae of a prior insult such as infection, ischemia, vasculitis, or demyelination. However, the neuroradiologists couldn’t exclude the possibility of an active process.

**Dr. Nordli:** We started off the conference concluding that his encephalopathy was due to acute symptomatic seizures. These scattered lesions are at the junction of the cortical gray mantle and the white matter. Although I agree that there’s a laundry list of past conditions that could be responsible for these lesions, I would still be very concerned about an acute process such as vasculitis or a demyelinating disease.

**Dr. Listernick:** Understood. However, at least for the short term, he remained well in the hospital and had no further seizures. In addition, he had a lumbar puncture that yielded completely normal cerebrospinal fluid.

**Dr. Greene:** I think that it’s reasonable to perform flexible sigmoidoscopy, given the high concern for FAP. At his age, he’s quite likely to have colonic polyps if he has FAP.

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