

Wilms Tumor Screening Is Unnecessary in Klippel-Trenaunay Syndrome

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ABSTRACT. *Background.* Children with hemihypertrophy are screened for Wilms tumor, because this condition is a risk factor for developing the neoplasm. Patients with Klippel-Trenaunay syndrome (KTS) are often considered potential candidates for Wilms tumor, because they have unilateral overgrowth of the lower limb. In our experience, however, an association between KTS and Wilms tumor has not been observed.

Methods. To determine whether KTS and Wilms tumor are associated, we reviewed our institutional experience for patients with both diagnoses and searched the Klippel-Trenaunay literature for patients with Wilms tumor. The National Wilms Tumor Study Group database also was studied to identify patients with KTS. Two-sided exact binomial tests were used to evaluate whether patients with 1 condition had an increased risk for the other. Ninety-five percent confidence intervals for these 2 risks were compared with the general population risks of Wilms tumor (1 in 10 000) and KTS (1 in 47 313).

Results. None of the 115 patients with KTS followed at our institution developed Wilms tumor. One case of Wilms tumor has been reported in 1363 patients with KTS in the literature, giving a confidence interval of (1/57 377) and (1/267). None of the 8614 patients in the National Wilms Tumor Study Group database had KTS, giving a confidence interval of (0, 1/2336). Because the risks of KTS and Wilms tumor in the population fall within these confidence intervals, one cannot conclude that the risks of KTS among Wilms tumor patients or Wilms tumor among KTS patients are any different from the corresponding risks in the general population.

Conclusions. Patients with KTS are not at increased risk for developing Wilms tumor and thus should not undergo routine ultrasonographic screening. *Pediatrics* 2004;113:e326–e329. URL: <http://www.pediatrics.org/cgi/content/full/113/4/e326>; *Klippel-Trenaunay syndrome, Wilms tumor, screening.*

ABBREVIATIONS. KTS, Klippel-Trenaunay syndrome; PWS, Parkes Weber syndrome; BWS, Beckwith-Wiedemann syndrome; NWTSG, National Wilms Tumor Study Group.

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Klippel-Trenaunay syndrome (KTS) is an eponym denoting a slow-flow, capillary-lymphatic-venous malformation in association with soft-tissue and/or skeletal overgrowth.¹ The syndrome was described first in 1900 and characterized by the classic triad of capillary malformation, venous varicosities, and limb hypertrophy.² KTS affects the lower extremity in 95% of patients, the upper extremity in 5% of patients, and least commonly the trunk.³ The capillary malformation is usually located over the lateral side of the extremity or trunk.¹ Superficial varicosities result from incompetent valves and deep venous anomalies. Various forms of lymphatic anomalies including lymphedema and macrocysts are present in 50% of affected individuals.¹ Limb overgrowth is obvious at birth, and hypertrophy may worsen during childhood. In contrast, Parkes Weber syndrome (PWS) is defined as a fast-flow lesion consisting of an arteriovenous, capillary, and venous malformation in association with limb hypertrophy.^{1,4,5}

Wilms tumor is a malignant embryonal neoplasm of the kidney that occurs in association with many congenital anomalies, including hemihypertrophy of the limbs.⁶ Hemihypertrophy is a known risk factor for Wilms tumor alone or as part of several overgrowth disorders including Beckwith-Wiedemann syndrome (BWS), Perlman syndrome, and Sotos syndrome.⁷ Children with isolated hemihypertrophy or BWS have a 3% to 5% risk of developing Wilms tumor.^{7,8} In addition, it is estimated that patients with Sotos or Perlman syndrome have a 3.9% and 36% risk of Wilms tumor, respectively.⁸

Because hemihypertrophy is a component of KTS and a known risk factor for Wilms tumor, many patients with KTS referred to our vascular anomalies center have had ultrasonographic screening for Wilms tumor. Because our center has not appreciated an association between Wilms tumor and KTS, we reviewed our experience with KTS and searched the KTS literature to determine whether Wilms tumor had been reported in patients with KTS. We also investigated the National Wilms Tumor Study Group (NWTSG) database to inquire whether KTS had been cited in patients with Wilms tumor.

METHODS

Patient Groups

We retrospectively reviewed the records of the 115 patients with KTS and 14 patients with PWS evaluated in the Vascular Anomalies Center at Children's Hospital Boston (Boston, MA) between 1999 and 2003. Specifically, records were examined for a

possible diagnosis of Wilms tumor. After reviewing our experience with KTS, an analysis of previously published reports of KTS between 1966 and 2003 was performed by using PubMed. All studies involving >3 KTS patients were reviewed further for evidence of Wilms tumor among the KTS patients presented in the articles.

After searching the literature for KTS patients with evidence of Wilms tumor, the NWTSG database was reviewed, looking for cases of KTS between 1969 and 2003. The database of patients with Wilms tumor was queried first for associated anomalies. The second database of anomalies then was reviewed for diagnoses of KTS. Records of patients diagnosed with KTS were obtained through the NWTSG to verify the diagnosis.

Statistical Analysis

A 2-sided exact binomial test was used to test whether patients with KTS have an increased risk of Wilms tumor, compared with the general population. Ninety-five percent confidence intervals were calculated to determine whether the incidence of Wilms tumor in patients with KTS was different from the incidence for each in the general population.

Estimates for the incidence of KTS and Wilms tumor in the population were obtained from the literature. The risk of Wilms tumor in the population is ~1 in 10 000 births, with almost 80% diagnosed by 5 years of age.^{9,10} The incidence of KTS, which is usually diagnosed at birth or shortly thereafter, has been documented in 3 different studies. Consequently, we tested the risk of KTS in each of the 3 populations, 1 in 14 430,¹¹ 1 in 27 472,¹² and 1 in 100 038,¹³ as well as their average, 1 in 47 313, in our analysis.

RESULTS

None of the 115 patients with KTS or the 14 patients with PWS in our Vascular Anomalies Center had Wilms tumor. The average age of the KTS and PWS patients was 14.3 years. The review of KTS literature revealed 8 independent studies of >3 KTS patients.^{14–21} Although anomalies associated with KTS were reported, no case of Wilms tumor was cited in the 1362 KTS patients described in the studies.

However, we found 2 possible case reports of Wilms tumor in patients with KTS in the literature.^{22,23} The first patient was described as having “unilateral hypertrophy of the left ear, tonsil, labium majus, and lower extremity (especially the third toe), cutaneous hemangiomas on the trunk, subcutaneous hemangioma of the left thigh, hyperpigmentation at the right neck and arm,” which is consistent with Proteus syndrome and not KTS.²³ The second patient had KTS and bilateral nephroblastomatosis, a precursor to Wilms tumor.²² Although this patient also may have had Proteus syndrome, magnetic resonance imaging is not available for diagnostic confirmation. Consequently, we cannot rule out KTS and thus we conservatively estimated 1 case of Wilms tumor in the search of 1478 patients with KTS.

The 95% confidence interval for the 1 case report in the literature from our series (115 patients) as well as the review of the literature (1362 patients) was (1/58 377; 1/267). Because the incidence of Wilms tumor in the population (1 in 10 000) is within this confidence interval, the risk of Wilms tumor in patients with KTS is not different from the risk of Wilms tumor in the general population ($P = .28$).

After searching patients with KTS for Wilms tumor, we investigated patients with Wilms tumor for an associated diagnosis of KTS. Of 5589 congenital anomalies found in the 8614 patients in the NWTSG

database, 289 patients had isolated hemihypertrophy, 2 patients were designated as having KTS, and 1 patient was diagnosed with Klippel-Trenaunay-Weber syndrome.

The records of the patients diagnosed with Wilms tumor and KTS were obtained through the NWTSG to confirm the diagnosis of KTS. Two of the patients had a common infantile hemangioma located on a hypertrophied leg that regressed and thus were misdiagnosed with KTS. The third patient, who had a capillary malformation and hypertrophy of the lower extremity, also did not have KTS, because he lacked venous or lymphatic malformations. Thus, none of the 8614 patients with Wilms tumor also had KTS.

The 95% confidence interval for the absence of KTS in the Wilms population (0 in 8164) was (0, 1/2336). The published risks of KTS in the general population (1 in 14 430, 1 in 27 472, and 1 in 100 038) and their average (1 in 47 313) all lie within the confidence interval. Thus, the incidence of KTS in the Wilms tumor population is not different from the estimated risks of KTS in the general population ($P = 1.0$).

DISCUSSION

Screening patients with BWS or isolated hemihypertrophy for Wilms tumor is presently advocated.⁸ Patients with BWS or idiopathic hemihypertrophy are known to have a 3% to 5% risk of developing Wilms tumor.^{8,24} Screening these patients has decreased the risk of presenting with late-stage disease.²⁵ Wilms screening for the hemihypertrophy-associated syndromes (Sotos and Perlman) also is performed.²⁴ Current screening recommendations include a baseline computed tomographic scan and renal ultrasonography every 3 months until 7 years of age, followed by physical examination every 6 months until adulthood.²⁴

Although screening for Wilms tumor has proved to be beneficial for patients with isolated or syndromic hemihypertrophy, these imaging studies are expensive and time consuming. In addition, screening can give false-positive findings, resulting in unnecessary operative exploration.²⁵ Consequently, Wilms tumor screening only should be performed in patients with clear risk factors. Because overgrowth is a component of KTS, patients with this syndrome are often screened for Wilms tumor. Although some authors consider KTS to be a risk factor for Wilms tumor,^{7,26} others do not consider KTS and Wilms tumor to be significantly associated.²⁷

The incidence of Wilms tumor in North America, Europe, and Australia is estimated to be ~1 in 10 000. Patients enrolled in the NWTSG are examined carefully, and all associated anomalies are recorded. Consequently, the diagnosis of KTS in this population is unlikely to be underreported. In fact, we found that KTS was overdiagnosed and that 3 patients originally listed as having KTS had other anomalies.

In the review of KTS patients, cases of Wilms tumor may not have been mentioned or may not have developed yet, although the early onset of both conditions make this less likely. In addition, the single patient reported to have KTS and Wilms tumor

may have been misdiagnosed, as occurred with the 3 patients in the NWTSG database. Specifically, this patient may have had Proteus syndrome and not KTS. Thus, it is possible that there are no patients in the literature or the NWTSG database with Wilms tumor and KTS.

Even with the most conservative estimates, the likelihood of Wilms tumor and KTS in the same patient is very small. Wilms screening is advocated currently for predisposing factors that carry a 3% risk, or screening 33 patients for every positive case of Wilms tumor. The risk of a Wilms patient having nonsyndromic hemihypertrophy from the NWTSG database was 3.4% (289 in 8614). Although the rate of isolated hemihypertrophy (1 in 86 000)²⁸ is similar to the risk of KTS in the population, a Wilms patient is at least 289 times more likely to have hemihypertrophy than KTS.

Wilms tumor was not found in any patients with PWS. The diagnosis of PWS is often confused with KTS. In addition, patients with either disorder are commonly mislabeled as having Klippel-Trenaunay-Weber syndrome. However, no patient in our experience, in the literature, or in the NWTSG had both PWS and Wilms tumor.

The pathogenesis of limb hypertrophy in KTS or PWS is different from that in patients with Wilms tumor. Limb hypertrophy in KTS or PWS is secondary to the vascular anomaly located on the affected limb. The lymphatic malformation associated with KTS is known to cause localized soft-tissue and skeletal hypertrophy.¹ The anomalous venous component of KTS and PWS causes venous hypertension in the affected extremity and thus enlargement. Capillary malformation, a component of KTS and PWS, also is associated with soft-tissue hypertrophy. Finally, the arteriovenous malformation associated with PWS causes increased blood flow and thus increased tissue growth as well.¹

In contrast to KTS or PWS, hemihypertrophy in patients with Wilms tumor may be due to a systemic increase in growth factors.²⁹ For example, patients with Wilms tumor have increased birth weights,²⁹ and patients with isolated hemihypertrophy have an increased risk of developing other types of cancer (5.9%).²⁸

Similar to isolated hemihypertrophy, syndromes with hemihypertrophy known to be risk factors for Wilms tumor have systemic signs of growth-factor excess as well. For example, BWS, Perlman, and Sotos syndromes have an increased risk of other malignancies.⁸ In addition, patients with BWS have macroglossia, Perlman syndrome is associated with fetal gigantism and islet cell hypertrophy, and Sotos syndrome consists of macrocephaly with advanced bone age.⁸

CONCLUSIONS

Isolated hemihypertrophy, as well as hemihypertrophy associated with BWS, Perlman, and Sotos syndromes, carries a minimum of a 3% to 5% risk of Wilms tumor. Consequently, screening 33 patients to identify 1 patient with Wilms tumor is clearly indicated. However, patients with KTS do not have an

increased risk of Wilms tumor compared with the general population. The etiology of limb hypertrophy in KTS may be secondary to the local vascular anomaly, whereas isolated hemihypertrophy and hypertrophy associated with BWS and Perlman and Sotos syndromes seem to be due to systemic factors. Consequently, we do not advocate routine Wilms tumor screening in patients with KTS.

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