A 3-Year-Old Girl With Vomiting and a Sixth Nerve Palsy

On physical examination she was a healthy appearing girl who was very cranky when approached, diagnosed as having left otitis media.

Robert Listernick, MD

CASE STUDY

This 3-year-old girl was transferred to Children's Memorial Hospital for evaluation of vomiting and irritability. She had been well until 2 weeks prior to this admission when she developed fever and irritability following an upper respiratory tract infection. She was diagnosed as having a left otitis media, and she was treated with amoxicillin. Although she defervesced after 36 hours, she started vomiting intermittently. When examined 3 days later, her ear infection was unchanged and the antibiotic was changed to amoxicillin-clavulanic acid. Over the next several days, she became increasingly irritable with persistent vomiting, necessitating hospitalization. During the first 3 days in the hospital, she received two intramuscular injections of ceftriaxone to treat the ear infection. Tympanocentesis yielded a small amount of clear fluid that was subsequently found sterile using bacterial culture. Magnetic resonance imaging (MRI) of the head 3 days prior to transfer was normal. Because of persistent vomiting and irritability, she was transferred. On the day of transfer, her parents noted that she was more irritable when sitting up and when watching television.

Her past medical history and family history were unremarkable and her development was normal. On physical examination, she was a healthy-appearing girl who was very cranky when approached. Her temperature was 37.2°C rectally, pulse 120, respiratory rate 26, blood pressure 90/60. Her weight, height, and head circumference were all in the 25th percentile. There were no masses or organomegaly. On neurologic examination, the deep tendon reflexes were normal and the plantar responses were flexor. She would not walk due to irritability. There was no apparent ataxia. Pupillary function was normal. Initial attempts to view the ocular fundi were not successful. She was unable to fully abduct her right eye. The remainder of her cranial nerve examination was normal.

Robert Listernick, MD, moderator: First impressions, anybody?

Gesina Keating, MD, pediatric neurologist: The combination of vomiting and a partial VI nerve palsy is a strong indication of increased intracranial pressure (ICP). At times, VI nerve palsy may be due to a post-viral demyelinating process. However, given the history of fever and prolonged antibiotic usage, I would have been concerned initially about partially treated bacterial meningitis or basilar meningitis caused by tuberculosis. Before proceeding, if I could not visualize the optic disks, I would have asked an ophthalmologist to look for the presence of papilledema.

Marilyn Mets, MD, pediatric ophthalmologist: I saw the child shortly after she was admitted to the
hospital. She definitely had a partial right VI nerve palsy and possibly a left VI nerve palsy as well. On fundoscopic exam, there was bilateral elevation of the optic nerve heads, indicative of papilledema. There was a nerve fiber layer hemorrhage under the left macula; there were no other hemorrhages or exudates. I suspect that her irritability when watching television was the result of diplopia caused by her VI nerve palsy.

Dr. Listernick: Can you distinguish between papilledema seen as a result of increased ICP and optic nerve neuritis seen in demyelinating diseases?

Dr. Mets: These two conditions may look very similar. However, central visual acuity usually deteriorates in optic neuritis, but remains stable in acute papilledema. In cases of longstanding, increased ICP the vision may deteriorate first in the periphery, followed by visual loss centrally. This child was very fussy on the first examination. We could only determine that the vision was “central, steady, and maintained.” In other words, she maintained steady gaze on an object without nystagmus.

Dr. Listernick: My first thoughts were that she had either a central nervous system infection, the course of which had been modified by antibiotics, or acute demyelinating encephalomyelitis, a post-viral demyelinating process. Since the MRI scan at the outside hospital was reportedly normal several days earlier (we did not have the actual scan to review), I doubted that she had a mass lesion causing hydrocephalus. At this point, was it safe to perform a lumbar puncture without any further neuroimaging, particularly since there were new physical findings of increased ICP?

Denise Goodman, MD, pediatric intensivist: Obviously I see all the worst complications of diseases, so my opinion may be somewhat skewed. However, this child’s MRI scan was performed several days earlier, and she now had clinical signs of increased ICP. Before performing a lumbar puncture, I would have ordered a computed tomographic (CT) scan without contrast infusion in order to be sure that there were no focal mass lesions that might precipitate herniation of intracranial contents.

Douglas Nordli, MD, pediatric neurologist: CT scanning is just going to delay by several hours performance of the crucial test, a lumbar puncture. I’d be most concerned that this child has a basilar process, such as tuberculous meningitis, in which a CT scan without contrast infusion would provide little useful information. She has had irritability and vomiting for the last 2 weeks, suggesting that the process was long-standing. If there were a mass lesion or hydrocephalus causing these symptoms, the previous MRI should have revealed it, as these are not subtle neuroradiologic findings.

Dr. Goodman: If she did have a basilar inflammatory process, isn’t it possible that over the last few days it might have led to obstruction of the fourth ventricle and hydrocephalus?

Dr. Nordli: Possible, but not very likely without other new neurologic findings such as difficulty with ocular convergence or a defect in upward gaze. Just so that I’m clear, she absolutely would have needed neuroimaging, in particular a MRI scan, if she had not had a scan several days previously.

Dr. Listernick: I opted for the more cautious approach; a CT scan without contrast infusion was normal. Following this, she underwent lumbar puncture. The opening pressure was greater than 400 mm Hg (normal, less than 200 mm H2O); approximately 8 cc of cerebrospinal fluid (CSF) was removed. The closing pressure was 170 mm H2O. The CSF cell count, glucose, and protein were all normal, and the Gram stain and antigen detection tests were negative.

Stan Shulman, MD, pediatric infectious disease physician: If the possibility of basilar meningitis was being considered, she should have had CSF sent for appropriate stains and cultures for both mycobacteria and fungi.

Dr. Listernick: She did, and all these tests were negative. What does all this information tell us?

Dr. Keating: She has a markedly elevated ICP and no evidence of either hydrocephalus or meningitis. This meets the case definition of pseudotumor cerebri (PC). These children often have sixth nerve palsies.

Dr. Listernick: What is the pathogenesis of PC?

Dr. Keating: ICP is determined by the three major components of the intracranial vault: brain, blood, and CSF. The ICP may become elevated if any of these components suddenly increases in volume without a compensatory decrease in one of the others. Studies have shown that the most common pathophysiologic basis for PC is an increase in the venous sinus pressure without any evidence of venous sinus throm-
basis. These children are labeled as having “idiopathic” PC.

**Dr. Listerick:** What are the other etiologies of PC?

**Dr. Keating:** There is a long list of secondary causes of PC that includes such diverse etiologies as the side effects of drugs (tetracycline, isotretinoin, corticosteroids, oral contraceptives), hematologic disorders (polycythemia, iron deficiency anemia), and metabolic diseases (hypoparathyroidism, Addison disease, and obesity). In addition, any process that interferes with the drainage of blood from the intracranial venous sinuses can lead to PC. This may be the result of infections such as mastoiditis or head trauma, either of which may lead to venous sinus thrombosis. Finally, a simple process such as gastroenteritis may lead to dehydration and venous sinus thrombosis.

**Alexis Thompson, MD, pediatric hematologist:** Any time a patient has thrombosis, an underlying thrombopholic state should be suspected. However, more often than not, the thrombosis in cases of PC is a secondary phenomenon due to an underlying process rather than the primary hematologic condition.

**Dr. Listerick:** What are the complications of PC about which we have to be concerned?

**Dr. Mets:** The primary long-term complication is the permanent loss of vision. Long-standing increased ICP can destroy the fibers of the optic nerve. Most often, there is damage to the peripheral fibers, which begins to move centrally. This is the biggest problem in following the ophthalmologic exam of young children — we have no good, reproducible way of following their peripheral vision. Three-year-old children are too young to participate in formal visual field testing. In these children, the treating physician must keep a very tight control on the increased ICP; there’s much less of a margin of error than in treating an adolescent.

**Dr. Listerick:** Immediately after performing the lumbar puncture, she had total relief of her symptoms. Her affect was normal and the vomiting disappeared. Her parents were amazed at the change. However, her sixth nerve palsy persisted. Before discussing treatment, let’s look at the MRI scan performed here.

**Francine Kim, MD, pediatric neuroradiologist:** There was no evidence of demyelination or basilar meningitis. The transverse sinuses in the brain are normally asymmetric, with one side being dominant. Normally, on the T1 weighted images, the transverse sinuses have signal voids, indicating vessels with high flow. This child’s left transverse sinus had an area of hyperintensity, suggestive of thrombosis. Secondly, there were signal abnormalities in the left mastoid air cells that demonstrated contrast enhancement. In order to study the venous sinus abnormalities more closely, phase contrast magnetic resonance venography was performed. This nicely demonstrated low flow in the left transverse sinus with several large areas of thrombosis. Finally, a high resolution CT scan revealed complete opacification of the left mastoid air cells with several areas of demineralization of the septae separating these cells.

**Dr. Listerick:** Do these radiographic findings mean that she has mastoiditis, even though there were no clinical findings on physical examination suggestive of it?

**Julie Wei, MD, pediatric otologist:** Her initial physical exam here demonstrated a normal tympanic membrane without any obvious middle ear disease. Acute mastoiditis develops in stages. During the first stage, any child who has acute otitis media can have an inflammatory process in the mastoid air cells; a CT scan performed at this time can show evidence of mastoid inflammation that disappears as the otitis resolves. However, in some children, the infection spreads to the periosteum of the mastoid, leading to acute mastoiditis with periostitis. The pinna protrudes forward and the posterior auricular sulcus is red and edematous. At this stage, antibiotic treatment may be curative, although surgery may be necessary if the patient fails to respond clinically with resolution of symptoms. Finally, the infection may spread, leading to destruction of the bony septae between the air cells and to a subperiosteal abscess. Coalescent mastoiditis occurs when all the septations are lost and the patient is left with a single large abscess. In these cases, mastoidectomy is necessary. The antibiotics that she received had quelled the middle ear disease but clearly didn’t eradicate the mastoid inflammation.

**Dr. Listerick:** How does this relate to her lateral sinus thrombosis?

**Dr. Wei:** Both lateral sinus thrombosis and PC, often called otitic hydrocephalus when associated with otitis media, may be intracranial complications of otitis media. Presumably, the lateral sinus thrombosis arises when the mastoid
infection, which is adjacent to the venous sinus wall, sets off the inflammatory cascade. Although the terminology becomes confusing, she does not have Gradengir syndrome, which is petrous apicitis. This is defined clinically by the triad of otorhoea, sixth nerve palsy, and ipsilateral retroorbital pain and headache. These patients require prolonged antibiotic therapy and, on occasion, drainage of a petrous bone abscess. Other potential intracranial complications of otitis media include meningitis, subdural empyema, and brain abscess.

**Dr. Listerick:** How was the mastoiditis treated?

**Dr. Wei:** First, we reviewed the MRI and CT scans to make sure that there was no congenital inner ear defect that might have led to a suppurative complication of otitis media. We performed a simple cortical mastoidectomy. The mastoid was exposed and we destroyed all the septations and cleaned out the chronic inflammatory tissue within the mastoid air cells, leaving one large empty cavity. Interestingly, the middle ear cavity had no disease, as was predicted from the external examination. However, we found inflammatory tissue that extended to an area of exposed dura along the tegmen. Eventually, untreated she could have developed an intracranial abscess.

**Dr. Listerick:** I find it incredible that she had no other symptoms or signs of an active inflammatory process. She had not had fever for more than one and half weeks, her white blood cell count was normal, and her erythrocyte sedimentation rate was 12 mm/h.

**Ben Katz, MD, pediatric infectious disease physician:** Could she have had a smaller antrum than normal, leading to less effective drainage of mastoid inflammatory secretions, which would have predisposed her to more serious complications of otitis media?

**Dr. Wei:** This may happen in select cases.

**Dr. Listerick:** Now that we know that she has a lateral sinus thrombosis, does she need an evaluation to see if she has a hypercoagulable state?

**Dr. Thompson:** As I said before, it’s unlikely that a thrombophilic state led to this child’s sinus thrombosis, as she had a clear precipitating event. We presently have identified a number of genetic defects that predispose individuals to thromboembolism; we are just beginning to compile adequate data in children. A significant percentage of Caucasians are heterozygous for a mutation such as in the gene for Factor V Leiden that lead to thrombosis in homozygous individuals. We don’t have a clear understanding of the risk of recurrent thrombosis in heterozygous individuals.

**Dr. Listerick:** Should we have considered anticoagulation in this case?

**Dr. Thompson:** The main reasons for anticoagulation would be to prevent progressive thrombosis leading to end organ damage or to reduce the risk of future embolic phenomena. Each of these is unlikely with this type of thrombosis. Chronic anticoagulation in children with either oral warfarin sodium (Coumadin) or subcutaneous low molecular weight heparin is not without risk and should be initiated with caution. In the absence of other evidence for an underlying clotting tendency, I agree with the decision to not institute anticoagulation therapy.
Dr. Listernick: If you want to investigate this child, what tests should have been performed?

Dr. Thompson: The list grows each day. I would have recommended testing for (1) protein C, protein S, and anti-thrombin 3 levels; (2) urine homocysteine; (3) Factor V Leiden mutation (resistance to activated protein C); (4) mutation in the gene for methylenetetrahydrofolate reductase; (5) mutation in the prothrombin gene (G20210A); (6) acquired antibodies against phospholipids (antiphospholipid syndrome); and (7) lupus anticoagulant.

Dr. Listernick: For better or worse, that entire evaluation was performed and was negative, save for a positive lupus anticoagulant. What is the significance of that abnormality?

Dr. Thompson: This is one reason not to perform the huge evaluation in some circumstances; often one is left with a laboratory abnormality, the significance of which is unknown. A positive lupus anticoagulant often is seen in the face of an acute infection, without any other evidence of an underlying rheumatologic process. Without any other findings suggestive of an antiphospholipid syndrome, I would not be overly concerned with an isolated positive lupus anticoagulant. As such, I would simply repeat it in several months.

Dr. Listernick: Four days after her first lumbar puncture, she again developed vomiting and irritability. A repeat lumbar puncture was performed and 18 cc of CSF were removed. The opening pressure was 350 mm Hg. Once again, her symptoms disappeared immediately following the test. Her visual acuity, as best as could be determined, remained normal, and the papilledema persisted. How should the PC be treated?

Dr. Keating: We should remember that the most important goal is preservation of vision. A single lumbar puncture is not going to be curative; often repeated lumbar punctures over a period of time are necessary in order to control both the symptoms and the visual deterioration. Occasionally, acetazolamide (10-30 mg/kg every 24 h) may be given to decrease CSF production. Corticosteroids may be helpful in some patients who do not respond to this therapy. Finally, if the ICP is uncontrollable and the vision continues to deteriorate, consideration can be given to placement of lumbar-peritoneal shunt. However, this is potentially fraught with complications and should be reserved for the most extreme cases.

Dr. Listernick: Over the next 10 days, she required lumbar puncture four times to control her symptoms of headache, vomiting, and irritability. Her visual acuity remained stable and the sixth nerve palsy disappeared. We have not discussed antibiotic therapy for the mastoiditis.

Dr. Katz: The microbiology of mastoiditis is somewhat different from that of acute otitis media. Although Streptococcus pneumoniae is still the most common organism isolated, other isolates include Staphylococcus aureus, Pseudomonas aeruginosa, and Streptococcus pyogenes. In the absence of a known pathogen, I would have chosen a broad spectrum antibiotic effective against these organisms. The length of treatment is arbitrary, but given the extent of involvement, I would have treated her for a fairly long time.

Dr. Listernick: All of the mastoid cultures obtained at surgery were negative. She was treated for 4 weeks with intravenous ceftriaxone.

Dr. Katz: I think that was a reasonable choice. If she had had an infection caused by P aeruginosa, the chances are quite good that it would have grown in culture.

Dr. Listernick: Over the month following discharge, she remained asymptomatic. Although her visual acuity was stable, the elevation of the optic heads on ophthalmologic exam never changed. She continued to take the acetazolamide and she will have repeated eye exams over the next several months.

Thank you, everybody.
HOW TO OBTAIN CME CREDITS BY READING THIS ISSUE

Pediatricians can receive Category 1 credits for the Physician’s Recognition Award of the American Medical Association by reading the following articles and successfully completing the quiz at the end of the issue. Complete instructions are given on the quiz pages.

The pretest below has been prepared to assist you in studying the following material. It indicates some of the areas to be covered and will make it possible for you to challenge your current knowledge of the material before reading further.

EDUCATIONAL OBJECTIVES

In this final segment in our series on terrorism and the role of the pediatrician, we discuss the unique role played by chemical weapons. Chemical agents have been deployed as weapons of mass casualty for decades. Only recently has one such weapon been used against a civilian population. Yet, beyond chemical weapons we must also turn our attention as well to toxic industrial compounds, which if used appropriately, pose an even greater threat to our population as weapons of opportunity. This issue of Pediatric Annals provides excellent reviews on several classes of chemical agents that may be used by terrorists and their unique effects on children. After reviewing this issue, the reader will be able to participate as a valued resource to community services as they prepare medical responses to potential chemical attacks.

PRETEST

1. After biological agents, industrial chemicals pose the greatest potential as mass casualty weapons for use by terrorist groups.
   A. True.
   B. False.

2. Cyanide compounds are uniquely suited as outdoor poisons.
   A. True.
   B. False.

3. Nerve agents are typically colorless liquids at room temperature.
   A. True.
   B. False.

4. Unlike other chemical agents, the clinical effects of mustard exposure are delayed, typically for hours.
   A. True.
   B. False.

For answers, see page 268.