INDEX OF SUSPICION

# Infant with Acute Onset Esotropia

Adam René P. Rosenbaum, MD,* Jerry L. Jewell, MD,*† Justin B. Searns, MD*‡

*Department of Pediatrics,
†Department of Neurology, University of Colorado, Aurora, CO
‡Division of Hospital Medicine; Division of Infectious Diseases, Department of Pediatrics, University of Colorado, Aurora, CO

## PRESENTATION

A 9-month-old boy with a history of sickle cell trait presents with concern for 2 days of inability to abduct his left eye. His mother takes him for evaluation by an ophthalmologist who notes severe, grade 4+ papilledema of the bilateral optic nerves with dilation and tortuosity of retinal vasculature. The patient is referred to the pediatric emergency department for additional evaluation.

On further history, there are no recent illnesses or reported fevers. His parents deny any vomiting, apparent weakness, or abnormal movements. He has been feeding well and is active and playful. He has a reported history of a witnessed fall from the kitchen table 3 weeks before presentation that did not result in any loss of consciousness, and his parents did not seek medical attention because the infant was reportedly acting normal with no concerns at the time. For the past week, the infant has had increased fussiness in the morning and when lying flat. His milestones have been met on time since birth, and there is no history of regression. Neurology is consulted, and they note a bulging fontanelle and an intermittent left sixth cranial nerve palsy. A rapid-sequence brain magnetic resonance imaging (MRI) scan is obtained, out of expediency, and reveals distension of the optic nerve sheaths, protrusion of the optic discs, and thin bilateral subdural fluid collections but no other intracranial abnormality. Specifically, there is no evidence of mass effect, hemorrhage, or ischemia noted. The subdural fluid collections have signal intensity characteristics of cerebrospinal fluid (CSF) on MRI scan and are not consistent with new or old blood products. An unsedated lumbar puncture is performed, and the opening pressure is greater than 55 cm $H_2O$ (normal: ≤28 cm $H_2O$), with no closing pressure noted. (1) CSF analysis notes five nucleated cells, three hundred ten red blood cells, glucose of 45 mg/dL, and protein of 12 mg/dL, and bacterial culture and multiplex polymerase chain reaction testing result for meningitis and encephalitis are negative. The patient is subsequently admitted to the hospital for further management of symptoms.

On admission, the patient is noted to be in the 27th percentile for weight (Fig 1A) and third percentile for length (Fig 1B), whereas his head circumference is in the 99th percentile (Fig 1C). After lumbar puncture, his bulging fontanelle has now resolved and is soft and flat, and his extraocular movements are now intact on repeat examination. The remainder of the neurologic examination remains normal. His skin examination does not reveal any bruising or signs of physical trauma. The patient has a normal urinalysis, complete blood cell count, and complete metabolic panel. His erythrocyte sedimentation rate, thyrotropin, free thyroxine, parathyroid hormone, 25-hydroxy vitamin D, and ammonia concentrations are all within normal

**AUTHOR DISCLOSURE:** Drs Rosenbaum, Jewell, and Searns have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

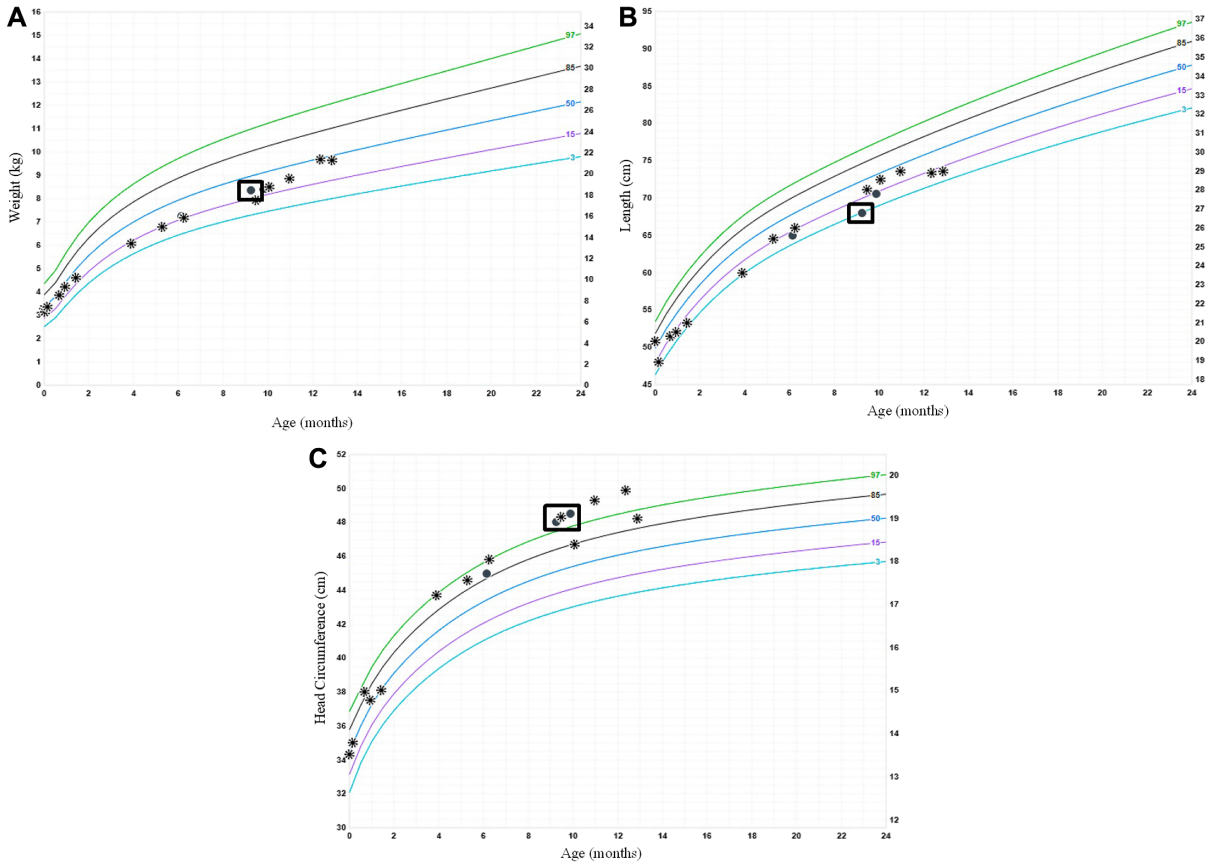


**Figure 1.** A. Patient's weight over time, with weight at presentation noted in the box. B. Patient's length over time, with length at presentation noted in the box. C. Patient's head circumference over time, with circumference at presentation noted in the box.

limits. On hospital day 2, the patient undergoes a sedated brain MRI scan with venogram without contrast, which shows a decrease in the size of the subdural fluid collections that were noted on initial limited rapid-sequence brain MRI and persistent bilateral optic nerve head edema; the left is greater than the right. There is no evidence of diffuse axonal injury. The remainder of the brain MRI scan with venogram is normal.

## DISCUSSION

### Differential Diagnosis

The patient's acute presentation of intermittent left eye esotropia is concerning for a primary neurologic process. Likely etiologies to consider for his initial symptoms include: intracranial mass from neoplastic or traumatic sources, central nervous system infection such as meningitis or encephalitis, obstructive hydrocephalus, or vascular pathology such as cavernous sinus thrombosis or central venous sinus thrombosis. His papilledema, bulging fontanelle, large head circumference, and increased fussiness when lying flat are all suspicious for increased intracranial pressure (ICP), which is confirmed with his increased opening pressure on lumbar puncture. His other CSF results are not consistent with an infectious or inflammatory cause. Given the suspicion for potential intracranial mass, an initial rapid-sequence brain MRI scan is obtained and is reassuring; however, complete MRI scan with venogram is performed after admission to evaluate more thoroughly for worrisome etiologies, including malignancy, hemorrhage, abscess, or thrombosis. His MRI studies do not suggest a stenotic CSF outflow track and ventricles are normal in size, which is not supportive of obstructive hydrocephalus.

In the setting of bilateral subdural fluid collections, trauma, including physical child abuse, is high on the differential diagnosis. However, in further discussion with neuroradiology, the subdural fluid collections are not consistent with blood products (acute or chronic) because the signal intensity is that of simple CSF, and this finding is felt to be most likely an unrelated anatomical anomaly. In children younger than 2 years with macrocephaly, the rate of incidentally found subdural fluid collections can be as high as 3.9%. (2) In addition, the patient's notably large head circumference is more consistent with a chronic process than an acute traumatic event. The MRI scan also does not reveal

any evidence of diffuse axonal injury to suggest trauma. Furthermore, the history of presentation remains consistent after multiple clinicians' interviews of the family. There is no evidence of trauma on physical examination, including an ophthalmologic examination that does not identify any retinal hemorrhages and no skin bruising. Moreover, on chart review, a chest radiograph obtained 2 months before admission for evaluation of chronic cough does not reveal evidence of rib fractures, which further provides comfort against a previous history of trauma.

Additional considerations, which are all less common, for his elevated ICP include metabolic, iatrogenic, endocrinologic, and nutritional causes. Hyperammonemia has been described as a cause of increased ICP in the setting of acute liver failure, Reye syndrome, and inherited metabolic disorders of the urea cycle; however, suspicion is low in the setting of a previously healthy infant with a normal ammonia concentration. (3) In addition, the patient's normal development, otherwise normal physical examination, and normal electrolytes and liver function studies offer further reassurance against a metabolic source of his increased ICP. The patient has no known medication exposures, including tetracycline antibiotics, retinoids, or lithium, which have been implicated as iatrogenic causes of elevated ICP. (4) Vitamin D deficiency is also a potential cause of elevated ICP, but the patient's vitamin D concentration is checked and is normal. (5) Thyroid gland dysfunction and hypoparathyroidism have both been associated with increased ICP, although the patient's thyroid and parathyroid hormone testing is normal. (5)

## Actual Diagnosis

After the exclusion of all other potential etiologies of elevated ICP, the patient is diagnosed with idiopathic intracranial hypertension (IIH) in discussion with the neurology, neurosurgery, radiology, and ophthalmology consulting teams.

## Pediatric IIH

IIH is a diagnosis characterized by ICP of unclear etiology and is typically a diagnosis of exclusion. It most commonly presents in women of childbearing age who have obesity. (4)(6) Within pediatrics, it is a rare diagnosis, with an estimated incidence of 0.5 per 100,000 children per year. (7) For infants specifically, there have only been 25 cases of IHH previously reported in the literature. (7) Possible risk factors include topical corticosteroids, hypophosphatemia, vitamin D deficiency, and human herpesvirus-6 positive test result, although our patient did not have any of these suggested risk factors. (7)

The modified Dandy diagnostic criteria were first proposed nearly 40 years ago as a clinical tool to distinguish IIH from secondary causes of elevated ICP and have recently been updated. (8) Using these revised criteria, patients must meet all of the following to earn a diagnosis of IIH: 1) have signs and symptoms of increased ICP, 2) not have any localized neurologic findings, 3) be awake and alert, 4) have no identified cause of ICP, and 5) have normal neurodiagnostic studies other than changes expected to be seen with increased ICP, such as a lumbar puncture opening pressure of >20 cm $H_2O$, or imaging that shows an empty sella turcica, an optic nerve sheath with filled out CSF spaces, or a smooth-walled non–flow-related venous sinus stenosis or collapse. (8) For patients who have only moderately increased CSF opening pressure (20–25 cm $H_2O$), additional clinical or imaging criteria must be met. (8)

Classically, IIH presents with symptoms including daily headache, pulse synchronous tinnitus (ringing in the ears corresponding to heartbeat), transient visual disturbances, and an enlarging blind spot. (4) Papilledema can be a sign of IIH, with the potential for loss of vision. (4) Apart from irritability from potential headache or vision changes, the aforementioned symptoms are difficult to assess in infants, and the reported incidence of IIH in young children might be underestimated because of missed cases of mild or moderate IIH in these patients. Physical examination findings are therefore crucial for identifying the correct diagnosis. In addition to papilledema, a sixth cranial nerve palsy is the most common neurologic deficit seen in pediatric IIH and is the result of elevated ICP causing a downward displacement of the brain stem that stretches the sixth cranial nerve as it crosses over the petrous ridge and enters the Dorello canal. (4)(9) Although sixth nerve palsies can be the result of increased ICP from any number of causes, it is estimated to be a presenting finding in 12% of pediatric IIH cases. (9) Sixth cranial nerve palsy is by far the most common cranial nerve deficit seen in IIH; however, cases have been reported in which patients presented with additional palsies of cranial nerves III, IV, VII, IX, X or XII, with even rarer cases in which there is only an isolated seventh cranial nerve palsy. (10)

As is the case for this patient, part of the diagnostic criteria for pediatric IIH includes an elevated opening pressure on lumbar puncture greater than 20 cm $H_2O$. There is a wide range of reported opening pressure in infants with IIH, from 25 to 77 cm $H_2O$, with this patient having an opening pressure of greater than 55 cm $H_2O$. (7) A helpful diagnostic finding appreciated by the admitting team is that this patient's sixth nerve palsy and bulging fontanelle resolve after his lumbar puncture, likely secondary to the acute reduction in ICP from CSF removal. During the rest of the admission, the patient is closely monitored for the development of these findings, which do not recur before initiation of medical treatment.

The initial treatment for IIH is acetazolamide, which functions as an inhibitor of carbonic anhydrase isoforms that are involved in CSF secretion. (4)(11) Inhibition of carbonic anhydrase in the brain and choroid plexus decreases CSF secretion, thus preventing progressive buildup of CSF leading to elevated ICP. (11) The adverse effects of acetazolamide include paresthesia, dysgeusia, polyuria, and fatigue. Metabolic acidosis is another potential consequence. Patients are monitored for tolerance and to titrate the dose as needed. (12) For patients who have treatment failure to acetazolamide, other medical options include topiramate, furosemide, and systemic corticosteroids, as well as surgical intervention, such as CSF diversion. (4)

## Patient Course

After diagnosis, the patient is started on 62.5 mg acetazolamide every morning and 125 mg every evening and monitored to ensure tolerance. At the time of discharge, the patient's fontanelle remains soft and ocular movements are intact; therefore, the patient is discharged from the hospital with plans for ophthalmologic and neurologic follow-up. At ophthalmologic follow-up 4 days after discharge, the patient is doing well, with no sixth nerve palsy appreciated; however, grade 3–4 bilateral papilledema persists. Two and a half weeks after hospital discharge at the neurology follow-up, the patient continues to tolerate his acetazolamide without any return of his previous abnormal eye movements or bulging fontanelle. Three months after discharge, at the patient's 12-month well-child check, he is noted to have normal growth and development for age. At a subsequent 4-month follow-up with ophthalmology, all ophthalmologic symptoms have now resolved, and the patient does not have any residual papilledema, strabismus, or optic atrophy apparent on examination. His parents elect to stop his acetazolamide with plans for close follow-up with ophthalmology to watch for signs of returning IIH that may need additional intervention.

## Lessons for the Clinician

- ICP in infants can present with fussiness, vomiting, a bulging fontanelle, and/or a sixth cranial nerve palsy.
- The differential diagnosis for increased ICP in children can include infectious, anatomical (vascular, hemorrhagic, neoplastic), endocrinologic, nutritional, metabolic, and medication-induced causes, in addition to IIH.
- Although rare, IHH can present in infants. Acetazolamide is thought to be a safe and effective treatment for this population, and patients should be monitored as outpatients by ophthalmology and neurology.

*References for this article can be found at*
*http://pedsinreview.aappublications.org/content/44/No. S1/55*