Title

Non-Surgical Management of Multicystic Dysplastic Kidney Editorial Comment

Journal

JOURNAL OF UROLOGY, 181(5)

ISSN

0022-5347

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Publication Date

2009

Peer reviewed

Does Early Treatment of Urinary Tract Infection Prevent Renal Damage?

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Pediatrics 2007; ***120:*** *e922–e928.*

Objective: Therapeutic delay has been suggested as the most important factor that is likely to have an effect on the development of scarring after acute pyelonephritis. However, this opinion has not been supported by prospective studies, so we tested it. Methods: In a prospective clinical study, we evaluated whether the time interval between the onset of the renal infection and the start of therapy correlates with the development of acute inflammatory changes and the subsequent development of renal scars, documented by dimercaptosuccinic acid scintigraphy. A total of 278 infants (153 male and 125 female) aged 0.5 to 12.0 months with their first urinary tract infection were enrolled in the study. Results: The median time between the onset of infection and the institution of therapy was 2 days (range: 1–8 days). Renal inflammatory changes were documented in 57% of the infants. Renal defects were recorded in 41% of the patients treated within the first 24 hours since the onset of fever versus 75% of those treated on day 4 and onward. Renal scarring was developed in 51% of the infants with an abnormal scan in the acute phase of infection. The frequency of scarring in infants treated early and in those whose treatment was delayed did not differ, suggesting that once acute pyelonephritis has occurred, ultimate renal scarring is independent of the timing of therapy. Acute inflammatory changes and subsequent scarring were more frequent in the presence of vesicoureteral reflux, especially that which is high grade. However, the difference was not significant, which suggests that renal damage may be independent of the presence of reflux. Conclusions: Early and appropriate treatment of urinary tract infection, especially during the first 24 hours after the onset of symptoms, diminishes the likelihood of renal involvement during the acute phase of the infection but does not prevent scar formation.

Editorial Comment: This important article reinforces the earlier concept that the quicker the treatment for urinary tract infection, the lower the risk of abnormal inflammation in the kidney, as measured by the 99mtechnetium dimercapto-succinic acid scan. However, what is interesting is that once the renal changes occur, the risk of persistent scarring (as measured with a repeat scan 5 to 26 months after successful therapy for the urinary tract infection) is the same regardless of the day of treatment initiation. Our job is to prevent renal inflammation. Once the renal change occurs, the sequence of events leading to permanent scar formation is already in motion.

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0022-5347/09/1815-2295/0
THE JOURNAL OF UROLOGY®

Vol. 181, 2295-2298, May 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.01.086

Non-Surgical Management of Multicystic Dysplastic Kidney

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BJU Int 2008; ***101:*** *804–808.*

Objectives: To better define the outcome and association of multicystic dysplastic kidney (MCDK) with hypertension, vesico-ureteric reflux (VUR), infection and cancer, as there is no consensus on the management of patients born with MCDK. The risk of cancer has dictated the surgical management of the disease in the past. Methods: The Medline database was searched for articles published between 1965 and 2006 and written in the English language, and containing the keywords 'multicystic dysplastic kidney'. Results: The inclusion criteria were met by 105 reports that were subsequently analysed. Of MCDK, 60% regress or involute within 3 years. About 25% of patients will have VUR into the contralateral kidney, of which 90% is grade <or=3. The risk of urinary tract infection appears to be associated with VUR or coexistent abnormalities rather than the MCDK. The risk of hypertension is no greater than that in the general population and nephrectomy is usually not curative. The overall risk of Wilms' tumour developing in a MCDK is <1 in 2000. All reported Wilms' tumours were identified before 4 years of age and 70% presented as a palpable mass. Conclusions: Published reports support the non-surgical management of MCDK. Common practice has been to remove palpable or growing MCDKs, although these represent a very small fraction of MCDKs. In theory, ultrasonographic surveillance until 4 years old might allow the earlier detection of a Wilms' tumour, and decrease the intensity of chemotherapy and improve prognosis. Previous reports do not prove or disprove this concept, and the appropriate frequency of surveillance is not evident.

Editorial Comment: Multicystic dysplastic kidney occurs in 1 of every 4,000 live births, and 60% of these cases involute. This MEDLINE® review suggests that the association of multicystic dysplastic kidney with Wilms tumor is not much higher than in the general population (between 1 in 2,000 and 1 in 4,300 vs 1 in 8,000 to 10,000). The risk of renal cell carcinoma in MCDK is even lower. There is no reported case of Wilms tumor in association with an involuted multicystic dysplastic kidney. These numbers are so low that at least 1 author calculated that nephrectomy would be required in at least 2,000 children to prevent a single case of Wilms tumor.[1] Vesicoureteral reflux, when associated with multicystic dysplastic kidney, almost always is low volume and rarely is symptomatic. The risk of hypertension in children with MCDK is no greater than in the general population, and nephrectomy usually is not curative. This study is important because it brings into focus, based on an exhaustive review of the literature, much of what most of us believe, namely that MCDK, although an anomaly that is easy to remove, rarely requires therapy.

Douglas A. Canning, M.D.

1. Noe HN, Marshall JH and Edwards OP: Nodular renal blastema in the multicystic kidney. J Urol 1989; **142:** 486.

Raised Risk of Wilms Tumour in Patients With Aniridia and Submicroscopic WT1 Deletion

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J Med Genet 2007; ***44:*** *787–790.*

Objective: The aim of this study was to determine if there is a significant difference in the risk of developing Wilms tumour between patients with submicroscopic and those with visible deletions of the WT1 tumour suppressor gene. Methods: To determine which subjects had WT1 deletions, high-resolution chromosomal deletion analysis of the 11p13 region was carried out in 193 people with aniridia. The rationale for this was that aniridia is caused by loss of function of one copy of the PAX6 gene, and although most patients with aniridia have intragenic mutations, a proportion has deletions

that also include the nearby WT1 gene. Fluorescence in situ hybridisation (FISH) analysis of patients with aniridia identifies people with WT1 deletions regardless of whether they have Wilms tumour, allowing the deletion size to be correlated with clinical outcome. Results: Wilms tumour was not observed in any case without a WT1 deletion. Of subjects in whom WT1 was deleted, 77% with submicroscopic deletions (detectable only by high-resolution FISH analysis) presented with Wilms tumour compared with 42.5% with visible deletions (detectable by microscopy). This difference was significant. Conclusions: High-resolution deletion analysis is a useful tool for assessing the risk of Wilms tumour in neonates with aniridia. People with submicroscopic WT1 deletions have a significantly increased risk of Wilms tumour, and a high level of vigilance should be maintained in such cases.

Editorial Comment: Boys and girls with aniridia and Wilms tumor 1 deletion are at greater risk for Wilms tumor. The authors note that most cases of aniridia are isolated but Wilms tumor eventually develops in about 5% of patients born with sporadic aniridia. Those with the WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies and mental retardation) have 11P13 deletions that encompass the aniridia gene and the Wilms tumor suppressor gene (WT1).

In this study by age 4 years (by which time the majority of tumors have presented) children with submicroscopic deletions were more than twice as likely to have Wilms tumor than those with visible deletions. The authors recommend that all neonates with aniridia be screened by FISH for deletion of WT1, and those with deletions be monitored regularly for tumor development. Those with submicroscopic deletions require even more vigilance.

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The National Wilms Tumor Study: A 40 Year Perspective

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Lifetime Data Anal 2007; ***13:*** *463–470.*

The National Wilms Tumor Study (NWTS) was the first pediatric intergroup clinical research unit in North America. It was thus able to collect data concerning children with malignant kidney tumors from each of the then-extant childhood cancer cooperative study groups. Enough patients-about 350 per year-could thus be gathered to study the nature and clinical characteristics of the various kidney malignant tumors of childhood. It also enabled randomized trials of comparative treatment regimens, patients stratified following stipulated risk criteria. The result has been a steadily increasing two-year survival rate to the 90% level while at the same time modulating the intensity of therapy according to well-defined needs. For example, routine post-operative radiation therapy, damaging to normal as well as neoplastic tissues, has been largely eliminated. The proportion of patients given doxorubicin, a cardiotoxic drug, also has been curtailed. These two therapies are now restricted to the 30% of patients who have more advanced or more aggressive disease. All this has been driven to meet the challenge inherent in the motto of pediatric oncology: "Cure is not enough"; that is, the cured child of to-day must not become the chronically ill adult of tomorrow, suffering from the delayed complications secondary to unnecessary, toxic therapies.

Editorial Comment: All pediatric urologists should read this important review. Written by one of the pioneers in Wilms tumor care, this review is a concise history of all that has been accomplished during 40 years of careful observation with well controlled, collaborative studies.

The annual incidence of Wilms tumor is about 8 per million in North Americans younger than 16 years. That means about 500 or so new patients were seen in the United States and Canada annually during the 1960s. The ability to track these patients as a group was the genius behind the National Wilms Tumor Study. The goals were 1) to establish the best

treatments for Wilms tumor stratified according to the extent of the disease, 2) to study the nature and biology of renal tumors of childhood, 3) to gather information regarding possible genetic correlates and 4) to determine whether the intergroup mechanism was feasible. During 40 years the group made a number of important discoveries. They found that dactinomycin and vincristine are the building blocks of therapy, and that the addition of doxorubicin to the other 2 drugs in children with more advanced disease provides better protection against relapse. They also observed that radiation therapy is unnecessary for children in whom the tumor is localized and totally removed, and that radiation therapy in the context of multimodal care can be used effectively at much lower doses. In addition, they found that chemotherapy given in single dose courses rather than multiple daily doses is effective, and that total treatment time can be reduced from about 15 months to 24 weeks. Lastly, they observed that certain histological and molecular genetic configurations within the tumor cells are associated with a more ominous outlook.

D'Angio shares with us his view of the future and emphasizes the need to collect information concerning the health status of long-term survivors, who now number more than 9,000. He closes by asking us to find ways to validate the results of clinical studies under even greater stringencies and to reduce the toxicity of the therapy because "cure is not enough."

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Familial Multilocular Cystic Nephroma: A Variant of a Unique Renal Neoplasm

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Urology 2007; ***70:*** *179.e9–179.e10.*

Multilocular cystic nephroma (MCN) is a benign renal lesion believed to be unilateral and nonfamilial. We present 2 cases of MCN in 2 brothers. The older brother had a 10-cm MCN and required radical nephrectomy, and the younger brother had bilateral lesions (6 cm and 3 cm) for which nephron-sparing surgery was possible. Both children underwent chest computed tomography to rule out pleuropulmonary blastoma. These cases suggest a genetic link to the pathogenesis of this lesion is possible and that although MCN can involve the collecting system, it can still be treated with partial nephrectomy.

Editorial Comment: These 2 brothers each had a large multilocular cystic nephroma that invaded the collecting system. The bilateral tumors in the younger brother were identified 3 years after the tumor was resected in the older brother. This finding followed a normal screening ultrasound in the younger child at age 6 months. Chest computerized tomography ruled out pleural pulmonary blastoma in each case.

These 2 cases are interesting in that they strengthen previous arguments that multilocular cystic nephroma may be familial in some instances. Although the literature is vague about the usefulness of nephron sparing surgery in these cases, our belief is that nephron sparing surgery can be safe and effective in these individuals.

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