Renal Failure in the Denys-Drash and Wilms’ Tumor-Aniridia Syndromes

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Abstract

Nearly 6000 patients enrolled in four clinical trials of the National Wilms’ Tumor Study Group during 1969–1995 were followed until death or for a median of 11.0 years of survival for the onset of renal failure (RF). Thirteen of 22 patients with Denys-Drash syndrome and 10 of 46 patients with the Wilms’ tumor aniridia syndrome developed RF. The cumulative risks of RF at 20 years from Wilms’ tumor diagnosis were 62% and 38%, respectively. Only 21 cases of RF were observed among 5558 patients with unilateral disease who did not have characteristic congenital genitourinary anomalies, and their risk was <1%. Although other explanations cannot be completely excluded, the high rate of RF in patients with the aniridia syndrome challenges the view that nephropathy is associated uniquely with missense mutations in the WT1 gene. It suggests the possibility of a further gradation in the spectrum of phenotypes associated with different WT1 mutations. Patients with Wilms’ tumor and aniridia or genitourinary abnormalities should be followed closely throughout life for signs of nephropathy or RF.

Introduction

Wilms’ tumor, an embryonal tumor of the kidney that affects about 1 child in every 10,000 in the United States, occasionally occurs as part of the rare WAGR syndrome (1) or DDS (2, 3) congenital malformation syndromes. Children with the WAGR syndrome invariably have a constitutional chromosomal deletion at 11p13, the location of the WT1 gene (4, 5). Those with DDS usually have a germ-line point mutation, which is predicted to result in an amino acid substitution, in the eighth or ninth exon of WT1 (6, 7). It has been suggested that the severe nephropathy associated with DDS, which frequently leads to early RF, may result from the action of altered WT1 in blocking the normal activity of the wild-type protein (8). By contrast, because of the less severe genitourinary anomalies and apparent lack of nephropathy associated with WAGR, a reduced WT1 dosage during embryogenesis is thought to have a less pronounced effect on development, especially on that of the renal system (6, 7, 9). However, exceptions to this model have been observed. Some patients with DDS have germ-line deletions predicted to result in truncated WT1 proteins, and one patient with a germ-line missense mutation in exon 9 was free of renal pathology (7). The present study was motivated by the clinical observation made by one of us (L. C. S.) of unexpected, late-occurring RF in some patients with the WAGR syndrome. This presented another potential challenge to the idea that nephropathy is associated particularly with WT1 missense mutations. The large, relatively unscreened, NWTSG patient population offered the opportunity to extend and quantify this observation by comparing rates of RF among subgroups of Wilms’ tumor patients who were followed systematically for reasonably long periods of time.

Patients and Methods

Patients. The study population consisted of 5976 patients enrolled between 1969 and 1995 at age 15 years or under in one of the first four NWTSG protocol studies. All patients had a diagnosis of Wilms’ tumor of favorable (5572) or anaplastic (404) histology according to the NWTSG Pathology Center (10). Congenital anomalies and syndromes including WAGR and DDS were ascertained from clinical records including registration forms filled out by the pediatric oncologist at the treating institution, operative notes and pathology narratives after nephrectomy, and flow sheets reporting the initial treatment. A few anomalies were ascertained from questionnaires completed by the family. Mention of aniridia on any of these records was taken to be evidence of the WAGR syndrome. Most such patients also had reports of GU anomalies or mental retardation. Whereas it should be emphasized that identification of the 46 patients with WAGR syndrome was based on clinical criteria only, all 18 of these for whom cytogenetic reports were available had a deletion or partial deletion at chromosome 11p13. A similar procedure was used for DDS, with the criterion being explicit mention of Drash syndrome or the combination of male pseudohermaphroditism or ambiguous genitalia with glomerulosclerosis or nephrotic syndrome. This syndrome was not well known during the early years of the study, and it is likely that there was some underascertainment due to failure of the institution to recognize the associated renal pathology (11). A third category of patients consisted of males with hypoplasia or cryptorchidism who were not already classified as having the WAGR syndrome or DDS. Continuing this hierarchical scheme, patients who had bilateral disease including metachronous disease in the contralateral kidney were classified in the fourth category if they did not already fall in one of the first three. The fifth and final category consisted of patients with unilateral disease and none of the congenital anomalies already mentioned. Identification of patients with congenital anomalies or syndromes was based on information available at the time of the Wilms’ tumor diagnosis or shortly thereafter. One patient with no reported anomalies at diagnosis of Wilms’ tumor developed renal pathology characterized by the institution as “Drash, nephrotic syndrome” some 20 years after Wilms’ tumor diagnosis and just 2 years before the onset of RF. This patient was not classified in the DDS subgroup, however, because the nephrotic syndrome was not evident at the time of the Wilms’ tumor diagnosis.

RF was ascertained as part of the NWTSG Late Effects Study, which also targeted second malignant neoplasms and congestive heart failure occurring in patients who were treated successfully for Wilms’ tumor. Patients were generally followed by their institutions for the first 5–10 years after the Wilms’ tumor diagnosis. Thereafter, some continued to be followed by the institution, whereas others were released for direct follow-up through the family or the adult patient by the NWTSG Data and Statistical Center. Approximately 20% of patients were lost to follow-up by 10 years, with even higher losses among certain ethnic minorities (12), but this is accounted for in the statistical analysis. The criterion for a classification of RF was explicit mention in clinical records or patient reports of chronic RF or end-stage renal disease, with repeated serum creatinine levels above 2.5 mg/dl in patients for whom this result was available. Patients with bilateral disease who had surgical removal of both kidneys because of progressive Wilms’ tumor were not counted as having had RF for purposes of this study, although they had been so counted in an earlier NWTSG report (13).

Statistical Analysis. The cumulative risk of RF was estimated using actuarial methods that account for variable follow-up times and losses to follow-up (14). The observation time for each subject was the elapsed time from Wilms’ tumor diagnosis until the earliest time of RF, death, or last follow-up report through December, 1999. Median follow-up of surviving patients was 11.0 years for the entire cohort, with a range of 10.9–12.2 years over the five subgroups. Of 5201 patients known to be alive at last contact, 1583 (30%) were followed for 15 or more years, and 598 (11%) were followed for at least 20 years.

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2 To whom requests for reprints should be addressed, at Department of Biostatistics, Mail Stop 357232, University of Washington, Seattle, WA 98195-7232.
3 The abbreviations used are: WAGR, Wilms’ tumor; aniridia, genitourinary malformation, and mental retardation; DDS, Denys-Drash syndrome; GU, genitourinary; ILNR, intralobar nephrogenic rest; NWTSG, National Wilms’ Tumor Study Group; RF, renal failure.
Results and Discussion

The cumulative risk of RF at 20 years ranged from 1–62% over the five subgroups (Table 1). Fig. 1 graphs the cumulative risk by time since diagnosis. Patients with DDS had the highest risk of early RF, but rates for those with the WAGR syndrome were higher in later years; hence, the two curves approached the same level after 25 years. The jump in the graph at time 0 for patients with DDS reflects the fact that five (23%) of these patients already had evidence of RF at the time of diagnosis of their Wilms’ tumor. One patient with the WAGR syndrome died of end-stage renal disease at the age of 27.0 years, having been diagnosed with Wilms’ tumor at age 1.2 years. However, because clinical records for the 10 years preceding death could not be accessed, the exact time of onset of RF was unknown. For purposes of the graph, onset was assumed to have occurred 20.8 years after diagnosis. An earlier onset date would have increased the estimated cumulative risk at 20 years for the WAGR group to 45%; a later onset date would have resulted in an estimated cumulative risk of 69% at 26 years. Table 2 displays key characteristics of the 14 patients with the WAGR syndrome or associated GU anomalies who developed RF. All but four had already undergone either renal dialysis or transplant by the time the data were compiled. One WAGR patient had focal glomerulosclerosis present at the time of the Wilms’ tumor diagnosis at age 6.9 years but did not develop RF until age 13.6 years. All but one of the patients with DDS who developed RF did so before 9 years of age (Table 3). In contrast, the affected patients with the WAGR syndrome ranged in age from 11.6–28.2 years (median, 14.6 years) at the time of RF. This suggests that the onset of puberty may trigger the events leading to RF in patients with the WAGR syndrome.

Eight of the 46 patients with the WAGR syndrome, including 2 of the 10 patients who developed RF, had bilateral disease at onset. The aniridia syndrome is also known to be associated with the precursor lesion known as ILNR (15). A reviewer of an earlier version of this article suggested that treatment of the remaining kidney for bilateral Wilms’ tumor or nephrogenic rests could possibly account for the high rate of RF observed in the WAGR subgroup. Whereas some such explanation cannot be entirely ruled out, it does not seem likely. Review of the available clinical records indicated that none of the patients with the aniridia syndrome were treated surgically for the presence of nephrogenic rests. All 10 patients who developed RF had disease of favorable histology. Five had stage I disease and were treated with dactinomycin and vincristine only. Three had stage II disease (one received daцитinomycin and vincristine only, one also received abdominal radiation, and one also received doxorubicin and abdominal radiation). The two patients with bilateral (stage V) disease received daicitinomycin and vincristine, and one patient also received abdominal radiation. These treatments are no different from those of the vast majority of patients who did not have characteristic anomalies or syndromes and for whom the rates of RF were substantially lower. None of the 10 patients had a relapse of their Wilms’ tumor.

The presence of ILNR in patients with unilateral disease but with no anomalies or syndromes did increase the risk of RF. Restricting attention to those diagnosed since 1980 for whom the presence of nephrogenic rests was evaluated, 5 cases of RF were observed among 593 patients who had ILNR, whereas only 3 cases of RF were observed among 2788 patients who did not have ILNR (P < 0.01). The cumulative risk of RF at 20 years from Wilms’ tumor diagnosis was 3.3% for those with ILNR and 0.7% for those without ILNR. Because loss or mutation of WT1 is associated with ILNR, this provides indirect evidence that WT1 mutations may possibly play a role in some cases of RF observed in patients who lack the associated malformation syndromes.

One of 16 female and 9 of 30 male patients with the WAGR syndrome developed RF. The difference is not statistically significant with these

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### Table 1 Incidence of RF by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>RFs</th>
<th>Percent with renal failure at 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDS</td>
<td>22</td>
<td>13</td>
<td>62.4</td>
</tr>
<tr>
<td>WAGR syndrome</td>
<td>46</td>
<td>10</td>
<td>38.3</td>
</tr>
<tr>
<td>Male GU anomalies</td>
<td>153</td>
<td>4</td>
<td>10.9</td>
</tr>
<tr>
<td>Bilateral</td>
<td>397</td>
<td>7</td>
<td>5.5</td>
</tr>
<tr>
<td>Unilateral</td>
<td>5358</td>
<td>21</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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### Table 2 Characteristics of patients with the WAGR syndrome or associated GU anomalies who developed RF

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at Wilms’ tumor (yr)</th>
<th>Congenital anomalies</th>
<th>Age at renal failure (yr)</th>
<th>Dialysis</th>
<th>Transplant</th>
<th>Laterality</th>
<th>Age at last contact (yr)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>1.2</td>
<td>AN/CR/RD</td>
<td>17–27†</td>
<td>?</td>
<td>?</td>
<td>U</td>
<td>27.0</td>
<td>Dead/ESRD</td>
</tr>
<tr>
<td>M</td>
<td>2.2</td>
<td>AN/CR/RD</td>
<td>28.2</td>
<td>No</td>
<td>No</td>
<td>U</td>
<td>29.1</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>2.0</td>
<td>HS/RD</td>
<td>21.8</td>
<td>No</td>
<td>No</td>
<td>LB</td>
<td>23.9</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>0.9</td>
<td>AN/HS</td>
<td>14.9</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
<td>24.9</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>0.6</td>
<td>CR</td>
<td>16.6</td>
<td>Yes</td>
<td>No</td>
<td>B</td>
<td>21.6</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>1.4</td>
<td>CR</td>
<td>20.1</td>
<td>No</td>
<td>Yes</td>
<td>U</td>
<td>23.6</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>1.0</td>
<td>AN/CR/HS/RD</td>
<td>17.5</td>
<td>Yes</td>
<td>Yes</td>
<td>U</td>
<td>22.9</td>
<td>Alive</td>
</tr>
<tr>
<td>F</td>
<td>2.1</td>
<td>AN/RD</td>
<td>19.0</td>
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<td>Yes</td>
<td>U</td>
<td>21.2</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
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<td>AN/CR/RD</td>
<td>12.0</td>
<td>Yes</td>
<td>No</td>
<td>U</td>
<td>12.4</td>
<td>Dead/ESRD</td>
</tr>
<tr>
<td>M</td>
<td>1.9</td>
<td>AN/CR/RD</td>
<td>14.2</td>
<td>Yes</td>
<td>Yes</td>
<td>U</td>
<td>18.4</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>5.7</td>
<td>AN</td>
<td>11.8</td>
<td>Yes</td>
<td>Yes</td>
<td>U</td>
<td>20.4</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>6.9</td>
<td>AN/CR/HS/GS</td>
<td>13.6</td>
<td>No</td>
<td>Yes</td>
<td>U</td>
<td>17.9</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>1.4</td>
<td>CR</td>
<td>13.1</td>
<td>No</td>
<td>No</td>
<td>U</td>
<td>15.0</td>
<td>Alive</td>
</tr>
<tr>
<td>M</td>
<td>1.0</td>
<td>AN/CR/HS</td>
<td>11.6</td>
<td>No</td>
<td>No</td>
<td>B</td>
<td>11.9</td>
<td>Dead/ESRD</td>
</tr>
</tbody>
</table>

† AN, aniridia; CR, cryptorchidism; HS, hypospadias; RD, retardation; GS, glomerulosclerosis.

B, bilateral at onset; LB, late bilateral; U, unilateral.

Exact age unknown; see text.

ESRD, end-stage renal disease.
small numbers ($P = 0.13$). Nonetheless, it is interesting in light of the finding that germ-line WT1 mutations in Wilms’ tumor patients occur almost exclusively among those who either DDS or male GU anomalies suggestive of an incomplete form of DDS (16). WT1 mutations are a plausible explanation for the elevated rates of RF seen here (Tables 1 and 2) for male patients with GU anomalies who did not have the aniridia or nephropathy associated with the WAGR and DDS, respectively. The four RFs that occurred among male patients with GU anomalies exceed the 1.25 RFs that would have been expected based on rates among patients without congenital anomalies or syndromes, even after adjustment for bilaterality ($P = 0.01$). These patients also received only standard treatment. Extrapolating from the results of Diller et al. (16), as many as one of four male patients with GU anomalies may carry germ-line WT1 mutations, most of which would be predicted to result in truncated protein. The fact that all four RFs observed among male patients with GU anomalies also took place after the onset of puberty, at ages ranging from 13.1–28.1 years, is consistent with the idea that a reduced WT1 dosage could be responsible for both their nephropathy and that seen in the patients with the WAG syndrome. The high rate of RF eventually observed among patients with the WAG syndrome and the presence of glomerulosclerosis at the diagnosis of Wilms’ tumor in one of them suggest that the DDS and WAG phenotypes are perhaps not so distinct as has been commonly presumed.

These results suggest the possibility of a gradation in phenotypes associated with WT1 mutations. It starts with the group of patients having GU anomalies and a moderate long-term risk of RF, progresses to the group of patients with the WAG syndrome who have more severe GU anomalies and a high long-term risk of RF, and finishes with the group of patients with DDS who have markedly distorted GU development and a high risk of early RF. Sequencing of WT1 for patients with the male GU anomalies or ILNR who develop late RF could help to sort out the correlation between genotype and phenotype. A weakness of the present report is the fact that little or no information was available regarding the renal pathology that led to end-stage renal disease. Biopsy of the renal lesions in patients enrolled in the third or fourth studies (NWTS-3 and -4). Elimination of these 10 events reduced the estimated rates of RF at 20 years from Wilms’ tumor diagnosis from 5.5% to 4.5% among those with bilateral disease and from 1.0% to 0.6% for those with unilateral disease (Table 1). Thus, the risk of RF in patients whose unilateral Wilms’ tumor does not occur as part of a known congenital syndrome or in conjunction with one of the characteristic congenital anomalies is projected to be exceptionally low, provided that they are successfully treated with modern front-line chemotherapeutic regimens.

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**References**


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