Abdominal Masses in Children: Neuroblastoma, Wilms tumor, and Other Considerations

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Abdominal Masses in Children: Neuroblastoma, Wilms tumor, and Other Considerations

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The questions below should help focus the reading of this article.

1. What conditions can produce abdominal masses as initial manifestations in infants and children?

2. How does the likelihood of each condition vary with age?

3. What clinical features support the diagnosis of neuroblastoma?

4. What clinical features support the diagnosis of Wilms tumor?

5. In preparation for referral for therapy or definitive diagnosis of infants or children suspected of having abdominal malignancy, what diagnostic procedures are appropriately carried out by the primary physician?

6. How have changes in therapy affected the prognosis of neuroblastoma or Wilms tumor?

EDUCATIONAL OBJECTIVES

4. The pediatrician should have an appropriate understanding of the inheritance pattern of unilateral and bilateral Wilms tumors. (Recent Advances, 90/91)

25. The pediatrician should have knowledge to make an appropriate evaluation of a 3-year-old girl with a large right upper quadrant abdominal mass, differentiating among neuroblastoma, Wilms tumor, hepatoblastoma, hepatocellular carcinoma, rhabdomyosarcoma, hepatomegaly, mesenteric cyst, intussusception, and malrotation, and develop an appropriate plan for management. (Topics, 90/91)

The identification of an abdominal mass in a child is a cause for concern because of the possibility of malignant disease. In addition, even benign conditions can be serious and warrant prompt evaluation and treatment. Although it is imperative that a child be referred quickly to the appropriate specialist (eg, pediatric oncologist, surgeon, nephrologist, gastroenterologist, gynecologist), evaluation by the pediatrician is of great value in deciding on initial management and in making the most appropriate referral.

The evaluation of a child with an abdominal mass involves a number of diagnostic considerations, and the possibilities considered depend to some extent on the age and sex of the patient, the location of the mass, and the presence or absence of other potentially related signs and symptoms, as well as features of the physical examination. Determination of the organ or tissue of origin of the mass can narrow down the diagnostic possibilities considerably. Thus, a completion of a careful history and physical examination, baseline laboratory studies, and limited diagnostic imaging studies can provide sufficient information to determine the diagnosis or to choose the appropriate subspecialist.

Some conditions that might produce an abdominal mass in a child are listed in Table 1 and are categorized by the organ of origin. Not all of these possibilities need be considered in every patient; many can be eliminated on the basis of the age and sex of the patient, the location and type of mass, and features of the history or physical examination. The two malignant tumors in children for which an abdominal mass is a common initial manifestation are neuroblastoma and Wilms tumor (nephroblastoma); these diseases are reviewed here in some detail.

EVALUATION OF ABDOMINAL MASSES IN CHILDREN

Age

Malignant tumors are uncommon in the newborn period. Neuroblastoma and extragonadal germ cell tumors are most common, followed by hepatoblastoma and Wilms tumor. Abdominal masses in newborns are frequently of renal origin. Mesoblastic nephromas generally are not considered malignant and can usually be cured by surgical removal alone. Posterior urethral valves are manifested during the newborn period by a very large urinary bladder. Hydronephrosis secondary to distal obstruction may result in a unilateral or bilateral flank mass. A multicystic kidney also may be found at this time. Other considerations include developmental abnormalities, such as duplications or cysts of abdominal organs.

Abdominal masses are more likely to be malignant in older children than in infants. Neuroblastoma and hepatoblastomas are more common in children younger than 2 years of age, whereas Wilms tumor, hepatocellular carcinoma, rhabdomyosarcoma of the genitourinary tract, and ovarian germ cell tumors are more common in older children. Intussusception occurs most commonly between 6 months and 2 years of age, and the presence of this disorder in older patients suggests that some underlying gastrointestinal abnormality is a lead point, such as Meckel diverticulum, duplication, Henoch-Schoenlein purpura with lymphoid hyperplasia, polyps, or B-cell lymphoma. Polycystic kidneys are usually bilateral and develop during later childhood.

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TABLE 1. Differential Diagnosis of Abdominal Masses in Children

Organ	Malignant Diseases	Nonmalignant Diseases
Adrenal	Adrenal carcinoma Neuroblastoma Pheochromocytoma	Adrenal adenoma Adrenal hemorrhage
Gall bladder	Leiomyosarcoma	Choledochal cyst Gall bladder obstruction Hydrops (eg, leptospirosis
Gastrointestinal tract	Leiomyosarcoma Non-Hodgkin lymphoma	Appendiceal abscess Intestinal duplication Intussusception Malrotation Mesenteric cyst
Kidney	Lymphomatous nephromegaly Renal cell carcioma Renal neuroblastoma Wilms tumor	Hydronephrosis Multicystic kidney Polycystic kidney Mesoblastic nephroma
Liver	Hepatoblastoma Hepatocellular carcinoma Liver metastases Mesenchymoma	Focal nodular hyperplasia Hepatitis Liver abscess Storage disease
Lower genitourinary tract	Ovarian germ cell tumor Rhabdomyosarcoma of bladder Rhabdomyosarcoma of prostate	Bladder obstruction Ovarian cyst
Spleen	Acute or chronic leukemia Histiocytosis X (possibly nonmalignant) Hodgkin lymphoma Non-Hodgkin lymphoma	Congestive splenomegaly Mononucleosis Portal hypertension Storage disease
Miscellaneous	Hodgkin lymphoma Non-Hodgkin lymphoma Pelvic neuroblastoma Retroperitoneal neuroblastoma Retroperitoneal rhabdomyosarcoma Retroperitoneal germ cell tumor	Aortic aneurysm

Sex

Many malignant diseases are slightly more common in boys than in girls, including neuroblastoma and Wilms tumor. Ovarian germ cell tumors and cysts are restricted to girls, and rhabdomyosarcoma of the prostate or paratesticular area occurs only in boys. Gonadoblastoma may occur in the undescended testes of boys or of phenotypic girls with testicular feminization.

Location

Masses of the right upper quadrant are frequently of hepatic origin but may also represent an enlarged gall bladder (hydrops), tumors of the right kidney (eg, Wilms tumor) or adrenal gland (eg, neuroblastoma), as well as other retroperitoneal masses (eg, adrenal hemorrhage in the newborn). A tumor of the left upper quadrant may be an enlarged spleen, but an enlarged left kidney or adrenal mass must also be considered. Tumors of the right lower quadrant may represent lymphoma of the ileocecal area, or ovarian tumors in a girl. Except for ovarian tumors, left lower quadrant masses are uncommon. An upper midline mass may be caused by air or fluid in the lesser omental bursa, a retroperitoneal tumor, or intussusception, whereas a lower midline mass is likely to be caused by a distended urinary bladder or pelvic neuroblastoma.

History

Abdominal distension with watery diarrhea is a common initial manifestation of a vasoactive intestinal peptide-secreting neuroblastoma (described below). Also, opsoclonus-myoclonus syndrome is associated with this tumor. Hematuria indicates a lesion of the genitourinary tract, and up to 25% of patients with Wilms tumor will have this history. Oliguria suggests either renal failure or distal genitourinary obstruction. A long history of abdominal distension throughout several months or years is more consistent with a benign process, whereas rapid increase in abdominal girth is suggestive of a malignant process, such as B-cell lymphoma or neuroblastoma. A history of cramping, abdominal pain, and vomiting suggests a lesion of the gastrointestinal tract, such as intussusception or volvulus.

Physical Findings

Patients with periorbital ecchymosis or proptosis are likely to have metastatic neuroblastoma. Subcutaneous nodules and hepatomegaly represent a special pattern of disseminated disease that is more likely to occur in infants and is generally associated with a good outcome. Patients with aniridia and an abdominal mass are likely to have Wilms tumor. However, patients with hemihypertrophy or the Beckwith-Wiedemann syndrome may have Wilms tumor, hepatoblastoma, or adrenocortical carcinoma. Children with features of Cushing syndrome may have an adrenal adenoma or adrenocortical carcinoma. Fever would suggest an abscess or infectious process such as hepatitis, mononucleosis (splenomegaly), or leptospirosis (hydrops of the gall bladder).

A detailed discussion of the diagnostic considerations resulting in an abdominal mass in a child is beyond the scope of this review. However, because neuroblastoma and Wilms tumor are the two most common ma-

lignant tumors manifested by an abdominal mass in the first decade of life, the natural history, current management, and future prospects of these two tumors will be reviewed in detail.

NEUROBLASTOMA

Neuroblastoma, a tumor of postganglionic sympathetic neurons, is probably the most fascinating and enigmatic of childhood neoplasms from both a clinical and biologic viewpoint. This tumor has more varied clinical manifestations of primary or metastatic disease, including several paraneoplastic syndromes, than any other tumor. Neuroblastomas may regress or mature spontaneously in some patients, yet grow relentlessly in others. Recent progress has been made in identifying specific genetic and biologic features associated with neuroblastoma that have diagnostic and prognostic value.

General Features

Neuroblastoma is the most common extracranial solid tumor in children, accounting for 8% to 10% of all childhood cancers. The prevalence is about 1 case per 10 000 live births, and there are more than 500 cases of neuroblastoma diagnosed per year in the United States. The tumor is more common in whites than in blacks, and it is more common in boys than in girls (sex ratio of 1.2 to 1, respectively). The median age at diagnosis of children with neuroblastoma is 22 months. Thirty-seven percent of patients are less than 1 year of age, 81% are less than 4 years of age, and 97% are diagnosed by 10 years of age.

The etiology of neuroblastoma is unknown in most cases, but it is unlikely that environmental exposures play a major role. There have been a few reports of neuroblastoma associated with the fetal hydantoin, phenobarbital, or alcohol syndromes, suggesting that prenatal exposure to these substances may increase the risk of neuroblastoma. However, this association has not been confirmed. Indeed, the relatively uniform incidence of neuroblastoma worldwide suggests that industrial or other environmental exposures associated with developed countries have not had a significant impact on the incidence of this disease.

Genetic Factors

A subset of patients with neuroblastoma exhibit a predisposition to develop this disease, which follows an autosomal dominant pattern of inheritance. There have been a number of reports of familial neuroblastoma, as well as bilateral or multifocal disease, consistent with hereditary predisposition. Although the proportion of cases with a family history is probably no more than 1%, it is estimated that as many as 20% of all neuroblastomas could be the result of a germinal mutation, and these individuals could pass on this predisposition to their offspring. No constitutional predisposition syndrome nor associated congenital anomalies have yet been identified for neuroblastoma. Several cases of constitutional chromosome abnormalities detected by banding have been reported in patients who have neuroblastoma, but no consistent pattern has emerged.

Clinical Manifestations

Neuroblastomas are tumors of sympathetic nervous tissue, and the majority of tumors originate in the adrenal medulla, along the sympathetic chain, or in other sympathetic ganglia. Half of these tumors originate in the adrenal glands and an additional 30% occur below the diaphragm in pelvic or visceral ganglia, paraganglia, or the organ of Zuckerkandel. About 15% to 20% originate in cervical or thoracic sites, and occasionally a primary site cannot be found. There are a myriad of clinical symptoms, manifestations, and complications of patients who have neuroblastoma, perhaps more than with any other pediatric cancer (Table 2). Some initial complaints relate to pain, mass, or organ dysfunction of the primary tumor, whereas others are due to metastatic disease or to paraneoplastic syndromes associated with neuroblastoma.

Primary Tumors. Neuroblastomas most commonly originate in the abdomen, and the usual complaint on initial examination is abdominal pain or mass (Fig 1). Anorexia, vomiting, or abdominal tenderness may also occur. Tumors originating in pelvic ganglia may cause mechanical difficulty with defecation or urination. Paraspinal tumors in the abdomen or chest may invade the spinal canal through neural foramina (Fig 2). This may lead to back pain or paraplegia, whereas lower neural compression may lead to retention or incontinence of stool or urine.

Primary thoracic tumors are associated with dysphagia or dyspnea, and predisposition to respiratory infections. Tumors affecting the superior stellate or cervical ganglion can result in Horner syndrome (unilateral ptosis, miosis, and anhidrosis). Con-

TABLE 2. Initial Signs and Symptoms of Neuroblastoma*

Primary tumor	Abdominal mass or pain; respiratory distress or dysphagia; cord paralysis; bowel or bladder dysfunction; Horner syndrome or heterochromia of iris on affected side; incidental finding on chest radiograph
Metastatic disease	Hepatomegaly; lymphadenopathy; bone pain; periorbital ecchymoses; subcutaneous nodules; bone marrow replacement with anemia, fever, or bruising; systemic illness; failure to thrive; fever of unknown origin
Paraneoplastic syndromes	Vasoactive intestinal peptide syndrome (chronic watery diarrhea and distension), opsoclonus-myoclonus or cerebellar ataxia syndrome, or excessive catecholamine syndrome (hypertension, headaches, flushing, sweating, tachycardia, palpitations)

* Modified from Brodeur GM. Neuroblastoma and other tumors of the peripheral nervous system. In: Fernbach DJ, Fietti TJ, eds. *Clinical Pediatric Oncology*. 4th ed. St. Louis, MO: CV Mosby; 1990. In press.

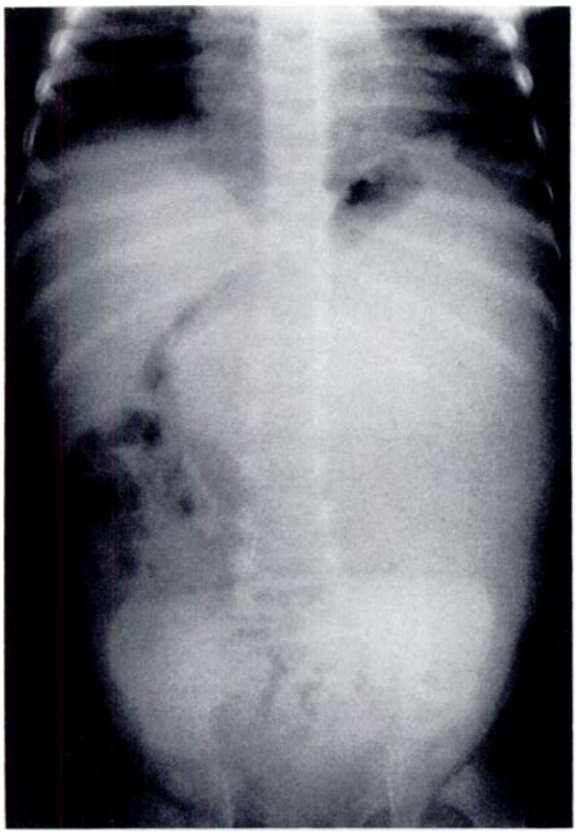

Fig 1. Plain abdominal radiograph of a 1-year-old boy who has neuroblastoma. Initially, abdominal mass was detected while the asymptomatic patient was bathing. This radiograph shows displacement of stomach bubble medially. Virtually all hollow viscera have been displaced to right side of peritoneal cavity by a large mass in left retroperitoneal space. The skeleton is normal radiographically.

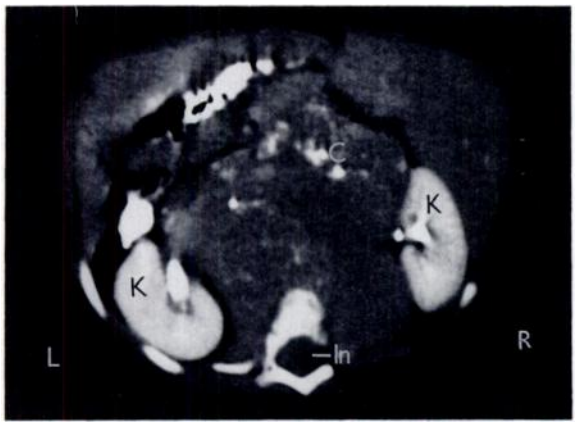

Fig 2. Computed tomography of abdomen of a 9-month-old girl who has neuroblastoma. Large retroperitoneal midline mass is displacing both kidneys (K) laterally, and hollow viscera are displaced anteriorly and laterally. Tumor has many discrete areas of dense calcification (C) and is invading right side of spinal canal (In).

genital tumors in this site may cause heterochromia of the iris with decreased pigmentation of the iris on the affected side. Occasionally, tumors in the neck may be palpable. Finally, some thoracic tumors may be identified incidentally when a chest radiograph is obtained for unrelated reasons.

Metastatic Disease. Neuroblastomas metastasize to regional and distant lymph nodes, cortical bone, bone marrow, liver, skin, and other sites. Unlike many solid tumors, neuroblastomas rarely metastasize to the lungs, except as a terminal event. Involvement of the central nervous system is usually by direct extension of skull metastases, but meningeal and parenchymal brain metastases have been described. Some patients may have vague systemic symptoms such as failure to thrive or fever of unknown origin.

The most common distant lymph nodes involved are the left supraclavicular, cervical, and inguinal nodes. Cortical bone involvement is common in patients who have metastatic disease and may produce localized or generalized bone pain. Neuroblastoma has a propensity to involve the bones of the skull and orbit, and the most characteristic findings are periorbital ecchymosis and proptosis (unilateral or bilateral), as well as other masses of the skull or jaw. Liver involvement can lead to massive hepatomegaly and abdominal distension. Skin involvement, which is usually restricted to infants with stage 4S (Table 3), can appear as multiple subcutaneous nodules that may have a bluish hue.

Bone marrow involvement may be minimal and asymptomatic, or it may be extensive with generalized pain and evidence of bone marrow failure (anemia, thrombocytopenic purpura and petechiae, or leukopenia with infection and fever). Neuroblastoma cells in the bone marrow may appear as dispersed, single cells that are undifferentiated and nondescript, but they appear more commonly as clumps or syncytia of cells. It may be difficult to identify minimal bone marrow involvement without the aid of immunocytology, but such involvement should not be symptomatic. Bone marrow review requires careful examination of multiple smears as well as adequate specimens from several sites.

Paraneoplastic Syndromes. About 1% to 5% of patients with neuroblastoma will have hypertension, which can result from lateral displacement of the kidney by an adrenal or paraspinal primary tumor, with stretching of the renal artery and stimulation of the renin-angiotensin system. Alternatively, patients may have episodes of flushing and hypertension due to release of catechol-

TABLE 3. International Staging System for Neuroblastoma*

Stage 1	Localized tumor confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage 2A	Unilateral tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage 2B	Unilateral tumor with complete or incomplete gross excision; positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically
Stage 3	Tumor infiltrating across the midline with or without regional lymph node involvement, or unilateral tumor with contralateral regional lymph node involvement, or midline tumor with bilateral regional lymph node involvement
Stage 4	Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver and/or other organs (except as defined in Stage 4S)
Stage 4S	Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin and/or bone marrow

* Modified from Brodeur GM, Seeger RC, and twenty-four other contributors. International criteria for diagnosis, staging and response to treatment in patients with neuroblastoma. *J Clin Oncol.* 1988;6:1874–1881.

amines from the tumor, but this appears to be rare. Neuroblastomas are also known to produce vasoactive intestinal peptide, which causes abdominal distension and watery diarrhea. This is known as the vasoactive intestinal peptide syndrome. In general, tumors that produce vasoactive intestinal peptide are ganglioneuroblastomas or ganglioneuromas, and the outcome is almost uniformly good. Neurologists may be the first to see patients with the opsoclonus-myoclonus syndrome, which consists of myoclonic jerks and chaotic conjugate eye movements. Progressive cerebellar ataxia and other neurologic or neuromuscular syndromes have also been described. These syndromes are due neither to direct involvement of the central nervous system by tumor nor to the production of catecholamines. Although the mechanism is unclear, they usually resolve after the tumor is removed.

Differential Diagnosis of Neuroblastoma

Neuroblastoma cells are small, round, and blue with conventional stains. The tumor generally originates in the adrenal medulla or sympathetic chain during childhood. An agreement on criteria for a diagnosis of neuroblastoma has been reached by an international group of conferees representing most of the major pediatric oncology groups in the world. These conferees and corresponding participants agreed that a diagnosis of neuroblastoma is established if: (1) an unequivocal pathologic diagnosis is made from tumor tissue by standard methods, including electron microscopy if necessary; or (2) bone marrow contains unequivocal tumor cells (eg, syncytia) and urine contains increased urinary catecholamine metabolites (vanillylmandelic acid or homovanillic acid >3 SD more than the mean per milligram of creatinine, adjusted for age). Both the vanillylmandelic acid and homovanillic acid should be measured, usually by a sensitive high-pressure liquid chromatography or gas chromatography method. Calculation of the amount per milligram of creatinine, corrected for age, makes a timed collection unnecessary and avoids potential false negatives due to dilute urine.

Owing to the many potential clinical manifestations, a neuroblastoma may be confused with a variety of other neoplasms as well as non-neoplastic conditions. This is a particular problem regarding the 5% to 10% of tumors that do not produce catecholamines, as well as those that do not have an obvious primary tumor. Alternatively, neuroblastoma should be considered in the differential diagnosis of a variety of non-neoplastic conditions with similar initial symptoms. Clinically, patients with disseminated bone disease may resemble those who have systemic infections or inflammatory diseases, such as osteomyelitis or rheumatoid arthritis. The vasoactive intestinal peptide syndrome can be confused with infectious or inflammatory bowel disease, and the opsoclonus-myoclonus and ataxia syndromes can resemble primary neurologic disease. Neuroblastoma may be confused with calcified adrenal gland(s) following adrenal hemorrhage, and the diagnosis of cystic or storage diseases must be considered for patients with hepatomegaly.

Histologically, neuroblastoma tissue may be quite undifferentiated and, because of its appearance as a "small, round, blue-cell tumor," it may be confused with other cancers, both in terms of the primary tumor and metastases to other sites such as bone marrow or lymph nodes. Other primary abdominal tumors in the chest and abdomen must be considered, such as rhabdomyosarcoma, Ewing sarcoma, peripheral neuroepithelioma, germ cell tumors with neural differentiation, and lymphoma. Differential diagnosis of metastatic disease involving the bone marrow must include rhabdomyosarcoma, Ewing sarcoma, lymphoma, and leukemia. A battery of monoclonal antibodies is being developed that should allow diagnosis of these various disease entities to be made with greater objectivity and confidence.

Diagnostic Imaging Studies. The most appropriate initial studies to be performed on a pediatric patient who has an abdominal mass are abdominal ultrasonography and chest radiography. A plain radiograph of the abdomen may reveal some useful information, such as calcification characteristics of a neuroblastoma, but it is usually not diagnostic. Abdominal ultrasonography usually can distinguish whether the mass originates in the adrenal or paraspinal area, as opposed to an intrinsic renal mass. However, a small percentage of neuroblastomas do originate in the kidney. The chest radiograph can identify lymph node metastases or additional primary tumors in the posterior mediastinum. Pulmonary metastases

are seen rarely in patients with neuroblastoma.

Diagnostic imaging studies likely to be done at a referral center are computed tomography of the chest and abdomen, a bone scan or skeletal survey, and a bone marrow aspiration or biopsy. These studies are best done at the referral center because they may have to be repeated there, and awaiting results of initial studies may delay the referral of the patient for a definitive evaluation and surgery.

Pathology. Currently, tumors that are classified with neuroblastoma include ganglioneuroblastoma and ganglioneuroma. Although each of these histologic types may be viewed as a discrete entity, together they represent a continuum of differentiation ranging from neuroblastoma, through ganglioneuroblastoma, to ganglioneuroma. Ganglioneuroblastomas may be predominantly immature or mature, and the areas of maturation may be focal or diffuse. Whereas there is a general trend to associate the more differentiated tumors with more localized disease or a better prognosis, this association is not absolute. As a rule, if a substantial proportion of the tumor is composed of immature elements, the tumor generally behaves as a neuroblastoma. Neuroblastoma cells in the bone marrow may appear as dispersed, single cells that are undifferentiated and nondescript, so that they may be difficult to recognize. They also appear as clumps or syncytia of cells, sometimes with surrounding neurofilamentous material. On rare occasions, the tumor cells form structures resembling the Homer-Wright pseudorosettes seen in tissue sections.

Catecholamine Metabolism. Because neuroblastomas are tumors of postganglionic sympathetic neurons, they should have an adrenergic neurotransmitter phenotype. The fact that 90% to 95% of tumors produce catecholamines provides a tremendous diagnostic advantage, because these compounds or their metabolites can be measured in serum or urine. Not only does the excretion of catecholamine metabolites provide an advantage in confirming the diagnosis of neuroblastoma, but it may also be used to follow-up disease activity in those patients whose tumors do secrete. Catecholamine precursors are converted primarily to homovanillic acid, whereas norepinephrine and epinephrine are converted primarily to vanillylmandelic acid. Most laboratories involved in diagnosis of neuroblastoma measure both urinary vanillylmandelic acid and homovanillic acid and normalize per milligram of creatinine, corrected for age, which obviates the need for timed collections. Although a vanillylmandelic acid "spot" test is helpful if it is positive, the likelihood of false positives and false negatives is too great for it to be a reliable indicator.

Staging

Clinical staging of neuroblastoma is outlined in Table 3. The distribution of patients by stage or extent of disease differs, depending on the age at diagnosis. For instance, in a consecutive series of 1001 patients enrolled on Pediatric Oncology Group protocols during the past 8 years and staged by the Group's staging system, only 43% (158/369) of patients less than 1 year of age had advanced stages of disease (C and D), whereas 78% (493/632) of older patients had advanced stages of disease. In addition, all 70 patients with stage D-S (4S) were infants. These findings explain, in part, the generally better outcome for infants who have neuroblastoma, compared to their older counterparts, but they do not account fully for the difference.

Until recently, there were several different staging systems used for neuroblastoma throughout the world. In general, the various staging systems gave comparable results in distinguishing low-stage, good-prognosis patients from high-stage, poor-prognosis patients. However, some of the differences between the staging systems were substantial, particularly as applied to individual patients, so the results of one group could not readily be compared with another.

International Neuroblastoma Staging System. The recently proposed International Neuroblastoma Staging System is based on clinical, radiographic, and surgical evaluation of children with neuroblastoma. This staging system utilizes the most important components of previous systems. To distinguish the International Neuroblastoma Staging System from previous systems, Arabic numbers are used rather than Roman numerals or letters of the alphabet. The outline of the staging system is presented in Table 3; the details and rationale for this staging system have been presented in detail elsewhere (Brodeur et al. *J Clin Oncol.* 1988;6:1874–1881).

Biologic Studies. A great deal of progress has been made in the past 10 to 15 years in understanding human neuroblastoma at a biologic level. Indeed, a variety of biologic studies have been done on serum or tumor tissue of patients with neuroblastoma that have some diagnostic or prognostic value. Serum levels of ferritin, neuron-specific enolase, G_{D2}, and lactate dehydrogenase can assist in making a diagnosis of neuroblastoma or in observing disease activity. In addition, serum ferritin and lactate dehydrogenase levels can have prognostic value for subsets of affected patients. Assessments of tumor tissue include tumor karyotype, DNA index, and N-*myc* copy number. These latter studies have been shown to have significant value in predicting response to particular treatment regimens or in predicting outcome. For instance, tumors with a high DNA index respond well to cyclophosphamide and doxorubicin, and tumors with N-*myc* amplification are almost always associated with rapid tumor progression and short survival.

Treatment

The primary modalities of conventional therapy include surgery, radiation therapy, and chemotherapy. Because of the propensity of this disease to have become disseminated at the time of diagnosis or to metastasize subsequently, most children require chemotherapy for a realistic chance of cure. The caveat to this general principle is that occasional patients (especially infants) with limited dissemination, as seen in stage 4S (Table 3), may have spontaneous regression or differentiation of their tumors. It is likely that a composite of

clinical and biologic markers may allow patients with a particularly good or bad prognosis to be identified and the most appropriate therapy to be selected.

Spontaneous Regression or Differentiation. A great deal has been written concerning the ability of neuroblastomas to regress or mature spontaneously. Although the frequency of this occurrence is difficult to establish because many patients undergo some form of therapy (such as removal of the primary tumor, low doses of irradiation, or short courses of "mild" chemotherapy), the actual incidence of regression overall is probably no more than 5% to 10%, and the majority of these patients are infants. Because more than half of the patients with neuroblastoma eventually die of their disease, a diagnosis of neuroblastoma should not be taken casually. In selected patients, such as infants with stage 4S disease and favorable biologic markers, initial observation may be reasonable. However, these patients should be observed very closely, because they can get into difficulty very quickly, especially from massive abdominal enlargements with respiratory compromise.

Surgical Intervention. In most cases, surgical intervention is necessary to verify the diagnosis of neuroblastoma and to distinguish this tumor from other malignant or benign conditions. Patients with localized disease, who have their tumor removed completely or who have only microscopic residual disease, have an excellent change of cure without further therapy. In some cases, surgery is for diagnostic purposes only, whereas in others it may serve more of a palliative role, such as surgical removal of a tumor that is compressing other vital organs or structures, causing pain or organ dysfunction. Because primary tumors may be unresectable initially, it is now common practice to delay surgery or to perform "second-look" surgery. This approach can help assess the response to initial treatment, as well as assist in decisions regarding subsequent management. Finally, the surgical placement of central venous catheters has become common practice, greatly facilitating the treatment of patients requiring intensive chemotherapy.

Radiation Therapy. Radiation therapy has a relatively limited role in the overall management of individuals who have a neuroblastoma because of the high frequency of metastatic disease. Indications for radiation therapy include: (1) control of localized tumors that cannot be excised and that do not respond completely to chemotherapy; (2) palliative treatment of unresectable masses causing pain or organ dysfunction; and (3) the "treatment" stage of 4S neuroblastoma (Table 3). The last category relates to the observation that this unusual clinical syndrome of 4S neuroblastoma sometimes responds to doses of radiation that generally are considered subtherapeutic (eg, 400 to 800 cGy) and are delivered to ports that do not encompass all known disease.

Chemotherapy. Chemotherapy is the mainstay of treatment for neuroblastoma, because this tumor is frequently widespread at the time of diagnosis or may recur in metastatic sites. A variety of single agents produce responses in patients with neuroblastoma, but only a subset produce a substantial frequency of meaningful responses, such as partial or complete responses in conventional doses in more than 25% of individuals. These include cyclophosphamide, doxorubicin, platinum analogs, epipopophyllotoxins, and vincristine. Pairs and combinations of these drugs have been developed that are more effective than the single agents alone. The most effective of these pairs include cyclophosphamide plus doxorubicin, or cisplatin plus a form of epipopophyllotoxin. The schedules for administering the two pairs of drugs have a cytokinetic rationale and, indeed, have proven very effective in producing responses. However, although improvement in the survival of infants with advanced stages of disease has been noted, none of these regimens has had a significant impact on the older child with advanced disease. A more recent tendency has been to use two or more of the drugs in continuous infusions or in higher doses, because there are a limited number of effective agents and a limited duration of responses in patients with advanced disease treated with conventional doses.

Bone Marrow Transplantation. Some of the current regimens are so intensive that bone marrow toxicity is the dose-limiting toxicity, and this can be overcome by autologous or allogeneic bone marrow transplantation. Indeed, bone marrow transplantation is a useful approach in patients with a poor long-term prognosis who have achieved complete or very good partial remission with chemotherapy. Some preparative regimens use conventional approaches similar to those used for patients with acute leukemia (cyclophosphamide and total body irradiation). However, others include either high-dose melphalan or chemotherapeutic agents known to be effective in neuroblastoma (such as ciplatin and epipopophyllotoxins in much higher doses). Autologous bone marrow transplantation can be tried, especially in patients who do not have an acceptable sibling donor. However, rigorous efforts must be made to eradicate or "purge" tumor cells from the bone marrow before reinfusion.

Novel Approaches to Treatment. Two approaches have been used to target delivery of therapeutic agents to the tumor cells in patients with neuroblastoma. These include the use of: (1) monoclonal antibodies, which recognize epitopes that are relatively specific for neuroblastoma cells (such as (G_{D2}); and (2) radioactively labeled drugs that are taken up preferentially by cells that produce adrenergic neurotransmitters (such as meta-iodobenzylguanidine). There are problems with both of these approaches, so currently they are used only after conventional approaches have failed. An exciting, but still very preliminary, approach to the treatment of neuroblastoma is the induction of differentiation. This approach is particularly attractive because some neuroblastomas mature (with or without treatment) into benign ganglioneuromas, and neuroblastoma cells in culture can be induced to differentiate with a variety of agents. Not all neuroblastomas may be capable of undergoing differentiation, but certain subsets of patients or clinical situations are likely candidates for

initial attempts with such agents as retinoic acid or nerve growth factor.

Prognosis of Neuroblastoma

Clinical Variables. The most important clinical variables in determining the prognosis for an individual who has a neuroblastoma are the clinical stage of disease, the age of the patient at diagnosis, the site of the primary tumor, and the histology of the tumor. The overall cure rate of infants with low stages of disease for recovery is between 85% and 90%, whereas older patients with advanced stages of disease have a progression-free survival rate of 15% to 30%. The prognosis for infants younger than 1 year of age is substantially better than older patients with the same stage of disease, particularly those with more advanced stages of disease. Patients with primary tumors in the adrenal gland or with less differentiated histology appear to do worse than others, but this does not appear to add substantially to the prognostic variables of age and stage.

Biologic Variables. Ferritin levels are rarely elevated in patients with low stages of disease, whereas up to half of patients with advanced stages have significant elevations (>142 ng/mL) and a much worse progression-free survival rate ($P < .001$). Survival is substantially worse in patients with serum neuron-specific enolase levels greater than 100 ng/mL ($P < .01$). Increased lactate dehydrogenase levels are more common in patients with extensive or progressive disease, and levels of greater than 1500 IU/L have been strongly associated with a poor prognosis in infants with neuroblastoma. Tumor cells with a "hyperdiploid" karyotype (or increased DNA content) are more likely to have lower stages of disease and to respond to cyclophosphamide and doxorubicin, whereas those with a "diploid" DNA content are more likely to have advanced stages of disease and not to respond to this combination. The presence of N-*myc* amplification in tumor cells is found predominantly in patients with advanced stages of disease, but N-*myc* amplification is associated with rapid tumor progression and a poor prognosis, regardless of clinical stage. Finally, there appears to be a strong correlation between a chromosome 1p deletion and poor survival.

Future Prospects

There is a variety of areas in which improvement in the treatment of patients with neuroblastoma may come in the near future. These include: (1) the identification of individuals with a genetic predisposition to develop this disease; (2) general population screening approaches for early detection and treatment; (3) better biologic and immunologic characterization of tumors for classification and prognostication; (4) the identification of new markers, in addition to urinary catecholamine metabolites, to follow tumor response to treatment; and (5) improvements in treatment, including therapy to induce differentiation, targeted drug delivery, tumor-specific agents, and immunotherapy with monoclonal antibodies and biologic response modifiers. The mandate for the future is to translate promising biologic studies into clinical applications and to continue to look for new insights into mechanisms of neuroblastoma transformation and progression that can be used to clinical advantage.

WILMS TUMOR

Wilms tumor (nephroblastoma) is a tumor of the developing kidney and is the second most common malignant solid tumor in children (next to neuroblastoma). Recent genetic studies have led to the identification of at least two chromosomal loci associated with the predisposition to develop Wilms tumor. In addition, there has been tremendous success in improving the outcome for children with this disease due to advances in surgery, radiation therapy, and chemotherapy. Subsets of individuals whose tumors have "unfavorable" history can be identified and treated more intensively. Alternatively, patients with localized tumors of favorable histology now are being treated less aggressively to reduce the acute toxicity and long-term sequelae of therapy.

General Features

Wilms tumor accounts for about 7% of childhood cancers and is the most common renal cancer in children. The incidence of Wilms tumor is 7 per million children younger than 15 years of age per year, resulting in a prevalence of about 1 child in 12 000 live births. The incidence is so similar throughout the world that Wilms tumor is used as an index cancer by which the incidence of other cancers can be compared. The lack of substantial geographic or racial variation suggests that there is a balance between basic genetic and environmental factors. This further suggests that the influence of various environmental factors in industrial nations or underdeveloped countries is limited. Wilms tumor also is considered a prototype for the success of cancer chemotherapy, because the survival rates have improved from less than 30% to almost 90% since the advent of modern chemotherapy. It is rare in children younger than 6 months of age or older than 10 years of age, although there are reports of Wilms tumors in adults.

Genetics

There are a number of families demonstrating an autosomal dominant pattern of inheritance of the predisposition to develop Wilms tumor, with somewhat variable penetrance. However, the sudden appearance of Wilms tumor in several members of a family without cases of this tumor in preceding generations is somewhat difficult to explain. At least two constitutional chromosome abnormalities have been associated with the development of Wilms tumor. The first is the aniridia association, sometimes associated with genitourinary anomalies (such as cryptorchidism and hypospadias) and mental retardation, which is seen in patients with constitutional deletion of chromosome 11p13. The second abnormality is the Wilms association with the Beckwith-Wiedemann syndrome (or possibly with hemihypertrophy), which is associated with rearrangement of chromosome 11p15. The latter locus is also associated with the development of hepatoblastoma, adrenocortical

carcinoma, and embryonal rhabdomyosarcoma.

These important findings have been made more exciting by the recent report that a suppressor gene, which may represent the predisposition locus, has been cloned from the 11p13 locus. However, the significance of this finding is hard to explain because of the recent observation by two independent groups that familial Wilms tumor in the absence of the associations described above is not linked to the short arm of chromosome 11. The ultimate elucidation of this increasingly complex genetic condition must await additional studies but will have importance for the genetic counseling of individuals with bilateral, multifocal, or familial disease.

Clinical Presentation

The initial examination of patients with Wilms tumor is somewhat more straightforward than for neuroblastoma. Many children have an asymptomatic abdominal mass, first identified by the parent while bathing the child or by the pediatrician on routine physical examination (Fig 3). One third of patients will have intermittent abdominal pain that may be exacerbated by a fall or abdominal trauma. Gross or microscopic hematuria is found in up to 25% of patients but is usually not painful unless clots are passed. Hypertension also is present in about 25% of patients. This may be due to renin secreted by the tumor or to renovascular hypertension from displacement of the kidney or renal artery by tumor growth. Finally, fever malaise or other systemic symptoms may occur, especially in patients with bleeding into the tumor and associated anemia. Although pulmonary or other metastases may be present at the time of diagnosis, they are rarely an initial finding in patients who have Wilms tumor.

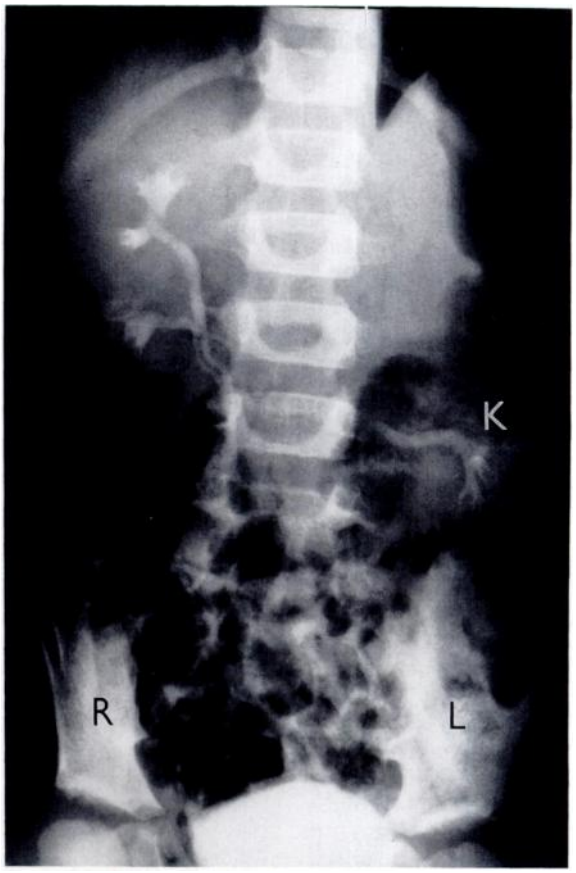

Fig 3. Plain abdominal radiograph of a 5-year-old boy who has Wilms tumor. Gross hematuria and left flank pain after a fall prompted patient to seek medical care. Clinical examination revealed bulging left flank mass. Intravenous urogram shows left renal collecting system (K) displaced downward. Upper pole shows no secretion.

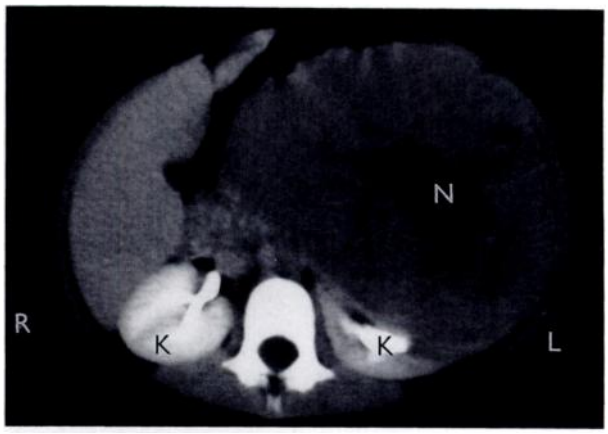

Fig 4. Computed tomography of the abdomen of a 5-year-old boy who has Wilms tumor. There is almost complete obliteration of the upper pole of the left kidney (K) by a large mass, apparently originating from this site. The mass has a large area of decreased attenuation, probably representing necrosis (N) in its center.

Diagnosis

A diagnosis of Wilms tumor is suspected in a child with an apparently intrarenal mass. Frequently, the tumor is quite large at the time of diagnosis, with replacement of most if not all of the involved kidney (Fig 4). About 5% of the time, a Wilms tumor is bilateral, but usually one kidney is more involved than the other. The diagnosis of Wilms tumor is based on examination of the primary tumor with the finding of a consistent histologic pattern.

The principal consideration in the differential diagnosis of an abdominal mass in a child, in addition to Wilms

tumor, is neuroblastoma. This distinction generally can be made by distinguishing between a primary renal and extrarenal tumor. However, because a small percentage of neuroblastomas do originate in the kidney, histologic tests ultimately will be required. Other conditions that may mimic unilateral or bilateral renal enlargement are nephroblastomatosis, mesoblastic nephroma, and involvement of the kidney by non-Hodgkin lymphoma. Mesoblastic nephroma is limited to babies younger than 6 months of age and is invariably benign. Clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, and renal cell carcinoma are less common diagnostic considerations.

Diagnostic Imaging Studies. The most appropriate initial studies to be performed on a pediatric patient who has an abdominal mass is abdominal ultrasonography and chest radiography. A plain radiograph of the abdomen may provide some useful information, such as rim calcification, which is suggestive but not diagnostic. Abdominal ultrasonography usually can distinguish whether the mass is intrarenal or extrarenal, unilateral or bilateral, unifocal or multifocal, or solid or cystic. It can also show the presence or absence of: (1) a tumor in the renal vein or inferior vena cava, (2) abdominal lymph node involvement, or (3) liver metastases. The chest radiograph can identify pulmonary metastases, which are found at the time of diagnosis in approximately 10% of patients who have Wilms tumor, but rarely in patients who have neuroblastoma. The diagnostic imaging study likely to be done at a referral center is computed tomography of the chest and abdomen. A bone scan and skeletal survey are likely not to be required unless an unfavorable histology of the tumor is identified. These studies are best done by the referral center to avoid delay in referral of the patient for definitive management.

Pathology. The gross primary tumor is frequently confined to the kidney by the renal capsule and Geroda fascia, even when pulmonary metastases are present. Although most of the affected kidney is usually replaced, a small portion or rim of normal renal tissue may be evident. Gross calcification is not common, but, when it is seen, it is usually secondary to hemorrhage and has a "rim-ring" appearance. Cysts may be found and are occasionally large, but much of the tumor is solid. The classic histology is triphasic, with blastemal, epithelial and stromal elements. There is frequently evidence of tubular and glomerular formation. The tumor may be simply biphasic, with blastemal and stromal tissue. Together these histologic patterns constitute 90% of the tumors seen and represent the "favorable" histology.

The remaining 10% of Wilms tumors have anaplastic or unfavorable histologic findings. In addition, clear cell sarcoma of the kidney and rhabdoid tumor of the kidney may cause symptoms identical to those of a typical Wilms tumor. However, these histologies are associated with a much worse prognosis and are generally distinguishable from Wilms tumor. Clear cell sarcoma of the kidney frequently metastasizes to bone and brain, and this tumor is more responsive to doxorubicin. Rhabdoid tumor of the kidney characteristically is found in very young infants or children and is associated with pulmonary metastases as well as separate primary neuroectodermal tumors of the brain.

Other histologic patterns include nodular renal blastema and nephroblastomatosis. Both of these patterns are considered precursors to Wilms tumor and are seen predominantly in individuals with multifocal or bilateral primary tumors, who are considered generally to have genetic predisposition to the development of Wilms tumor.

Staging

Staging of Wilms tumor is dependent on whether or not the primary tumor is confined to the renal capsule, the presence or absence of abdominal lymph node involvement, rupture of the tumor before or during surgery, and hematogenous dissemination to distant sites, such as liver, lung, bone, or brain. The staging system used by the National Wilms Tumor Study is presented in Table 4. This staging system has prognostic significance, especially for patients with favorable histology. Although patients with unfavorable histology are also staged in a similar way, their prognosis is worse, so treatment must be aggressive.

Treatment

Treatment generally consists of a combination of surgery and chemotherapy, but the choice of chemotherapeutic agents and duration of therapy depend on the extent of disease.

Surgical Intervention. Surgical resection of the primary tumor is important for both diagnosis and treatment. Resection generally involves removal of the involved kidney, evaluation and biopsy of the opposite kidney, and evaluation of possible tumor extension, lymph node involvement, or liver metastases. If the tumor cannot be completely removed primarily, it sometimes can be re-

TABLE 4. Clinicopathologic Staging of Wilms Tumor Utilized by the National Wilms Tumor Study Group

Stage I	Tumor limited to the kidney and completely excised; no invasion through the renal capsule, no rupture of the tumor at surgery, and no distant spread.
Stage II	Tumor extended beyond the kidney, but is excised completely. Extension may be through the capsule and into perirenal soft tissue, or infiltration of vessels outside the kidney. There may be local spillage of tumor localized to the flank.
Stage III	Residual nonhematogenous dissemination of tumor confined to the abdomen. This may include tumor beyond the surgical margins of resection, abdominal lymph node involvement, tumor spillage, or peritoneal implants.
Stage IV	Hematogenous dissemination of tumor to liver, lung, bone, brain or other sites; or distant lymph node dissemination.
Stage V	Bilateral renal involvement at diagnosis.

moved in a delayed or "second-look" procedure.

Radiation Therapy. With the advent of effective chemotherapeutic agents, radiation therapy has taken a secondary role in the treatment of Wilms tumor. Currently, it is not used in the treatment of patients with stage I or II disease and favorable histology. Its role in stage III disease with favorable histology is still being tested, but it appears that a dose of 1000 cGy delivered to the tumor bed is adequate to provide the beneficial effects of radiation seen in this group of patients. Radiation therapy to the lungs was evaluated in the past for patients with pulmonary metastases, but it is not current practice.

Chemotherapy. Vincristine and actinomycin-D are the mainstays of therapy for Wilms tumor, although doxorubicin is useful for patients with advanced stages of disease. A series of studies have been undertaken by the National Wilms Tumor Study, and the current study is the fourth in this series. In this study, patients with stages I and II disease with favorable histology are treated for 3 to 5 months with vincristine and actinomycin-D, and the major differences in the treatment regimens consist of differences in the drug delivery schedule. Differences in drug delivery schedule are also part of the treatment regimens for the more advanced stages, although these regimens are more intensive than for lower stages and they involve the use of doxorubicin.

Prognosis

The most impressive advancement in the treatment of any solid tumor has been seen in the case of Wilms tumor. More than 85% of patients can be cured (that is, have a 5-year disease-free survival, with minimal chance of recurrence) with current approaches. Thus, future approaches are beginning to focus on decreasing the toxicity of treatment by eliminating doses of drugs, duration of therapy, and the use of radiation. Currently, the 2-year survival of children with favorable histology is 98% for stage I, 95% for stage II, 90% for stage III, and 80% for stage IV. The prognosis for unfavorable histology of any stage is a survival rate of about 80%.

Future Prospects

With the availability of effective chemotherapeutic agents to treat most patients with Wilms tumor, the focus of future studies will be to decrease toxicity. On the other hand, more effective approaches must be developed for patients with advanced disease and unfavorable histology. Recent progress in understanding the development of Wilms tumor and mapping predisposition loci promises to provide new approaches to identify individuals at increased risk for developing this tumor. Although the genetic basis of Wilms tumor appears to be more complex than that seen for retinoblastoma, molecular genetic approaches are likely to begin to have clinical applications within the next 5 to 10 years. Such approaches may provide insight into malignant transformation and provide ways to classify tumors or predict prognosis more objectively. In addition, they may identify critical genetic pathways on which future therapeutic approaches may be focused.

CONCLUSION

Any abdominal organ or tissue is capable of developing into a mass. The spectrum of affliction includes dilated hollow viscera, inflammatory masses, and cystic or solid tumors (malignant or benign). The keys to the most favorable outcome lie in prompt diagnosis and skillful management with the choice of an appropriate therapeutic regimen.

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Self-Evaluation Quiz

1. Among the following conditions producing abdominal masses in infants, which is *least* typical with respect to the age of the patient?

A. Multicystic kidney in a newborn.
B. Wilms tumor in a 3-month-old infant.
C. Neuroblastoma in a 1-year-old child.
D. Intussusception in a 9-month-old infant.
E. Posterior urethral valves in a 1-month-old infant.

2. Of the following, which finding is *least* likely to be associated with neuroblastoma?

A. Diarrhea.
B. Opsoclonus.
C. Hematuria.
D. Abdominal calcification.
E. Proptosis.

Abdominal Masses in Children: Neuroblastoma, Wilms tumor, and Other Considerations

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