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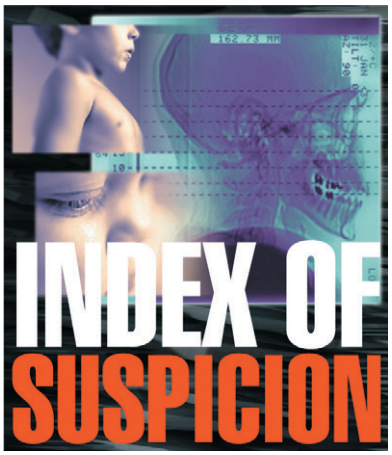

The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

The editors and staff of *Pediatrics in Review* find themselves in the fortunate position of having too many submissions for the Index of Suspicion column. Our publication slots for Index of Suspicion are filled through 2013. Because we do not think it is fair to delay publication longer than that, we have decided not to accept new cases for the present. We will make an announcement in *Pediatrics in Review* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors. We are grateful for your interest in the journal.

Author Disclosure

Drs Caldwell, Cearley, Hanson, Jones, Newgent, Kelly, and Madikian 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.

Case 1: Prolonged Leg Pain and Restricted Hip Movements in a Teenage Boy
Case 2: Headaches, Hypertension, and Ear Abnormalities in a Teenage Girl
Case 3: Sudden Increase in Intracranial Pressure in a 15-month-old Girl Who Has Hydrocephalus

Case 1 Presentation

A 14-year-old boy comes to the adolescent clinic with a report of right leg pain for the past 2 years. The pain has increased drastically over the past 6 months to the point that he is unable to play sports, particularly football. Other than mild asthma and allergic rhinitis, he is in good health.

The patient, who moved to this area 4 years ago, has been seen in this clinic three times previously for management of asthma and for a routine health assessment 2 years ago. At those visits, he did not report hip pain or any limitation of activities. His past medical records are unavailable.

On physical examination, the patient is alert and pleasant and has height and weight at the 25th percentile. His right hip has flexion to approximately 90 degrees, internal rotation to less than 10 degrees, and external rotation to 25 degrees, all with pain at the extremes of movement. His left hip has flexion to 125 degrees, internal rotation to 15 degrees, and external rotation to 40 degrees, with no pain at the extremes of motion. When he is standing, his leg length is symmetrical. He has an antalgic gait on the right. His muscle strength and sensation, as well as his distal pulses, are normal. An imaging study confirms the diagnosis.

Case 2 Presentation

A 15-year-old girl presents to the clinic with episodic headaches occurring two to three times per week for the last 6 months. The headaches do not awaken her from sleep and are not associated with nausea, vomiting, or visual auras. She denies exercise intolerance, syncope, hematuria, and skin, hair, or nail changes. She does not take any medications, denies tobacco, alcohol, and drug use, and is not sexually active. She has been seen in the emergency department for headaches on two occasions and was found to have elevated blood pressure. Family history reveals mild left-sided conductive hearing loss and unilateral renal agenesis in the father and a paternal cousin who had renal failure of unknown cause at age 32 years.

Physical examination reveals an afebrile adolescent girl who has a blood pressure of 140/88 mm Hg in the right arm and 142/86 mm Hg in the right leg, heart rate of 86 beats/min, and a BMI at the 83rd percentile. There is no papilledema. There is no thyromegaly, but she has symmetric pits along the anterior border of the sternocleidomastoid muscles bilaterally (Fig 1). Her auricles are hypoplastic, without preauricular pits or tags. The remaining physical findings are unremarkable.

Her complete blood cell count, complete metabolic profile, blood urea nitrogen, creatinine level, thyroid studies, and urinalysis are within normal limits. The results of a urine pregnancy test are negative. She is referred to otolaryngology and nephrology for further evaluation.

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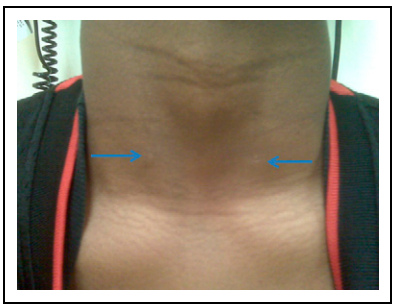

Figure 1. Pits are located symmetrically along the anterior border of both sternocleidomastoid muscles.

Case 3 Presentation

A 15-month-old girl who has a medical history of mild hydrocephalus, hypotonia, and global developmental delay presents with a 3-day history of symptoms consistent with increased intracranial pressure (ICP). She has been sleepy and less playful and has experienced regression of developmental milestones and myoclonic jerks of the upper extremities. Her mother believes that there is an increase in her daughter's head size. A computed tomography (CT) scan of the head demonstrates hydrocephalus with severe enlargement of the lateral and third ventricles and mild-to-moderate enlargement of the fourth ventricle. A ventriculoperitoneal (VP) shunt is placed on the day of admission.

On the fourth hospital day, the patient is noted to have significant abdominal distension. Radiographs demonstrate evidence of ascites, and she is treated with furosemide. The serum albumin concentration is normal, as are the complete blood cell count, serum electrolyte levels, and coagulation studies. A CT scan of the head demonstrates prominent dilatation of both lateral and third ventricles, with a lesser degree of dilatation of the fourth ventricle, and an intact VP shunt. A CT scan of the abdomen and pelvis shows a large amount of peritoneal and subcutaneous fluid. The VP shunt is externalized subsequently and noted to have a high volume of drainage (~1,400 mL/day). Cerebrospinal fluid (CSF) analysis demonstrates less than one white blood cell and two red blood cells per high-power field, a glucose concentration of 68 mg/dL, and a protein level of 8 mg/dL. The CSF Gram stain and culture yield negative results. Another imaging study reveals the diagnosis.

Case 1 Discussion

The mother reveals later that the boy was born by cesarean delivery for breech presentation. Radiographs of the hips show the acetabula to be dysplastic and shallow bilaterally. The femoral heads are "nonconcentrically located within the acetabula with bilateral coxa valga." (Figs 2 and Figs 3) The impression is developmental dysplasia of the hip and degenerative changes of the femoral heads. The radiograph also reveals a "2.5 × 1.5 cm geographic, well-defined lytic lesion with sclerotic margins at the right acetabular roof," which most likely represents a subchondral cyst. A similarly appearing, but much smaller 4-mm lesion is noted at the left acetabular roof." The disease process, including osteoarthritic changes, is more advanced on the right, which is associated with more pronounced symptoms.

Differential Diagnosis

The most worrisome cause of a limp, pain, and decreased range of motion in any adolescent is a slipped capital femoral epiphysis, occurring when the femoral neck slips anteriorly and superiorly relative to the proximal femoral epiphysis. Typically, the patient is obese and will have difficulty with abduction and internal rotation of the hip. Radiographs usually are diagnostic, although magnetic resonance imaging (MRI) may be necessary in early or mild cases. Failure to diagnose this condition can result in progression of the slip or avascular necrosis of the femoral head.

Other entities presenting with hip pain include iliopsoas tendinopathy, in which the iliopsoas tendon becomes irritated as it passes over the pelvis or femoral head, femoroacetabular impingement, and hip labral tears. Femoroacetabular impingement occurs when the femoral head impinges on the edge of the acetabulum because of aberrations in shape

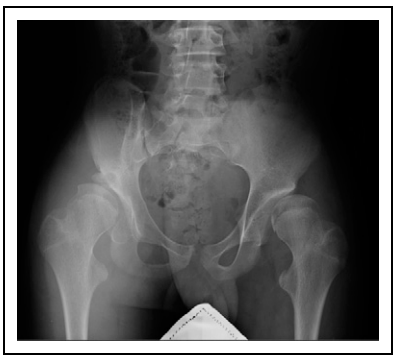

Figure 2. Radiographs of the hips show dysplastic and shallow acetabula with the femoral heads located nonconcentrically within the acetabula bilaterally with bilateral coxa valga.

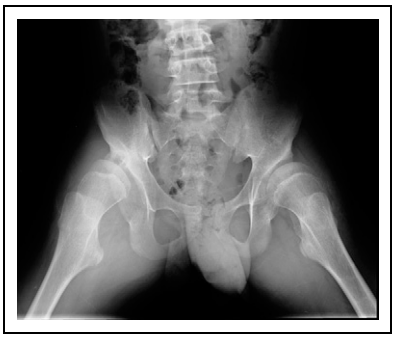

Figure 3. Frogleg lateral radiograph shows a 2.5 x 1.5 cm geographic, well-defined lucent lesion at the right acetabular roof, which represents a subchondral cyst. The femoral heads show degenerative changes with smaller subchondral cysts.

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or previous hip disease; the impingement can lead to labral tears.

The Condition

Developmental dysplasia of the hip (DDH) refers to the acquisition of an abnormal position of the femoral head in the acetabulum, which may be present at birth or may develop over time. The term refers to a spectrum of disorders, along a continuum of severity from unstable hips, including frank dislocation (luxation), partial dislocation (subluxation), and intermittent dislocation, to abnormalities in the formation of the femoral head or acetabulum in a stable hip. DDH is more common in girls, infants born in a breech position, and infants who have a family history of DDH. The incidence ranges from 1 to 8/1,000 births, depending on ethnicity. Presentation of acetabular dysplasia in the adolescent or adult is less well understood and may represent an independent entity or a later manifestation of undetected or treated DDH from childhood.

Clinical Manifestations

In the newborn period, physical examination remains the most appropriate screening method for detecting a dislocated hip through the use of the Ortolani and Barlow maneuvers. In the presence of an equivocal finding or normal examination results with a history of risk factors for DDH (such as breech-positioned girls), ultrasonography is recommended to reduce the rate of late-presenting DDH, which carries a worse prognosis. Some children will have normal findings on examination and few or no risk factors, so that radiographic imaging may not be indicated, allowing for DDH to go unrecognized.

Mild dysplasia in a stable hip often resolves on its own, but some cases may persist, diagnosed either incidentally or once pain develops, progressing to osteoarthritis over time if untreated, as in this patient. Pain usually develops gradually in the hip or groin but may not generate a limp. Patients commonly see multiple providers before diagnosis, which may be delayed months or years from the onset of symptoms.

Management

Early diagnosis of acetabular dysplasia, before degenerative changes have occurred, allows for treatment with periacetabular osteotomies of the pelvis to improve the relationship between the acetabulum and femoral head, relieve pain, and delay the progression of disease. The benefits of surgery in asymptomatic patients (who are diagnosed incidentally on radiographs for other reasons) is controversial and often delayed until symptoms occur. By the time this patient was diagnosed, he had already developed degenerative changes in his hips and was no longer a candidate for a reconstructive osteotomy.

In the past year, his symptoms have not worsened significantly, but his physical activities have been reduced markedly. He is not allowed to play sports or march in the band. He uses nonsteroidal anti-inflammatory medicines about once a week and takes glucosamine and calcium supplements. Because of the advanced nature of his findings, he will eventually require total hip replacements, when his symptoms become unbearable.

Lessons for the Clinician

- All infants should have their hips examined with each health supervision visit until walking is accomplished.
- Infants in the highest risk infant category (girls born in a breech position) should have close follow-up and ultrasonography by age 6 weeks.
- Universal hip ultrasonography of all infants has not been endorsed by the American Academy of Pediatrics. In addition to being costly, the procedure may cause overdiagnosis, unnecessary treatment, and parental anxiety.
- With an examination with otherwise normal results, soft-tissue clicks are benign.
- Adolescents experiencing the atraumatic onset of hip or groin pain should be evaluated for acetabular dysplasia with radiographic imaging and referred to an orthopedist as soon as the diagnosis is made.

(*Alice Little Caldwell, MD, David Cearley, MD, Georgia Health Sciences University, Augusta, GA*)

Case 2 Discussion

Upon further questioning, the patient had noticed these two small "holes in her neck" since age 5 years. She experiences a clear discharge from the pits during eating and swallowing, which increases in amount during consumption of spicy foods. Her 5-year-old brother has similar pits, just superior to the clavicles, but does not have hearing loss, ear pits or tags, or renal problems. Her father and paternal cousin have unilateral ear pits.

Further evaluation for her hypertension revealed normal levels of urine vanillylmandelic acid, urine metanephrines, plasma renin (5.1 ng/mL per hour), and aldosterone (10.8 ng/dL). Renal ultrasonography did not show any evidence of renal dysplasia or anomalies. Echocardiography showed normal cardiac structure and function. The findings of the audiology evaluation were normal. She was started on amlodipine for hypertension, and surgical resection of her branchial fistulae was performed because of the risk of abscess formation.

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Differential Diagnosis

The differential diagnosis for hypertension in an adolescent is extensive. However, in this patient, given the family history of renal failure and hearing loss, Alport syndrome should be considered in the differential diagnosis. Also known as familial nephritis, Alport syndrome is characterized by microscopic hematuria, which this patient has not had. Alport syndrome is inherited most often via an X-linked pattern and occasionally an autosomal recessive pattern. Branchial fistulae, however, are not consistent with Alport syndrome. Findings of external ear anomalies and neck pits in this family suggest branchio-oto-renal (BOR) syndrome.

The Condition

Unsuccessful closure of the first, second, third, or fourth branchial clefts during embryonic development may lead to a persistent sinus or cyst in the neck. A remnant of the second branchial cleft is the most common form, which opens along the anterior border of the sternocleidomastoid muscle, and may connect with the tonsillar fossa in the pharynx. As a result, the fistula may drain salivary secretions. If the track does not connect to the cutaneous surface, a firm but mobile cyst may develop that carries a risk of superinfection.

Branchial cleft cysts and sinuses may occur alone, or as part of a larger collection of clinical symptoms, such as in BOR syndrome, which is an autosomal dominant disorder described in 1975 and characterized by branchial arch anomalies (branchial clefts, fistula, cysts), auditory anomalies (malformation of the auricle with preauricular pits, conductive or sensorineural hearing impairment), and renal malformations (urinary tract malformations, renal hypoplasia or agenesis, renal dysplasia, or renal cysts). Cases that do not have renal features are referred to as branchio-oto-syndrome.

Major criteria for diagnosis include branchial anomalies, deafness, preauricular pits, and renal anomalies, and are features that occur in more than 20% of patients affected with BOR syndrome. External, middle, and inner ear anomalies, preauricular tags, facial asymmetry, and palate anomalies constitute the minor criteria. To meet the classification of BOR syndrome, an individual must satisfy either three major criteria, or two major criteria and two minor criteria, or one major criterion in association with having an affected first-degree relative who meets criteria for BOR syndrome.

This patient has one major criterion (branchial anomalies), one minor anomaly (hypoplastic auricles), and a first-degree relative, her father, who meets criteria for BOR syndrome. Her father has hearing loss, a preauricular pit, and unilateral renal agenesis, and therefore satisfies criteria for BOR syndrome. Thus, this patient satisfies the criteria for BOR syndrome. Although the patient has hypertension, no evidence of renal dysplasia has yet been demonstrated on ultrasonographic imaging.

The incidence of BOR syndrome is 1 in 40,000 in the general population; however, the condition occurs in 2% of severely deaf children. Hearing impairment affects 70% to 93% of affected persons and may occur at any time, from early childhood to young adulthood. Preauricular pits or tags are seen in 77% of cases of BOR syndrome; however, only 1 in 200 infants born with a preauricular pit will have profound hearing loss. Infants born with BOR syndrome may exhibit a wide variety of kidney malformations, which, if undiagnosed, may result in kidney dysfunction or failure in adulthood.

BOR syndrome is both clinically and genetically heterogeneous. Variable expressivity has been documented repeatedly within family pedigrees. Three known genetic loci have been linked to the BOR phenotype. Point mutations and deletions in the EYA1 gene, located on chromosome 8, are implicated in 40% of patients with the BOR phenotype. Mutations in the SIX 1 and SIX 5 genes are less frequent causes of the BOR phenotype. The BOR caused by SIX5 and SIX1 mutations are referred to also as BOR2 and BOR3, respectively. The severity of the phenotype is unrelated to the type of mutation. The family of this patient opted to defer having the genetic studies done at this time.

Treatment and Prognosis

Treatment is directed at the systems affected by the syndrome. Complete resection of fistula tracts is necessary to prevent abscess formation or recurrence of cystic lesions. Regular audiologic evaluation aids in the early identification of hearing loss, which may not occur until later in life. Blood pressure control in those with hypertension is an important part of improving long-term survival. In addition, genetic evaluation may be helpful in detecting asymptomatic carriers within the family and assessing for risk of the disease in offspring.

Lessons for the Clinician

- The differential diagnosis for hypertension in an adolescent is broad.
- If the patient who has hypertension has associated external ear anomalies, brachial fistula or cysts, evidence of hearing loss, findings suspicious for renal pathology, or similarly affected family members, additional evaluation should be performed to evaluate for the

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possibility of branchio-oto-renal syndrome.

(*Amy Hanson, MD, Carolyn Jones, MD, Loyola University Medical Center, Maywood, IL*)

Case 3 Discussion

Brain MRI demonstrated dilatation of the ventricular system and symmetric enlargement of the choroid plexus in the lateral ventricles. In conjunction with the increased CSF output, the differential diagnosis included choroid plexus villous hyperplasia versus choroid plexus tumor.

The patient underwent right choroid plexus resection and partial obliteration of the left choroid plexus. Complete resection was not possible because of potential neurologic damage. Histopathology was consistent with bilateral choroid plexus papillomas. Postoperative CSF volume remained elevated, likely owing to the remaining portion of the papilloma, requiring reinternalization of the VP shunt for continued management of the patient's hydrocephalus.

At age 4 years, the patient remains well-managed with a VP shunt. Although still developmentally delayed, her development has progressed. There has been no evidence of tumor recurrence or progression to carcinoma.

Differential Diagnosis

The differential diagnosis for abdominal distension is broad and includes ileus, obstruction, infection, ascites, and neoplasm. In patients who have a VP shunt, the differential diagnosis also must include conditions associated with overproduction and overshunting of CSF. Most of these conditions can be differentiated with simple laboratory tests or imaging.

Ileus is common during hospitalization and after abdominal surgery. Ileus presents typically with painless abdominal distension, absence of bowel movements, and intestinal dilatation on abdominal radiographs. An obstruction is a clinical diagnosis based on history and physical examination. Patients present typically with abdominal distension, bilious emesis, or absence of stool, as well as pain. Imaging studies are indicated if an obstruction is suspected.

A multitude of infectious processes can cause abdominal distension, including peritonitis, abscess, or, in the presence of a VP shunt, a shunt infection. These processes can be excluded when there is an absence of fever, lack of leukocytosis, and normal CSF analysis, as well as appropriate imaging findings.

The cause of ascites is a bit more difficult to differentiate without paracentesis. A normal white blood cell count and lack of fever make an exudative process due to infection unlikely. Normal serum transaminase, albumin, blood urea nitrogen, and creatinine concentrations make a transudative process from hepatic or renal failure unlikely. In addition, echocardiography can rule out congestive heart failure. Finally, imaging can identify the presence of an intra-abdominal neoplasm as a cause for abdominal distension.

Overshunting of CSF can be identified by imaging of the brain and treated with recalibration of the shunt by a neurosurgeon. Overproduction of CSF can be caused by intracranial infections, meningitis, hemorrhage, or choroid plexus abnormalities, including tumors, and may result in hydrocephalus. Overproduction of CSF may manifest with signs of increased ICP, including altered mental status, bulging fontanelles, increasing head circumference, headache, emesis, and regression of developmental milestones. Infections, meningitis, and hemorrhages can be ruled out with CSF analysis. Overproduction of CSF due to abnormalities of the choroid plexus, including cysts, hyperplasia, and tumors, can be diagnosed with brain CT scan or MRI and be confirmed by histopathology.

The Condition

CSF is produced primarily by ependymal cells in the choroid plexus, located within the ventricular system. CSF flows from the lateral ventricles through the interventricular foramen into the third ventricle. From there, CSF enters the cerebral aqueduct and flows into the fourth ventricle. CSF then enters the subarachnoid space and is absorbed subsequently into the venous circulation through arachnoid villi. Approximately 500 mL of CSF is produced daily. The brain, however, can contain only approximately 100 to 150 mL of CSF, resulting in significant absorption.

Choroid plexus tumors are rare neoplasms, accounting for less than 1% of intracranial tumors. These tumors are more common in children, most commonly occurring before age 2 years and accounting for approximately 3% of intracranial neoplasms in the pediatric population. Choroid plexus papilloma occurs more frequently than choroid plexus carcinoma. Choroid plexus papillomas are benign lesions composed of epithelial cells of the choroid plexus, occurring most commonly in the lateral ventricles in children. The occurrence of bilateral choroid plexus papilloma is very rare and must be distinguished from diffuse villous hyperplasia of the choroid plexus, which involves diffuse enlargement of the choroid.

Patients who have choroid plexus tumors present typically with signs of increased ICP, including headache, emesis, bulging fontanelles, increasing

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head circumference, lethargy, and regression of developmental milestones. These signs and symptoms are the result of hydrocephalus, secondary to overproduction of CSF or obstruction of the ventricular outflow tracts.

Diagnosis

Choroid plexus tumors and diffuse villous hyperplasia of the choroid plexus can be difficult to differentiate. Imaging, however, can be helpful. Choroid plexus papillomas typically appear as discrete, lobulated, homogenous, hypodense, intraventricular masses on CT scan, whereas MRI shows homogenous, hyperdense masses. Bilateral enlargement of the choroid plexus is typical of diffuse villous hyperplasia of the choroid plexus, whereas choroid plexus papillomas typically are unilateral. Choroid plexus carcinomas are more heterogeneous, with invasion of adjacent parenchymal tissue and surrounding edema. In all cases, MRI is superior to CT scan for diagnosis. The differentiation between hyperplasia, papillomas, and carcinomas, however, can be difficult with imaging alone. Diagnostic confirmation requires histopathologic analysis.

Treatment and Prognosis

Treatment of choroid plexus tumors is aimed at gross total resection. Location and vasculature, however, make resection challenging. Total surgical resection of choroid plexus papillomas should be curative. Choroid plexus papillomas, however, can recur, and a small percentage evolve into choroid plexus carcinomas. Treatment of choroid plexus carcinoma and recurrent choroid plexus papilloma includes gross total resection with adjuvant chemotherapy or radiation. Treatment of recurrent choroid plexus papilloma and choroid plexus carcinoma includes gross total resection with adjuvant chemotherapy or radiation. Both choroid plexus papilloma and choroid plexus carcinoma carry favorable prognoses with appropriate treatment. Treatment options for diffuse villous hyperplasia of the choroid plexus include VP shunt placement, ventriculoatrial shunt placement, or choroid plexus resection.

Lessons for the Clinician

- Abdominal distension in a patient who has a ventriculoperitoneal shunt should prompt clinicians to consider the possibility of abnormal cerebrospinal fluid production.
- Imaging and neurosurgical intervention should be pursued when appropriate.

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Thank You!

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