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Harish S. Rudra, Jin H. Park, Najla Wehbe-Hijazi, Mohammed Alfaifi, Muhammad Alrifai, Dena Nazer, Lakshmi Srinivasan and Deepak Kamat
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Author Disclosure
Drs Rudra, Park, Wehbe-Hijazi, Alfai, Alrifai, Nazer, Srinivasan, and Kamat did not disclose any financial relationships relevant to these cases.

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Frequently Used Abbreviations
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BUN: blood urea nitrogen
CBC: complete blood count
CNS: central nervous system
CSF: cerebrospinal fluid
CT: computed tomography
ECG: electrocardiography
ED: emergency department
EEG: electroencephalography
ESR: erythrocyte sedimentation rate
GI: gastrointestinal
GU: genitourinary
Hct: hematocrit
Hgb: hemoglobin
MRI: magnetic resonance imaging
WBC: white blood cell

Case 1 Presentation
Introduction
A 7-week-old girl of Middle Eastern descent is admitted to the hospital for a cough of 10 days’ duration that is worsening and has produced post-tussive emesis for the last 7 days. An episode of perioral cyanosis lasting less than 1 minute was noted 5 minutes after a feeding. There has been no fever, rhinorrhea, emesis, or diarrhea. The baby was born at term without perinatal complications.

Three days into her illness, the child’s pediatrician had placed her on nebulized bronchodilator therapy for presumed viral bronchiolitis. Re-evaluation on the day of admission shows no improvement. A chest radiograph reveals marked cardiomegaly with clear lung fields.

The physical examination reveals a well-nourished baby who looks alert but manifests slightly decreased activity. Her heart rate is 130 beats/min, respiratory rate is 35 breaths/min, blood pressure is 85/45 mm Hg, and pulse oximetry saturation is 100% in room air. The child’s length is at the 95th percentile, and her weight and head circumference are at the 75th percentile. Auscultation reveals scattered end-expiratory wheezes, more prominent at the bases, but no grunting, retractions, or nasal flaring. A soft grade I/VI systolic flow murmur that does not radiate is audible at the left sternal border. Both heart sounds are normal. The baby appears well perfused and has normal femoral pulses. The rest of her physical findings are normal.

CBC, electrolyte levels, and liver function tests all yield normal results. Further laboratory studies reveal the diagnosis.

Case 2 Presentation
A 7-year-old girl who has type 1 diabetes mellitus is admitted to the hospital with a 1-month history of intermittent weakness of her lower extremities associated with pain in her feet and lower legs. The weakness is worse in the morning, when she is unable to walk. She has no associated numbness, and her weakness is not related to activity, food, or cold.

The physical examination reveals an alert, oriented girl who has normal cardiovascular, pulmonary, and abdominal findings. The neurologic examination shows intact cranial nerves. She has good tone and strength levels of 5/5 in her arms and 4/5 in her legs, with preserved sensation and deep tendon reflexes throughout. She is able to bear weight with help but cannot take any independent steps. Laboratory tests to determine the cause of her muscle weakness show a normal CBC and chemistry panel, thyroid-stimulating hormone level of 0.97 U/L (normal, 0.35 to 5.5 U/L), free thyroxine of 15.6 pmol/L (normal, 11.5 to 22.7 pmol/L), creatine kinase of 66 U/L, ESR of 40 mm/hr, and ECG that shows a corrected QT interval of 0.44.

Case 3 Presentation
A 4-year-old Arabic boy has experienced leg pain for the past 2 months. He localizes the pain to the middle of his right thigh, sometimes extending to his knee. He is able to run and play, but pain recurs at the end of vigorous play, is worse at the end of the day, and often wakes him at night. It is relieved by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). There is no history of trauma, redness, swelling, fever, weight loss, or rashes. The patient has had no similar complaints in the past. There is no family history of bone or joint diseases. He was born in the United States but has lived in Lebanon for the past year.
On physical examination, the boy’s temperature is 99.1°F (37.3°C), pulse is 108 beats/min, respiratory rate is 28 breaths/min, and blood pressure is 103/68 mm Hg. He localizes pain to the middle of his right thigh, but there is no tenderness, swelling, or erythema in that area. There is full range of motion at both the right hip and knee joints, and strength is 5/5.

Laboratory values include a WBC count of $8.5 \times 10^3$/dL ($8.5 \times 10^9$/L), Hgb level of 13.3 g/dL (133 g/L), platelet count of $455 \times 10^3$/dL ($455 \times 10^9$/L), ESR of 22 mm/hr, and C-reactive protein level of 2.85 mg/dL. An imaging test reveals the diagnosis.

Case 1 Discussion
An ECG revealed tall QRS complexes with inverted T waves consistent with a strain pattern indicative of left ventricular hypertrophy (Fig. 1). The PR interval was slightly shortened at 80 msec. An echocardiogram revealed moderate-to-severe hypertrophic cardiomyopathy affecting both ventricles. Diastolic dysfunction was moderate to severe.

The clinical picture clearly indicated a hypertrophic cardiomyopathy. Viral titers for coxsackievirus, enterovirus, and Epstein-Barr virus were negative. Carnitine levels were normal. Based on the ECG and echocardiographic results, suspicion was high for Pompe disease. A skin biopsy for fibroblast culture and a blood assay for acid alpha-glucosidase activity revealed diminished activity, thus confirming the diagnosis.

The Disorder
Pompe disease belongs to a group of inborn errors of metabolism referred to as glycogen storage diseases. Affected children typically appear normal at birth but soon develop generalized muscle weakness, feeding difficulties, macroglossia, hepatomegaly, and progressively worsening heart failure due to hypertrophic cardiomyopathy. The classic ECG finding consists of high-voltage QRS complexes with a shortened PR interval (Fig. 1). Death usually results from cardiorespiratory failure or from aspiration pneumonia.

The juvenile-onset form usually presents in adolescence but can manifest as early as age 1 year with delayed motor development or difficulty walking. Affected children develop oromotor dysfunction and swallowing difficulties. Death may occur before the second decade from cardiorespiratory failure. The degree of cardiomegaly is variable, but overt cardiac failure unusual. An adult form also presents as a slowly progressive myopathy.

A Misleading Sign
This case shows that not all wheezing should be assumed to be a result of acute bronchiolitis. Wheezing occasionally is heard in patients who have congestive heart failure. In hypertrophic cardiomyopathic states, the reduction in ventricular compliance and relaxation leads to elevated diastolic and end-diastolic pressures, which cause elevated left atrial pressure and volume and increased pulmonary venous and pulmonary capillary pressure. If the latter exceeds the plasma oncotic pressure, interstitial lung fluid develops initially, followed by alveolar edema. The clinical counterparts are moist rales and, occasionally, wheezing. Marked cardiomegaly, as in this case, can cause wheezing by extrinsic pressure on airways.

Figure 1. ECG tracing for a child who has Pompe disease reveals high-voltage QRS complexes with shortened PR intervals.
Differential Diagnosis
Given the unique and acute constellation of findings, the differential diagnosis of infantile Pompe disease is limited. However, valuable time can be lost between the onset of symptoms and consideration of the diagnosis. Most infants survive only a few months beyond the time of diagnosis, necessitating the need for a rapid diagnosis so supportive therapy can be started. Diagnosing this condition requires considerable suspicion and awareness of the disease on the part of pediatricians and specialists. In older children, signs and symptoms can be insidious and attenuated, thus delaying the diagnosis.

Diseases that have been mistaken for infantile Pompe disease because they cause either hypotonia or cardiomyopathy include Werdnig-Hoffman disease, hypothyroidism, myocarditis, endocardial fibroelastosis, Krabbe disease, congenital muscular dystrophy, and respiratory chain disorders. Few, if any, diseases are associated with both hypotonia and cardiomyopathy in infancy. Werdnig-Hoffman disease, a type of spinal muscular atrophy (SMA), presents with hypotonia but also can be associated with structural congenital heart defects, but not cardiomyopathy. Type III SMA is associated with hypotonia and dilated cardiomyopathy but presents in adolescence. Congenital hypothyroidism is associated with hypotonia but not (usually) cardiomyopathy. The presence of hypotonia along with cardiomegaly virtually confirms the diagnosis of Pompe disease. Diseases that can mimic some of the symptoms of the juvenile form include poliomyelitis, limb-girdle muscular dystrophy, Becker muscular dystrophy, and myasthenia gravis.

Laboratory Findings
Laboratory findings consist of elevated creatine kinase, AST, and lactate dehydrogenase levels. Chest radiography reveals massive cardiomegaly and often provides the first clue that the child has Pompe disease. Echocardiography and electrocardiography are used to assess the degree and severity of cardiac involvement. Echocardiography demonstrates hypertrophic cardiomyopathy with thickening of both ventricles and the interventricular septum. ECG findings are as mentioned previously. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen. The definitive diagnosis is established by testing for the absence or reduced levels of acid alpha-glucosidase in muscle, cultured skin fibroblasts, or blood. Skin biopsy is preferred.

Therapy
No definitive treatment exists for Pompe disease. A high-protein diet may be beneficial in the juvenile and adult forms. Nocturnal ventilatory support for patients who have late-onset disease improves the quality of life and can be beneficial during the phase of respiratory decompensation. Recent clinical trials involving enzyme replacement therapy with recombinant acid alpha-glucosidase have shown a decrease in cardiomegaly and improved cardiac and skeletal muscle function, with increased survival. These trials offer some hope in the treatment of an otherwise devastating disease.

Lessons for the Clinician
Pompe disease is a rare but devastating disease that has a unique constellation of signs and symptoms. Diagnosis requires a high degree of suspicion; a timely diagnosis can help ensure that the child receives proper supportive therapy. This case also illustrates how an uncommon disease such as Pompe disease can present with common symptoms such as coughing or wheezing. (Harish S. Rudra, DO, Jin H. Park, MD, Inova Fairfax Hospital for Children, Falls Church, Va.)

Case 2 Discussion
Because of the unusual manifestations of the child’s muscle weakness involving only the lower extremity, with no cranial nerve involvement, no relationship to activity, worsening of weakness on school days, and improvement during holidays and weekends, in addition to a recent history of school difficulty, a diagnosis of conversion disorder was entertained.

A simple test strongly supported that diagnosis; 1 mL of intravenous normal saline was administered to the child after it was explained to her that this could cure her illness. Shortly after the injection, the child stood up alone and walked unassisted back and forth in the hallway. Psychiatric consultation identified school as a major stressor in the patient’s life. The presence of type 1 diabetes, with its daily testing and insulin injections, was identified as a vulnerability that might have triggered the conversion reaction.

Physical therapy was initiated and the parents advised about the nature of the problem. Strategies were offered to alleviate the stressors in the child’s life. The family also was advised to shift attention from the child’s symptoms and to focus on recovery. The girl responded well to treatment, and follow-up showed better coping abilities and amelioration of her muscle weakness.

The Condition
Conversion disorder should be suspected when a patient’s symptoms do not fit into the framework of known medical illnesses or when appropriate evaluation reveals no or-
ganic disease or plausible pathophysiologic explanation. Conversion disorders in children do not indicate a major psychiatric disorder but represent the child’s subconscious plea for help in situations in which he or she cannot cope. These situations can arise from a variety of stressors, such as struggles in school, family disharmony, and sexual and physical abuse. Symptoms are referable to the CNS in 65% of children who have conversion disorders. The most usual presentations are episodic loss of awareness, such as pseudoseizures and syncope; motor dysfunction, including gait disturbances and paresis; sensory abnormalities, primarily pain and numbness; and disorders of the special senses.

Diagnosis

Once the diagnosis of conversion disorder is suspected in a child who has persistent and debilitating symptoms, a sensible evaluation plan should be created. In severe cases, hospitalization may be warranted. During the evaluation, focused investigation and testing should be pursued to be reasonably certain that there is no medically treatable cause. Psychiatric evaluation instituted simultaneously should concentrate on five main areas: 1) the levels of stress or anxiety in the child and family, 2) any special predisposing vulnerabilities in the child that might lower the threshold for coping with stress and anxiety (eg, learning disabilities, peer pressures, problems of body image, chronic illness, and family disharmony or conflict), 3) a possible temporal relationship between a specific stress and the onset of symptoms, 4) role models from whom the symptoms might have been learned, and 5) evidence of primary or secondary gain from the symptom.

Differential Diagnosis

The differential diagnosis of a child presenting with intermittent muscle weakness includes familial periodic paralysis (hypokalemic or normokalemic); metabolic myopathies, including myophosphorylase deficiency and mitochondrial deficiency; limb-girdle muscular dystrophy; myasthenia gravis; and endocrinopathies such as thyroid disorders and adrenal disorders. Delineation of the clinical pattern and laboratory testing should allow the clinician to determine if any of these disorders is present. If no other disorder fits and if significant stress is evident, a psychosomatic cause should be considered.

Treatment

Once the evaluation has been completed, a treatment plan is presented to the parents and the child. The first step is to explain that the symptom is real but that no organic disease has been demonstrated. Anxiety or stress has led to the symptom, and this element must be understood and relieved for the child to get better. The treatment must be tailored to the problem, with set goals and the provision of positive feedback as goals are achieved. In addition to measures aimed at understanding and relieving stress, treatment for a patient complaining of weakness might involve “graded” physical therapy.

Removing the secondary gain achieved by the symptom is essential for recovery and to eliminate perpetuation of the symptom. Examples of secondary gain include missed school days and increased parental attention because of the symptom. It is essential that the treatment provide “escape with honor” and that the regimen give some control to the child. After discharge, continued psychotherapy should be aimed at allowing the child to give up the sick role and cope with future stress and anxiety more productively.

Prognosis

Except for children who have pseudoseizures, most children who have a conversion disorder have no underlying major mood disorder or psychiatric illness. Major mood disorders have been identified in 32% of children who have pseudoseizures. A history of sexual abuse is common in patients who have conversion disorders.

Because children are still in the formative stages of personality development, the adult diagnosis “hysterical personality,” now called “histrionic personality disorder,” is questionable when applied to children who have conversion disorder. Histrionic personality disorder comprises a constellation of traits, including dependency, immaturity, egocentricity, attention-seeking behavior, and manipulation. With timely intervention, the child who has a conversion disorder will develop better coping abilities and give up the sick role, thus aborting perpetuation of the symptom and progression to an adult histrionic personality disorder.

Further Observations

This patient had a chronic illness and had become aware of its power to influence the adults in her world. Another example of this effect is that pseudoseizures are common in children who have true epilepsy.

Clinical testing should be judicious because the tests themselves promote anxiety and confirm and reinforce the power and seriousness of the symptom. The child herself is deceived about the source of her symptoms, and families of children who have conversion disorders tend to have conversion symptoms, reinforcing the impressionable child’s
symptomatology. The clinician must be firm in the diagnosis of conversion and resist his or her own anxiety, which tends to produce the need to do more testing. The simple test employing intravenous saline was an effective diagnostic tool in this case, but it is important that clinicians undertake such procedures with sensitivity to avoid their being perceived by the patient as a trick, potentially undermining trust.

The use of physical therapy was a face-saving treatment for the patient and more likely to be acceptable to patient and parents than a purely psychiatric approach, which can be counterproductive if instituted at the wrong time. Similarly, early hospitalization can raise the stakes ominously. Sometimes, psychotherapy will be acceptable if the reason given for recommending such treatment is “to help you cope with the stress of being ill for so long.”

**Lessons for the Clinician**

Conversion disorder represents a child’s expression of a difficult or stressful situation through a physical symptom. The pediatrician, being familiar with the child and parents, should be able to gain the trust of the child and identify stressors and difficulties in the child’s life. Psychiatric referral and sometimes hospitalization are crucial for the recovery of children whose symptoms are prolonged and unresponsive to counseling by the pediatrician. (Najla Wehbe-Hijazi, MD, Mohammed Alfatih, MD, Muhammad Alrifai, MD, King Abdul Aziz Medical City for National Guard, Riyadh, Saudi Arabia)

**Case 3 Discussion**

A plain radiograph of the right hip and femur showed an approximately 1-cm, focal, lytic lesion with sclerotic margins at the interior cortex of the proximal right femoral diaphysis (Fig. 2). There was no evidence of periosteal reaction, associated soft-tissue mass, or pathologic fracture. The soft tissue was unremarkable. The visualized hip and pelvis were within normal limits. Findings were believed to be consistent with osteoid osteoma, and the CT scan made that diagnosis more certain (Fig. 3). Histologic examination of a specimen obtained by CT-guided biopsy of the lesion confirmed the diagnosis of osteoid osteoma.

**The Condition**

Osteoid osteoma is a common benign bone tumor. Most patients are 5 to 20 years old. The most common sites of involvement are the proximal femur and tibia, but any bone can be involved, including the posterior elements of the spine. Pain is the symptom that causes the patient to seek care.

The physical examination may reveal tenderness to touch or pressure. Patients also may have diurnal atrophy, painful scoliosis, or limb-length discrepancy.

**Differential Diagnosis**

Leg pain in childhood has many causes, ranging from benign conditions requiring no treatment to malignant tumors necessitating immediate intervention. This boy’s history was inconsistent with “growing pains,” a controversial term diagnosed only by exclusion of other disorders. “Growing pains” usually are bilateral, intermittent, worse in the evening, not present the next morning, and associated with normal physical and laboratory findings.

The differential diagnosis of leg pain includes infections (septic arthritis, osteomyelitis), malignancies not primarily derived from bone (leukemia, neuroblastoma), and primary malignant and benign bone tumors.

This patient’s history was consistent with his diagnosis. Patients who have osteoid osteoma classically present with gradually increasing sharp focal pain that is worse at the end of the day or at night. Pain from osteoid osteomas located in bones of the leg usually is not related to activity, which helps differentiate this condition from a stress fracture, and the pain responds dramatically to NSAIDs, including aspirin. Constitutional symptoms usually are absent.

A normal CBC and peripheral smear along with the radiologic findings made leukemia unlikely. This
child’s age is younger than the age range for primary bone tumors, which also may cause leg pain but usually present in the second decade of life.

**Evaluation**

When evaluating a child who has leg pain, the clinician should start with the history and physical examination. Initial investigations include a CBC, ESR, and radiographs. A radiograph of the normal side is recommended for comparison.

Osteoid osteoma generally can be diagnosed by clinical presentation and radiologic appearance. It usually appears as a small spherical or oval lytic lesion surrounded by soft-tissue edema and reactive bone formation on plain radiographs. Most osteoid osteomas are cortical or periosteal, but 20% arise within the marrow. Osteoid osteoma is visualized better by CT than by MRI. CT is used for precise localization of the lesion and as a guide for percutaneous biopsy and ablation. A biopsy confirms the diagnosis when the history, clinical examination, location, or radiographic findings are nonclassical or suspicious of any other etiologies. Most patients do not require a biopsy because the CT so often is diagnostic.

Small lytic lesions can be caused by infections, benign neoplasms of the bone, and leukemia. Benign neoplasms include osteoid osteoma, periosteal chondroma, chondroblastoma, eosinophilic granuloma, hemangioma, and intracortical osteosarcoma. The most common of these lesions is osteoid osteoma. Given the history of relief with NSAIDs, physical findings, small size of the lesion, and location in the diaphysis, osteoid osteoma was the most likely diagnosis in this patient. Orthopedic surgeons elected to perform a biopsy due to a second lesion that appeared on further evaluation. Biopsy provided confirmation of the diagnosis and ruled out other conditions.

**Management and Prognosis**

Osteoid osteoma is a benign bone tumor that does not progress or have malignant potential. Some lesions may regress spontaneously. The primary goal of treatment is pain control with medications, usually NSAIDs. However, if pain is not controlled by medications alone or the patient has complications of osteoid osteoma, such as neuropathy, synovitis, growth disturbances, or scoliosis, the lesion should be removed surgically or by radiofrequency ablation. Surgical options include en bloc excision, curettage, or CT-guided removal. However, radiofrequency ablation, when possible, is a less invasive, effective treatment that may avoid complications of an open procedure. A relative contraindication to radiofrequency ablation is an osteoid osteoma adjacent to vital structures such as the spinal cord, which may be damaged by heat from the procedure.

**Lessons for the Clinician**

Leg pain in children is due most often to a benign condition. However, if the pain is persistent, unilateral, interferes with daily activities or sleep, or is associated with systemic manifestations, the clinician should start appropriate investigations. A history, physical examination, CBC, ESR, and radiographs are good initial components of the evaluation. Leg pain, although common in children, may be a symptom of a severe underlying disease. (Dena Nazer, MD, Lakshmi Srinivasan, MD, Deepak Kamat, MD, Children’s Hospital of Michigan/Wayne State University, Detroit, Mich.)
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