Clinical Presentation, Evaluation, and Management of Neuroblastoma

Richa Sharma, MD,* Jesse Mer, MD,† Alex Lion, DO MPH,‡ Terry A. Vik, MD‡

*Department of Pediatrics; †Department of Radiology; ‡Department of Pediatrics, Division of Pediatric Hematology-Oncology, Indiana University School of Medicine, Indianapolis, IN

Education Gap

Pediatricians play a pivotal role in the diagnosis of neuroblastoma and as such should be aware of the elusive signs and symptoms to provide clinical surveillance, appropriate referral, and medical support as part of the patient’s multidisciplinary team.

Objectives

After completing this article, readers should be able to:

1. Identify signs and symptoms of neuroblastoma.
2. Identify patients who require emergency care for a life-threatening presentation.
3. Discuss the basics of clinical presentation, diagnostics, and management of neuroblastoma.

INTRODUCTION

Pediatric cancers occur in 171 per 1 million children in the United States each year and are the leading cause of disease-associated death in children. (1) Neuroblastoma is not only the most common cancer in infancy but also the most prevalent solid tumor outside the cranium, (2) and it sometimes requires the most aggressive treatment plan in pediatric oncology. Therefore, pediatricians should be familiar with clinical presentations that should prompt appropriate and timely referral. In this review, we present neuroblastoma, which exemplifies several principles of pediatric oncology, including its multidisciplinary treatment approach.

EPIDEMIOLOGY

The annual incidence of neuroblastoma is approximately 700 cases in North America. (1) In a review of national cancer registries from 2001 through 2009, a diagnosis of neuroblastoma or ganglioneuroblastoma was found in approximately 6% of the cases. (1) Neuroblastoma is more common in the white population (9.7 per 1 million) than in the African American population (6.8 per 1 million) (2) and more common in males (8.5 per 1 million) than in females (7.6 per 1 million).

AUTHOR DISCLOSURE

Drs Sharma, Mer, Lion, and Vik 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.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>complete blood cell</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>HVA</td>
<td>homovanillic acid</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemical</td>
</tr>
<tr>
<td>IL-2</td>
<td>interleukin-2</td>
</tr>
<tr>
<td>mIBG I-123</td>
<td>metaiodobenzylguanidine</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>OMS</td>
<td>opsoclonus myoclonus</td>
</tr>
<tr>
<td>VMA</td>
<td>vanillylmandelic acid</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
</tbody>
</table>

194 Pediatrics in Review
(3) Although the median age at diagnosis of neuroblastoma is 18 months, (4) there is a wide age range, from in utero diagnosis to individuals in their 20s. (5) Research studies have interrogated several exposures, including viruses, chemicals, radiation, and drugs. No strong causality has been found to support a role of environmental risk factors in the pathogenesis of neuroblastoma.

PATHOPHYSIOLOGY

Neuroblastoma arises from abnormal growth of embryonic neural crest cells that normally make up the sympathetic ganglia and the adrenal medulla. (6) As in all cancers, this aberrant growth is caused by gene mutations. Serving as a starting point, the gene mutation may be germline (occurring in sperm or eggs, thereby hereditable) or somatic (in other cells of the body, which become a tumor).

In some cases, hereditable gene mutations predispose to neuroblastoma. A germline mutation in the ALK oncogene accounts for less than 2% of all neuroblastoma cases and is known as familial neuroblastoma. Familial neuroblastoma often presents with severe clinical features, such as younger age at diagnosis, bilateral adrenal tumors, and multifocal primary neuroblastoma. (7) A PHOX2B loss-of-function mutation can result in neuroblastoma as one feature of congenital central hypoventilation syndrome. (8)(9) A neurocristopathy syndrome is a rare, heritable group of conditions that result from abnormal neural crest cell development and must be considered when seeing a child with simultaneous occurrence of Hirschsprung disease, congenital central hypoventilation syndrome, and congenital neuroblastoma.

In contrast, somatic mutations account for more than 98% of neuroblastoma cases. (10) Several genetic alterations have been identified, including gene amplification, chromosomal alterations, and gene polymorphisms. The most important biomarker in neuroblastomas, the MYCN gene, is amplified in approximately 20% of cases. (11) The ALK oncogene has also been shown to have gain-of-function somatic mutation in approximately 14% of neuroblastomas. (12) Both MYCN and ALK amplifications are associated with aggressive tumor phenotype and poor prognosis. Recurrent gain or loss of specific chromosomal segments is found in almost all high-risk neuroblastomas. The most important alterations include gain of 17q and loss of 11q and 1p. (6) Ongoing research efforts are underway to better understand genes that are housed in the aforementioned chromosomal regions, which are associated with aggressive neuroblastomas. Finally, the number of whole chromosomes in a cell, also known as ploidy, is another prognostic marker. Tumor cells can have more (hyperploidy) or less (hypoploidy) than the normal number of copies of whole chromosomes. As with neuroblastomas and most other pediatric cancers, hyperploidy is a more favorable prognostic sign than hypoploidy. (13) Conclusively, there is a great variety of genetic alterations possible, leading to a wide spectrum of clinical behavior of neuroblastomas. The following cases show the dramatic extremes of presentation.

CLINICAL PRESENTATION

Case 1

Katie is a 4-month-old healthy girl who is brought to her pediatrician by her mother with a concern of “projectile vomiting” for 3 days. Katie’s mother is worried that she may have pyloric stenosis just as her older brother did when he was an infant. The mother denies sick contacts. Urinary output has been adequate, and Katie is gaining weight adequately. Katie’s vital signs and physical examination findings are normal. A complete abdominal ultrasound is negative for pyloric stenosis. However, it is positive for an incidental finding of a 2-cm heterogeneous mass in the right retroperitoneal space. The mass may be arising from the adrenal gland, and it contains areas of calcification, with partial vascularity on Doppler, and is not causing mass effect. On consultation, a pediatric oncologist would like to see Katie in her clinic today, with plans to obtain a complete blood cell (CBC) count, basic metabolic panel, liver enzyme levels, coagulation profile, and random urinary catecholamine levels.

This case demonstrates 1 side of the clinical spectrum, in which a neuroblastoma may be discovered as an incidental radiologic finding. The symptoms, which brought her to the pediatrician, may very well be unrelated to the neuroblastoma. In addition, a small neuroblastoma may not be palpable on physical examination. The location of the mass on imaging gives a clue to the diagnosis. Although Katie’s tumor is located in the most common site, the adrenal gland, a neuroblastoma can occur anywhere along the sympathetic nervous system. These sites include the adrenal glands (>50%), the abdominal paraspinal ganglia (24%), the thoracic paraspinal ganglia (20%), the neck (3%), and the brain (rarely).

The CBC count shows a white blood cell (WBC) count of 10,200/µL (10.2×10⁹/L), with 56% neutrophils and 44% lymphocytes. The hemoglobin level is 12 g/dL (120 g/L), and the platelet count is 250×10⁹/µL (25×10⁹/L). Her electrolyte, liver enzyme, and fibrinogen levels and coagulation profile are all normal. Her urinary vanillylmandelic acid (VMA) level is 722 mg/g creatinine (reference range, <25.0 mg/g creatinine) and urinary homovanillic acid (HVA) level is 960 mg/g creatinine (reference range, <35.0 mg/g creatinine). The oncologist explains the laboratory values to the mother and states that the increase...
in urinary catecholamine levels combined with the ultrasonography findings raise concern for a neuroblastoma.

A diagnosis of neuroblastoma is suggested by laboratory, radiologic, and histologic findings (Table 1). Katie’s CBC count is normal, without findings of neutropenia, anemia, or thrombocytopenia, which most likely excludes bone marrow involvement. Abnormal liver enzyme levels and coagulation panel values are generally secondary to liver metastasis, which is not the case for Katie. Both VMA and HVA are catecholamine metabolites that are secreted by neuroblastoma cells and are elevated in 90% to 95% of patients with neuroblastomas. Of note, spot or random urinary catecholamine levels are not needed. Although radiologic studies such as ultrasonography or chest radiography are initially used, magnetic resonance imaging (MRI) (preferred) or computed tomography (CT) is required to better evaluate disease burden (Fig 1).

An abdominal MRI demonstrates a 2-cm heterogeneous mass with calcifications arising from the right adrenal medulla. No lymph node or perivascular involvement is noted.

Although Katie’s laboratory and MRI findings are favorable for localized disease, a metastatic evaluation is necessary for the management of a neuroblastoma. Indeed, metastatic disease to the bone marrow, liver, and skin is found in approximately 50% of patients during the initial presentation. These patients often present with constitutional symptoms such as fever, malaise, pallor, and fussiness. In addition, there may be refusal to walk/crawl, localized pain, and abdominal distention. A “blueberry muffin rash” is a cutaneous manifestation of a neuroblastoma in infants, representing tumor spread to subcutaneous tissue. These cutaneous nodules are purpuric lesions that blanch on palpation. When examining purpuric subcutaneous nodules, leukemic infiltrates and extramedullary hematopoietic centers must be included in the differential diagnosis because the location and appearance are similar. Orbital findings, including heterochromia irides and periorbital ecchymosis, or “raccoon eyes,” are secondary to metastatic spread to the retrobulbar region and are rare but suggestive findings for a neuroblastoma.

An I-123 metaiodobenzylguanidine (mIBG) scan is used to look for metastatic disease (Table 1). It uses a radiolabeled molecule that possesses structural similarity to noradrenaline and is taken up by neuroblastoma cells. Although mIBG is 99% specific for metastatic neuroblastomas, 10% of neuroblastomas are not mIBG-avid, which can then be detected using positron emission tomography and CT scan. (14)

An I-123 mIBG scan showed uptake in the tumor but was negative for metastatic disease. The oncologist explains that a right-sided abdominal mass in an infant, such as Katie, with elevated urinary catecholamine levels without systemic findings evident on laboratory evaluation is most likely to be a neuroblastoma. Fortunately, Katie is in the favorable age range (<18 months) where she is highly likely to have spontaneous regression of her neuroblastoma. After detailing Katie’s low-risk features, the oncologist converses with the mother and recommends monitoring as the best option for Katie.

Approximately half of all neuroblastomas found in infants spontaneously regress. In infants younger than 6 months, there are a few factors that ensure 98% event-free survival with observation alone. These factors include location (primary adrenal location, without metastases), size (<5 cm), clinical aggressiveness (<50% increase in tumor size during the screening phase), and laboratory evidence (<2-fold increase in urinary catecholamine levels starting from the time of diagnosis through the entire observation period). Observation consists of sequential abdominal ultrasonography and urinary catecholamine levels at 6 and 12 weeks, followed by serial screening every 3 months for the first year and every 6 months for the second year. Surgical evaluation and histologic assessment are necessary if the tumor grows during the screening phase.

**TABLE 1. Laboratory, Radiology, and Pathology Evaluation for Neuroblastoma (6)**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Complete blood cell count with peripheral smear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete metabolic panel, uric acid</td>
</tr>
<tr>
<td></td>
<td>Coagulation panel</td>
</tr>
<tr>
<td></td>
<td>Ferritin and lactate dehydrogenase levels</td>
</tr>
<tr>
<td></td>
<td>(nonspecific)</td>
</tr>
<tr>
<td></td>
<td>Urine vanillylmandelic acid and homovanillic acid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiology</th>
<th>Initial: chest radiograph or ultrasonography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urgent/emergency: CT scan</td>
</tr>
<tr>
<td></td>
<td>Preferred: MRI of primary site AND chest, abdomen, and pelvis</td>
</tr>
<tr>
<td></td>
<td>Metastatic: I-123 metaiodobenzylguanidine scan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Bilateral bone marrow aspirate and biopsy with IHC analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor biopsy with IHC analysis</td>
</tr>
<tr>
<td></td>
<td>DNA ploidy</td>
</tr>
<tr>
<td></td>
<td>Fluorescence in situ hybridization for MYCN</td>
</tr>
<tr>
<td></td>
<td>Segmental chromosomal alteration analysis</td>
</tr>
</tbody>
</table>

CT, computed tomographic; IHC, immunohistochemical; MRI, magnetic resonance imaging.
period. This mild presentation is contrasted by the opposite side of the clinical spectrum, as seen in the following 2 cases.

**Case 2**

Chase is a 3-year-old boy who presents to the pediatrician’s office with worsening hip pain, leg pain, and back pain for 3 weeks. He has numbness in both legs, and his mother has noted shortness of breath when he is active. Vital signs are normal in the office. Significant physical examination findings include decreased breath sounds over the right lung, a large nontender abdominal mass, and 1+ Achillies reflex bilaterally. Chase’s gait is weak and altered, with dragging of his right leg and frequent falls when taking a few steps. Laboratory results include a WBC count of 9,200/µL (9.2×10^9/L) with a normal differential count, a hemoglobin level of 13.4 g/dL (134 g/L), and a platelet count of 420×10^3/µL (0.42×10^9/L). Electrolyte levels are normal aside from an elevated creatinine level of 1.2 mg/dL (106 µmol/L). Liver enzyme levels and results of coagulation studies are normal. Emergency transport is arranged to take Chase to a pediatric hospital emergency department because of concern for spinal cord compression.

*Figure 1. A. Chest radiograph shows a soft tissue mass at the right lung base. B. Computed tomographic scan shows a large right paraspinal mass with partial enhancement, large areas of necrosis, and scattered calcifications. C. Growth of tumor through interpedicular spaces. D. T2-weighted magnetic resonance image demonstrates tumor neuroforaminal invasion in a classic “dumbbell” pattern.*
As in this case, a neuroblastoma may present with a clinical sign specific to the location of tumor invasion. Neuroblastoma is one of the most common neoplastic causes of spinal cord compression in children. Common features of spinal cord compression include pain, numbness, and limb weakness. Given that all these signs and symptoms can be subtle in a child, a high index of suspicion is necessary. Sphincter dysfunction, presenting as loss of bowel or bladder function, and loss of deep tendon reflexes are relatively uncommon but ominous signs of spinal cord compression requiring immediate neurosurgical evaluation. An MRI is the most sensitive modality for identifying spinal cord pathology.

A chest radiograph is obtained and demonstrates a large soft tissue mass displacing the right lung (Fig 1A). A contrast abdomin al CT scan shows a large lobulated partially enhancing mass with calcifications (Fig 1B). The tumor has displaced nearby structures and collapsed the right lung, with bony destruction of adjacent ribs and the vertebral column (Fig 1C). Spinal MRI depicts the tumor growing through the neuroforamina of the lower thoracic spine and compressing the spinal cord (Fig 1D).

Imaging studies can confirm spinal cord compression. A multidisciplinary approach, involving pediatric oncology and neurosurgery, is required to manage spinal cord compression secondary to a solid tumor. (16) When spinal cord compression is identified, dexamethasone is given with the intent to reduce spinal cord edema while the pediatric oncologist determines definitive therapy. In severe cases, surgical decompression or radiotherapy is used. There is some evidence that the most important component of managing spinal cord compression due to tumor is starting chemotherapy.

Although not seen in this case, pediatricians should also be familiar with 2 syndromes that should raise suspicion for a neuroblastoma. When a neuroblastoma impinges on the oculosympathetic tract, Horner syndrome becomes evident with ptosis, miosis, and anhydrosis. Opsoclonus myoclonus syndrome (OMS) is a paraneoplastic syndrome characterized by rapid multidirectional eye movements, involuntary muscle spasms, and irritability. Although the exact mechanism of OMS remains unknown, an autoimmune reaction is currently the leading hypothesis. Studies have shown the presence of autoantibodies against neuronal and cerebellar Purkinje cells in patients with OMS associated neuroblastoma.

Given the high mortality rate, the painful adverse effects of chemotherapeutic agents, and the long-term effects of high-risk neuroblastoma treatment, palliative care is a key component of comprehensive patient care. More than end-of-life care, palliative care involves control of symptoms while helping the patient live each day to the fullest. Palliative care often starts with the pediatrician, who has the deepest relationship with the patient and family. The pediatrician not only starts the palliation process, which involves quality of life discussions, establishing advance care goals, and providing social, physical, and spiritual support for the patient and family, but also provides an important link to the palliative care specialist.

Case 3
Kurt is a 5-year-old boy who presents to the clinic with fever, fussiness, and decreased activity for 2 weeks. Kurt has lost 2.2 lb (1 kg) since his last visit 4 months ago. On physical examination Kurt is febrile (102.7°F [39.3°C]) and tachycardic. He appears pale and listless. He has bilateral cervical lymphadenopathy, abdominal distention with some tenderness, and petechiae on his extremities. Kurt refuses to stand and starts crying. The CBC count shows a WBC count of 3000/μL (3×10³/L), with an absolute neutrophil count of 800/μL (0.80×10³/L), a hemoglobin level of 6 g/dL (60 g/L), and a platelet count of 13×10⁹/μL (0.013×10⁹/L).

The constellation of pancytopenia, fever, and weight loss raises a concern for a malignancy involving the bone marrow. Because a neuroblastoma commonly metastasizes to the bone marrow, it can present similarly to acute leukemia. A word of caution regarding the abdominal examination is warranted. The presence of ascites may make it difficult to palpate the margins of an abdominal mass. The other frequent abdominal tumor in children is a Wilms tumor. Due to concern for rupture of a Wilms tumor, (17) it is recommended that the abdominal examination not entail deep palpation. In this case, it is sufficient to know that there is no concern for a surgical abdomen and that follow-up imaging to rule out an abdominal mass is needed.

A CT scan of the chest, abdomen, and pelvis shows a large right adrenal mass with widespread lymphadenopathy notably in the right iliac chain, as well as with the right inguinal lymph nodes. The spleen is enlarged. The mIBG scan shows extensive axial and appendicular skeletal uptake (Fig 2). The oncologist performs bilateral bone marrow aspirates and biopsies, which show small clusters of round blue cells, separated by a fibrillar matrix (Homer-Wright rosettes). The small round blue cells are atypical mononuclear cells with irregular nuclei, clumped chromatin, and mostly indistinct nucleoli. Molecular studies from the tumor biopsy show MYCN amplification, gain of 17q, and hypoploidy. Histopathologic review of the tumor and lymph node biopsy samples demonstrate a stroma-poor, poorly differentiated neuroblastoma.

Given the wide variance in neuroblastoma behavior, from spontaneous regression (case 1) to metastatic disease (case 3), a rational treatment plan requires risk stratification. Prognostic variables taken into account for stratification are 1) age at diagnosis, 2) stage of disease, 3) molecular alterations, and 4) histopathologic analysis of the tumor. In case 3, Kurt’s age at presentation already places him as a
high-risk case. Genetic alterations, including MYCN amplification, hypoploidy, and the presence of chromosomal alterations, are poor prognostic features. The unfavorable histologic appearance of the tissue biopsy is in concordance with these molecular findings. Given these features, Kurt's case presents as a classic example of a high-risk neuroblastoma, which will require the most aggressive therapy. A detailed discussion of staging and risk stratification of neuroblastoma is beyond the scope of this review, but a brief stratification scheme is provided in Table 2, and excellent reviews have recently been published elsewhere. (6)(18)(19)

NEUROBLASTOMA TREATMENT

A discussion of treatment for high-risk neuroblastoma encompasses all modalities currently in use for pediatric cancer, which include surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy/biological therapy.

Surgery
Surgery was the only treatment available for solid tumors, such as neuroblastomas, before radiotherapy and chemotherapy were used. Because surgery was felt to be definitive treatment, and some neuroblastomas were not able to be surgically resected at the time of diagnosis, the first chemotherapy regimens were designed with an intent to make these tumors operable. (20) Most patients with low-risk neuroblastoma, such as a child with localized disease, favorable histologic findings, nonamplification of MYCN, and age younger than 12 months, are, indeed, cured with observation or surgery, when appropriate. (21)(22) However, with high-risk neuroblastoma behavior now elucidated, surgery is an ancillary part of the multimodal treatment. For example, after chemotherapy results in shrinking of the tumor, a second-look surgery is often performed for resection of the tumor. Of note, in a patient with MYCN amplification, micrometastases precipitate local recurrence and distant relapse, thereby making surgery alone insufficient for these patients.

Radiotherapy
A neuroblastoma is sensitive to radiotherapy, which has been used in combination with chemotherapy in many earlier neuroblastoma treatment plans. (23) However, radiotherapy carries a risk of late effects, including diabetes mellitus (24) and decreased height potential. (25) More importantly, radiotherapy carries an increased risk of secondary malignancy in

Figure 2. Anterior (A) and posterior (B) I-123 metaiodobenzylguanidine whole body views show abnormal uptake in the bilateral humeri, femurs, and axial skeleton, including the calvarium. There is also uptake in the right upper quadrant consistent with a known neuroblastoma tumor.
neuroblastoma survivors. (26) This has led to stem cell preparative regimens, which avoid total body irradiation by giving larger doses of chemotherapy. Given the discovery of intermediate-risk neuroblastoma being cured with chemotherapy and/or surgery alone, radiotherapy now is mostly reserved for high-risk neuroblastoma. (27)

**Chemotherapy**

Chemotherapy remains essential for patients with intermediate- and high-risk neuroblastoma. As with most cancers, to reduce the risk of selecting out cancer populations that become resistant to a single drug, multiagent regimens are used. Common chemotherapeutic agents considered include cyclophosphamide or ifosamide, cisplatin or carboplatin, vincristine, doxorubicin or adriamycin, etoposide, topotecan, and busulfan. The length of treatment has been reduced, and more moderate chemotherapy can be used for intermediate-risk patients. (28) Higher-dose chemotherapy with increased risk of toxicity is prescribed for children with high-risk neuroblastomas. The advent of stem cell transplant has enabled further intensification of chemotherapy for high-risk patients.

**Autologous Stem Cell Transplant**

Stem cell rescue is accomplished with the patient’s own peripheral blood stem cells, infused after a preparative regimen that suppresses the bone marrow. The myeloablative regimen continues to evolve, with variations involving the chemotherapeutic agents used, the number of sequential transplants performed, and perhaps most important for long-term adverse effects, whether radiation is used. In randomized controlled trials, autologous stem cell transplant decreases the risk of relapse by approximately 10%. (27)(29)

**Immunotherapy**

Fifty percent of children treated for high-risk neuroblastomas, despite achieving initial remission, will relapse. (30) To this end, a maintenance phase was developed involving isotretinoin, anti-GD2 antibody therapy, and cytokines, including granulocyte-macrophage colony-stimulating factor (sargramostim) and interleukin-2 (IL-2). Most familiar to pediatricians in its use for severe acne, isotretinoin is a vitamin A derivative. Also known as 13-cis-retinoic acid, isotretinoin acts on neuroblastomas by decreasing tumor cell proliferation and causing differentiation into nonmalignant cells. The attractive aspects of this drug are its ease of administration (given orally) and its relative tolerability. In fact, it can be given for an extended period, even for years. (31) In randomized controlled trials, isotretinoin alone reduces relapse risk at least by 10%, presumably by reducing minimal residual disease, an index used to describe the lowest residual disease burden after chemotherapy that is compatible with a cure, in addition to being used to define relapse.

Given its tolerability, isotretinoin can be combined with more intense maintenance therapy, namely, anti-GD2 antibody therapy. GD2 is one of the few disialoganglioside...
antigens expressed by most high-risk neuroblastoma cells. (32) The chimeric monoclonal antibody ch14.18 targets the GD2 protein, killing residual neuroblastoma cells via antibody-dependent immune activity. (33) This immune activity is augmented by giving the patient injections of granulocyte-macrophage colony-stimulating factor and by coupling the GD2 antibody with an infusion of IL-2. Given that GD2 is also expressed by peripheral nerve fibers, aggressive pain control is required during its infusion. In addition, the patient must be monitored during the infusion for capillary leak syndrome, which is a severe adverse effect of IL-2. Despite its severe potential adverse effects, the addition of anti-GD2 antibody and IL-2 to isotretinoin has reduced early relapse by approximately 20%, earning its place as part of the current standard therapy for high-risk neuroblastomas.

CONCLUSIONS

Neuroblastoma is a complex disease with diversity of presentation, clinical course, and treatment. Few other diseases may be treated with either intense multimodality treatment or mere observation. When signs and symptoms are recognized early, the pediatrician can help improve outcomes by making a timely referral to the oncologist. Although low-risk groups are highly likely to be cured, the pursuit to improve outcomes for high-risk patients continues. Despite multimodality therapy, cure rates for children with high-risk neuroblastomas remain approximately 50%. More research is needed to delineate treatment targets and new modalities of therapy.

ACKNOWLEDGMENT

We are indebted to the patients and families treated at Riley Children’s Hospital.

Summary

- On the basis of strong evidence, (2) a neuroblastoma is the most common extracranial solid tumor that requires multifaceted treatment, including observation, surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy.
- Based on strong evidence, (10) neuroblastoma is mostly due to somatic mutations that cause abnormal growth of neural crest cells of the adrenal medulla and sympathetic ganglia.
- On the basis of consensus, pediatricians play a pivotal role in the diagnosis of neuroblastoma. A high index of suspicion is required given the wide spectrum of clinical presentation by neuroblastoma. Neuroblastoma should be considered in children with findings of abnormal breathing, especially when associated with Hirschsprung disease, an abdominal mass, ambulating difficulties, bowel/bladder dysfunction, fever, malaise, bone pain, or abnormal skin findings.
- Based on strong evidence, (6) increased urinary catecholamine levels are highly sensitive for detecting a neuroblastoma, and further evaluation, including laboratory, radiographic, and histologic analyses, are necessary to confirm the diagnosis of a neuroblastoma and to guide medical therapy.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/4/194.supplemental.

Clinical Presentation, Evaluation and Management of Neuroblastoma

Richa Sharma, MD, Jesse Mcc, MD,
Jwai Lion, DO, MPH, Terry A. Vi, MD

References for this article are at http://pedsinreview.aappublications.org/content/39/4/194.
1. A 15-month-old girl presents to your office with a 3-week history of pain in both legs and refusing to stand, intermittent fever, and bruising. She has a decreased appetite and has lost 3 lb (1.4 kg) in the past 2 to 3 weeks. Vital signs show a temperature of 100.9°F (38.3°C), a pulse of 135 beats/min, a respiratory rate of 20 breaths/min, and blood pressure of 100/52 mm Hg. Physical examination shows an ill-appearing girl with scattered ecchymoses of the extremities and around the eyes. An abdominal mass is palpated in the right flank. Abdominal ultrasonography shows the right kidney to be displaced downward by a suprarenal mass. Which of the following is the most likely diagnosis in this patient?
   A. Hepatoblastoma.
   B. Lymphoma.
   C. Neuroblastoma.
   D. Ovarian germ cell tumor.
   E. Wilms tumor.

2. Further evaluation with I-123 metaiodobenzylguanidine (mIBG) scan shows enhancement of the right suprarenal mass with an enhancing mass in the central portion of the abdomen. Multiple areas of osseous uptake are seen in the arms, legs, vertebral bodies, and skull. Which of the following biomarkers is most likely to be elevated in this patient?
   A. Serum α-fetoprotein.
   B. Serum β-human chorionic gonadotropin.
   C. Serum carcinoembryonic antigen.
   D. Urine 5-hydroxyindole acetic acid.
   E. Urine vanillylmandelic acid (VMA).

3. The child is taken for biopsy of the abdominal mass and bone marrow aspirate and biopsy. Pathology shows neuroblastoma. Which of the following gene amplifications is most associated with neuroblastoma and is associated with aggressive tumor phenotype and poor prognosis?
   A. BRAF.
   B. BCR-ABL.
   C. MDR1.
   D. MYCN.
   E. P53.

4. A 1-week-old full-term infant is brought to your office for follow-up evaluation. He was found on prenatal ultrasonography to have an abdominal mass in the left suprarenal region. At the time of birth, a magnetic resonance image (MRI) of the abdomen showed a 2.5-cm mass in the left adrenal gland with no other abnormalities seen. An mIBG scan performed while he was in the nursery showed enhancement of the left adrenal mass but no other abnormal enhancement. A complete blood cell count and a comprehensive metabolic panel were normal. Urine for homovanillic acid (HVA) and VMA obtained in the nursery are reviewed and found to be elevated. Which of the following is the most appropriate next step in the management of this infant?
   A. Immunotherapy with anti-GD2 antibody.
   B. Isotretinoin.
   C. Observation with close follow-up.
   D. Radiotherapy to the mass.
   E. Surgical resection of the mass.
5. A 6-week-old infant presents with a 1-week history of vomiting and abdominal swelling. The mother has noted blue to purple nodules on his skin during the past few days. Physical examination shows a well-appearing infant with a temperature of 98°F (36.7°C), a pulse of 110 beats/min, and a respiratory rate of 24 breaths/min. There are several purple, blanching nodules on the skin. The lungs are clear to auscultation. The abdomen is protuberant, with the liver palpated 3 cm below the costal margin. He is moving all extremities. A complete blood cell count shows a white blood cell count of 2,500/μL (2.5 × 10⁹/L), a hemoglobin level of 9 g/dL (90 g/L), and a platelet count of 110,000/μL, with 30% neutrophils, 65% lymphocytes, and 5% monocytes. An MRI with contrast of the abdomen shows a 3-cm mass in the right adrenal gland and an enlarged liver with numerous enhancing nodules. An mIBG scan shows disease localized to the liver and right adrenal gland but without bony involvement. Urine for VMA and HVA showed elevated levels. A biopsy of the skin lesion confirms the diagnosis of neuroblastoma. MYCN and chromosomes 1p and 11q are normal. Which of the following represents the stage of neuroblastoma in this infant?

A. L1.
B. L2.
C. Metastatic.
D. Metastatic special.
E. Not enough clinical information to assign a stage.
Clinical Presentation, Evaluation, and Management of Neuroblastoma
Richa Sharma, Jesse Mer, Alex Lion and Terry A. Vik
Pediatrics in Review 2018;39;194
DOI: 10.1542/pir.2017-0087

| Updated Information & Services | including high resolution figures, can be found at: http://pedsinreview.aappublications.org/content/39/4/194 |
| References | This article cites 33 articles, 10 of which you can access for free at: http://pedsinreview.aappublications.org/content/39/4/194#BIBL |
| Subspecialty Collections | This article, along with others on similar topics, appears in the following collection(s):  
Medical Education  
http://classic.pedsinreview.aappublications.org/cgi/collection/medical_education_sub  
Journal CME  
http://classic.pedsinreview.aappublications.org/cgi/collection/journal_cme  
Hematology/Oncology  
http://classic.pedsinreview.aappublications.org/cgi/collection/hematology:oncology_sub  
Cancer/Neoplastic  
http://classic.pedsinreview.aappublications.org/cgi/collection/cancer:neoplastic_sub |
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://classic.pedsinreview.aappublications.org/site/misc/Permissions.xhtml |
| Reprints | Information about ordering reprints can be found online: http://classic.pedsinreview.aappublications.org/site/misc/reprints.xhtml |
Clinical Presentation, Evaluation, and Management of Neuroblastoma
Richa Sharma, Jesse Mer, Alex Lion and Terry A. Vik

Pediatrics in Review 2018;39;194
DOI: 10.1542/pir.2017-0087

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/39/4/194