Neuroblastoma in a Child With Persistent Hip Pain

May 01, 2009
By Nagendra Natarajan, MD, MPH [1], Arvind Hoskoppal, MD [2], Archana Chatterjee, MD, PhD [3], Meera Varman, MD [4], Rachel Mccann, MD [5], Paul Esposito, MD [6], and Bruce Gordon, MD [7]

A 4-year-old boy presented for further evaluation of persistent right hip pain of 2 months’ duration. Before the onset of the pain, he had been limping, favoring his right side. For several days before he was brought in for evaluation, he had had fevers and sweating in addition to the right hip pain.

A 4-year-old boy presented for further evaluation of persistent right hip pain of 2 months’ duration. Before the onset of the pain, he had been limping, favoring his right side. For several days before he was brought in for evaluation, he had had fevers and sweating in addition to the right hip pain. He had no history of seizure, trauma, nausea, vomiting, headache, change in appetite, or weight change.

He had been initially evaluated at a local hospital for right hip pain 2 months earlier. Appendicitis had been diagnosed based on abdominal CT scan findings, and an appendectomy was performed; however, results of pathological examination of the appendix were reported as normal by the referring hospital. During the week after the appendectomy, the patient continued to limp and complained of right hip pain. He was evaluated with a technetium-99 bone scan. Results led to concern for septic arthritis, and aspiration of the right hip was performed. Intravenous antibiotics were started but discontinued after the cultures of the synovial fluid were found to be negative.

Before the onset of symptoms, the child had been in good health. His medical history was unremarkable. He had no drug allergies. His immunizations were up-to-date. Family and social histories were noncontributory. He had no history of travel or exposure to sick contacts. Pets at home included some fish, a frog, and dogs. He was given acetaminophen or ibuprofen as needed for pain.

On examination, temperature was 37.9°C (100.3°F); heart rate, 128 beats per minute; respiration rate, 36 breaths per minute; and blood pressure, 120/75 mm Hg. Head, eyes, ears, nose, and throat were normal. No generalized lymphadenopathy was noted. A 2/6 ejection systolic murmur was heard at the apex. The lungs were clear to auscultation bilaterally. Examination of the hips was limited because of patient anxiety and pain. The right hip was noted to be externally rotated and flexed. Dermatological, neurological, abdominal, and genitourinary findings were all normal.

Laboratory evaluation revealed a hemoglobin level of 8.8 g/dL; hematocrit of 26.4%; and white blood cell count of 8000/μL, with 59% neutrophils, 29% lymphocytes, 2% monocytes, and 10% eosinophils. Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine levels were normal. Glucose level was 114 mg/dL and alanine aminotransferase level was 4 U/L. Protein, albumin, alkaline phosphatase, and aspartate aminotransferase levels were normal. Erythrocyte sedimentation rate was more than 100 mm/h; C-reactive protein level, 6.0 mg/dL (range, 0.0 to 0.7 mg/dL); C3 level, 191 mg/dL (range, 90 to 180 mg/dL); and C4 level, 43 mg/dL (range, 10 to 40 mg/dL). Blood cultures were negative.

A CT scan of the hip showed irregular sclerosis within the body of the ischium on the right (Figure 1). There was a calcified periosteal reaction along the medial and posterior aspect of the ischium. No other abnormalities were seen. No definite osteolysis was identified. The CT scan was reported as “partially treated osteomyelitis involving the body of the ischium on the right.” This corresponded to abnormally increased radiopharmaceutical accumulation that was noted on a repeated technetium-99 bone scan (Figure 2).

Figure 1 – A CT scan of the pelvis showed irregular sclerosis within the body of the right ischium. This was mistakenly identified as osteomyelitis. In retrospect, these findings probably represented bone...
metastases.

Figure 2 - The areas of increased uptake on a wholebody bone scan were interpreted as multifocal osteomyelitis but were actually indicative of metastatic neuroblastoma. A primary tumor was not identifiable on this scan.

The child underwent an arthrogram and aspiration of the right hip as well as irrigation, debridement, and curettage of the posterior wall of the right acetabulum and ischium. During the procedure, the right femoral head was noted to be smooth with patchy sclerosis of the right iliac bone. Multifocal osteomyelitis was diagnosed, and broad-spectrum antibiotic therapy with vancomycin and piperacillin/tazobactam was started. Although a complete blood cell (CBC) count at this time showed one peripheral blast, the hematology/oncology team recommended no further evaluation and the patient was discharged.

At follow-up a week later, a CBC count showed evidence of severe anemia, with a hemoglobin level of 3.9 g/dL (range, 10.5 to 12.7 g/dL) and peripheral blasts. The patient was readmitted for a blood transfusion. A bone marrow biopsy showed a metastatic malignant blue cell tumor, subsequently confirmed to be a neuroblastoma. The vanillylmandelic acid level was 68.6 mg/g creatinine (range, 0 to 9 mg/g) and homovanillic acid level was 9.3 mg/g creatinine (range, 0 to 15 mg/g). A primary source of the tumor was not identified.

The patient received intravenous cyclophosphamide (300 mg daily) and topotecan (0.9 mg daily) for 5 days. He also received mesna for urological prophylaxis. After the first cycle of chemotherapy, his right hip pain resolved. He was monitored by the hematology/oncology team thereafter.

**NEUROBLASTOMA: AN OVERVIEW**

Neuroblastoma is predominantly a childhood disease, with more than 90% of cases diagnosed in infants and toddlers. It is the most common extracranial solid tumor of childhood. The adrenal gland is most frequently affected (40% of cases), followed by the paraspinal ganglion (25%) and the thoracic (15%), pelvic (5%), and cervical (3%) regions; about 12% of tumors occur in other sites. In this case, the site of the primary tumor could have been the appendix, which was removed. (Attempts to obtain the original slides of the appendix to confirm this were unsuccessful.) It is also possible that the primary tumor was somewhere other than the appendix but could not be located by available imaging studies.

**Etiology.** The histological composition of neuroblastomas ranges from primitive neuronal cells to mature neurons or ganglion cells. Random genetic mutations appear to be the cause of most newly diagnosed neuroblastomas; however, rare familial cases can occur because of a germ line mutation on chromosome 16p12 to 16p13 or chromosome 4p12 (PHOX2B gene). Chromosomal abnormalities include deletion of the short arm of chromosome 1(1p), allelic loss of 11q, and gain of 1 to 3 additional 17q copies.

**Clinical features.** The signs and symptoms vary depending on the neuroendocrine function and size and location of the tumor. The clinical features can be grouped into several types:

- **GI (40% to 50%)**—abdominal mass (retroperitoneal or hepatic), abdominal pain or constipation, otherwise unexplained secretory diarrhea (from paraneoplastic production of vasoactive intestinal polypeptide), bladder dysfunction.
- **Orbital (8% to 10%)**—proptosis, periorbital ecchymoses (raccoon eyes, caused by orbital metastases), Horner syndrome (miosis, ptosis, anhidrosis), heterochromia iridis (partial or complete discoloration of the iris).
- **Rhinal**—unilateral nasal obstruction.
- **Systemic symptoms**—fever, weight loss, anemia, weakness (from spinal cord compression).
- **Cardiac**—hypertension.
- **Orthopedic symptoms** (20% to 25%)—bone pain, localized back pain, scoliosis.
- **Skin**—palpable nontender subcutaneous nodules.
- **Psychiatric (2%)**—opsoclonusmyoclonus-ataxia syndrome.
Laboratory and imaging studies. The CBC will likely show anemia of chronic disease. Levels of lactate dehydrogenase, ferritin, and urinary catecholamines (vanillylmandelic acid and homovanillic acid) may be elevated. In addition to neuronal/ganglionic features, characteristic histopathological findings may include tumor cell clumps or syncytia in bone marrow.

Plain radiographs and CT and MRI scans are used in the diagnosis and staging of the disease. A technetium radionuclide scan or iodine-131-meta-iodobenzylguanidine (MIBG) scan also may be used. MIBG is selectively concentrated in 90% of neuroblastoma cells, providing high sensitivity and specificity in diagnosing primary and metastatic disease.

Diagnostic criteria. Diagnosis of neuroblastoma requires that 1 of the following 2 criteria be met:

- An unequivocal histological diagnosis from tumor tissue by light microscopy, with or without immunohistochemistry, electron microscopy, or increased urine (or serum) catecholamines or their metabolites.
- Evidence of metastasis to bone marrow on an aspirate or trephine biopsy with concomitant elevation of urinary or serum catecholamines or their metabolites.

Prognosis. The prognosis is related to the age at diagnosis, clinical stage, site of primary tumor, tumor histology, presence of the N-myc protooncogene, and lymph node involvement in patients older than 1 year. Long-term disease-free survival is associated with a localized neuroblastoma, advanced disease in infancy, hyperdiploid tumor DNA (especially in infants), and expression of certain genes. Bad prognostic factors include advanced disease in later childhood, N-myc amplification, increased ratio of excreted catecholelamine metabolites, lack of expression of glycoprotein CD44 on the tumor cell surface, and elevated serum levels (ferritin, neuron specific enolase, and lactate dehydrogenase).

Treatment. Patients are classified as low-risk, intermediate-risk, and high-risk for recurrence based on their age, stage of the disease, and tumor biology. Low-risk patients are treated with surgery alone. Patients with spinal cord compression or respiratory compromise secondary to hepatic infiltration in advanced stages may be considered intermediate risk. Most intermediate patients are treated with surgery and 12 to 24 weeks of chemotherapy.

High-risk patients are treated aggressively with multiagent highdose chemotherapy until a response is achieved and resection of the primary tumor can be attempted. This is followed by myeloablative chemotherapy. Total-body irradiation and autologous stem cell transplantation have also shown promising results in high-risk patients. Radiation of the residual site and metastatic sites is usually performed either before or after myeloablative therapy. After recovery, these patients are treated with oral 13-cis-retinoic acid for 6 months.

PITFALLS IN DIAGNOSIS

Malignancy initially misdiagnosed as infection has been reported. In a retrospective study of 561 children with malignancy, 21 patients received an initial diagnosis of infection; of the 21 patients, 3 had both an infectious and malignant cause and 1 received the diagnosis of neuroblastoma. Another study showed that among 4 children in whom hip osteomyelitis was diagnosed on their initial visit to the emergency department, skeletal scintigraphy findings led to the correct diagnosis of neuroblastoma.

One study reported that of 12 patients with olfactory neuroblastoma, only 2 patients received an initial diagnosis of neuroblastoma; in the remaining 10 patients the condition was misdiagnosed. Misdiagnosis of neonatal paratesticular neuroblastoma as in utero torsion of the testes has also been reported.

This case emphasizes the need for a high index of suspicion when evaluating children with persistent pain. This patient probably had hip pain, with some referred pain to the right lower quadrant of the abdomen. That his pain and limping persisted after the appendectomy was key. Cancer could have
been considered when the bone scan showed abnormalities. The development of severe anemia and the presence of blasts on the peripheral smear were the strong signals that finally led to investigation for potential malignancy.

References: REFERENCES:

Source URL: http://www.physicianspractice.com/allergy/neuroblastoma-child-persistent-hip-pain

Links: