

PediatricsⁱⁿReview[®]

Wilms Tumor

Gregory J. Aune

Pediatrics in Review 2008;29;142

DOI: 10.1542/pir.29-4-142

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/29/4/142>

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2008 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



can be confounded by either NTM exposure or a history of BCG vaccination.

Routine screening for TB no longer is recommended. In a population in which the prevalence of TB is low, positive TSTs are more likely to represent false-positive results than true infection. However, children always should be tested if active disease is suspected, and in certain identifiable groups, the prevalence of disease is high enough that a TST is recommended. Such groups include contacts of individuals who have confirmed or suspected active TB; children who have clinical or radiographic findings suggestive of TB; and children emigrating from coun-

tries where TB is endemic, who visit these countries frequently, or who have frequent visitors from these countries. In addition, a TST should be performed in all children who will begin immunosuppressive therapy. Children infected with HIV and those who are incarcerated should have an annual TST. A positive TST result in a child or adolescent should be regarded as a marker for active disease within that community and should serve as a call to investigate contacts and to find and treat cases of latent TB infection.

Comment: In the 1990s, TB with multidrug resistance to isoniazid and ri-

fampin, the first-line drugs of choice, became a worldwide threat. Recently, the threat has become even more ominous, with the emergence of TB resistant to many second-line agents in addition to isoniazid and rifampin in at least 17 countries, including the US. The public health threat posed by extensively drug-resistant TB is a challenge to our ability to diagnose infection efficiently, determine drug susceptibility rapidly, and initiate appropriate monitored treatment.

Henry M. Adam, MD
Editor, *In Brief*

In Brief

Wilms Tumor

Gregory J. Aune, MD, PhD
Johns Hopkins Hospital
Baltimore, MD

Author Disclosure

Drs Aune and Serwint did not disclose any financial relationships relevant to this In Brief.

An X Chromosome Gene, *WTX*, Is Commonly Inactivated in Wilms Tumor.

Rivera MN, Kim WJ, Wells J, et al. *Science*. 2007;315:642–645

Current Therapy for Wilms Tumor.

Metzger ML, Dome JS. *Oncogene*. 2005;10:815–826

Renal Tumors. Dome JS, Perlman EJ, Ritchey ML, Coppes MJ, Kalapurakal J, Grundy PE. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2006:905–932

In 1899, surgeon Max Wilms published a report of seven children suffering from malignant tumors arising from renal parenchyma. Nephroblastoma now is recognized as the most common malignant renal tumor of childhood and is known more commonly as Wilms tumor. From 1975 to 1995, Wilms tumor was estimated to account for 6% of childhood cancers in the United States, with an approximate annual incidence of 500 cases. The incidence is slightly higher in females, with a male-to-female ratio of 0.92:1.00 for unilateral disease and 0.60:1.00 for bilateral disease.

Most children who have Wilms tumor are brought to their doctors when a parent or caregiver notices an abdominal mass when bathing or dressing the child. Hypertension is a frequent physical finding at diagnosis, occurring in approximately 25% of cases. The elevated blood pressure is believed to be caused by increased renin activity.

Other common findings at diagnosis include abdominal pain, gross hematuria, anemia, and fever.

In a small percentage of cases, Wilms tumor occurs as one component of the congenital syndromes WAGR and Denys-Drash. WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) results from a germline deletion in chromosome 11p. Mutations in the *WT1* gene, located within the same region of chromosome 11p, result in Denys-Drash syndrome, which is characterized by the presence of Wilms tumor, pseudohermaphroditism, and renal disease (most commonly nephrotic syndrome or glomerulonephritis). Hemihypertrophy is another congenital anomaly seen frequently in those who have Wilms tumor and may be an isolated finding or occur as part of other overgrowth conditions, including Beckwith-Wiedemann, Perlman, and Simpson-Golabi-Behmel syndromes. Other congenital anomalies as-

sociated with Wilms tumor are aniridia and genitourinary abnormalities, sometimes as components of a syndrome.

The genetics of Wilms tumor are more complex than originally proposed by Alfred Knudson, when he included the tumor along with retinoblastoma as the prototypes for his now famous "two-hit" hypothesis. Numerous genetic events are known to contribute to the formation of Wilms tumors and are associated with chromosome 11p (affected in WAGR and Denys-Drash syndromes) as well as multiple other loci. These loci include: 1) the first identified Wilms tumor gene, *WT1* at 11p13, which occurs in 5% to 10% of cases; 2) several candidate genes at 11p15, also known as the second Wilms tumor locus, *WT2*; 3) two familial Wilms tumor loci, *FWT1* and *FWT2*, located at 17q and 19q, respectively; and 4) alterations of p53 on chromosome 17p, which have been described frequently in anaplastic Wilms tumors.

Recently, a new Wilms tumor gene has been found on the X chromosome and is named *WTX*. In contrast to autosomal recessive tumor-suppressor genes, *WTX* is inactivated by a single hit to the only X chromosome in tumors from males and the active X chromosome in tumors from females. Such a monoallelic inactivation contradicts Knudson's two-hit hypothesis. The mechanism had been proposed previously in association with possible X chromosome tumor suppressor genes, but such genes had never been found to

exist. The discovery of this gene and its action adds yet another dimension to the complex genetics of Wilms tumors.

Treatment for Wilms tumor is determined by weighing a child's individual risk for recurrence and using individualized multimodal therapy, including radiation, surgical resection, and combination chemotherapy. Patients who have bilateral or anaplastic Wilms tumor are stratified to receive more aggressive therapy. The key components of all combination chemotherapy regimens used in the treatment of Wilms tumor are dactinomycin, vincristine, and doxorubicin. The treatment of recurrent Wilms tumor employs additional agents, including cyclophosphamide, ifosfamide, cisplatin, carboplatin, and etoposide. Newer agents under investigation include the topoisomerase I inhibitor topotecan (currently in phase II trials) and antiangiogenesis agents such as bevacizumab, an antibody directed against vascular endothelial growth factor (anti-VEGF).

Between 85% and 90% of children diagnosed with Wilms tumor are cured and enter the ranks of long-term survivors. Nevertheless, many clinical challenges remain. The identification of biologic prognostic indicators will help to stratify patients to lower risk groups who could receive less toxic therapy. Similarly, the addition of novel agents such as topotecan and anti-VEGF may add benefit without increasing acute toxicities and long-term adverse effects. Finally, the discovery of the new

WTX tumor suppressor gene provides the groundwork for a more meaningful understanding of the complex genetics of Wilms tumors, but more importantly, represents a new biologic pathway that could be targeted for therapy.

Comment: The improved prognosis for patients who have Wilms tumor is a great example of the power of multisite clinical trials in researching and identifying the best available therapies to provide the highest quality of care to patients. Interesting differences in treatment philosophies exist between the United States National Wilms Tumor Study Group, whose members advocate initial biopsy and tumor resection followed by chemotherapy, compared with the International Society of Pediatric Oncology, whose members advocate early chemotherapy followed by biopsy and resection once therapy has been initiated. Both approaches have resulted in excellent outcomes, but continued research is needed to clarify the advantages of each approach. Understanding the genetics behind Wilms tumor and future genome mapping may add tremendously to decision making in providing individualized therapy to patients and balancing the most effective treatments with the least toxicity.

Janet R. Serwint, MD
Consulting Editor

Wilms Tumor
Gregory J. Aune
Pediatrics in Review 2008;29;142
DOI: 10.1542/pir.29-4-142

Updated Information & Services

including high resolution figures, can be found at:
<http://pedsinreview.aappublications.org/content/29/4/142>

References

This article cites 2 articles, 1 of which you can access for free at:
<http://pedsinreview.aappublications.org/content/29/4/142#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Renal Disorders
http://pedsinreview.aappublications.org/cgi/collection/renal_disorders
Hematology/Oncology
http://pedsinreview.aappublications.org/cgi/collection/hematology:oncology_sub
Blood Disorders
http://pedsinreview.aappublications.org/cgi/collection/blood_disorders_sub
Nephrology
http://pedsinreview.aappublications.org/cgi/collection/nephrology_sub
Disorders of Blood/Neoplasms
http://pedsinreview.aappublications.org/cgi/collection/disorders_of_blood_neoplasms

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
</site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
</site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

