The Swedish Reflux Trial in Children: IV. Renal Damage

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Abbreviations and Acronyms

DMSA = ^{99m}technetium dimercapto-succinic acid

RCT = randomized, controlled trial

UTI = urinary tract infection

VCU = voiding cystourethrography

VUR = vesicoureteral reflux

Submitted for publication September 30, 2009.

Study received approval from research ethics committees at participating centers.

Supported by grants from the West Region, Sweden and Futurum, Jönköping County Council, Sweden.

Supplementary material for this article can be obtained at http://hdl.handle.net/2077/22171.

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Purpose: We compared the development of new renal damage in small children with dilating vesicoureteral reflux randomly allocated to antibiotic prophylaxis, endoscopic treatment or surveillance as the control group.

Materials and Methods: Included in the study were 128 girls and 75 boys 1 to younger than 2 years with grade III–IV reflux. Voiding cystourethrography and dimercapto-succinic acid scintigraphy were done before randomization and after 2 years. Febrile urinary tract infections were recorded during followup. Data analysis was done by the intent to treat principle.

Results: New renal damage in a previously unscarred area was seen in 13 girls and 2 boys. Eight of the 13 girls were on surveillance, 5 received endoscopic therapy and none were on prophylaxis ($p = 0.0155$). New damage was more common in children with than without febrile recurrence (11 of 49 or 22% vs 4 of 152 or 3%, $p < 0.0001$).

Conclusions: In boys the rate of new renal damage was low. It was significantly higher in girls and most common in the control surveillance group. There was also a strong association between recurrent febrile UTIs and new renal damage in girls.

Key Words: kidney, urinary tract infections, vesico-ureteral reflux, cicatrix, fever

More than 4 decades ago Hodson and Edwards drew attention to the association between chronic pyelonephritis and VUR.[1] There was increasing interest in VUR and reflux nephropathy soon became the standard term for permanent renal damage.[2] Lately the importance of VUR for renal damage has been questioned. Since DMSA scintigraphy is more sensitive than previously used techniques, it was noted that only half of damaged kidneys were drained by refluxing ureters.[3,4] However, the renal abnormality rate is significantly associated with VUR grade.[5,6] There is also a discussion about the etiology of renal defects with congenital damage in focus rather than acquired damage.[7] However, acquired damage is the dominant etiology in girls with febrile UTI while congenital damage is mostly seen in boys.[8]

There is doubt about the preventive value of antibiotic prophylaxis or surgical treatment in children with VUR.[9,10] Ureteral reimplantation has mostly been replaced by endoscopic injection but to our knowledge the latter technique has not been studied in relation to renal outcome.

Controlled studies are needed to provide an evidence base for treatment in children with VUR. The Swedish Reflux Trial was set up as a RCT to compare long-term antibiotic

0022-5347/10/1841-0292/0
THE JOURNAL OF UROLOGY®

Vol. 184, 292-297, July 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2010.01.060

prophylaxis, endoscopic correction and surveillance as the control group in children with dilating VUR in regard to the febrile UTI rate, and kidney and VUR status at 2 years. Secondary outcomes were complications and the impact of factors such as VUR grade, gender and bladder dysfunction. In the current report we analyzed the progression of renal defects present at entry and the development of new renal damage in the 3 treatment groups.

MATERIALS AND METHODS

The study design was previously described in detail.[11] Briefly, in this multicenter, open, prospective, controlled trial 128 girls and 75 boys 1 to younger than 2 years with grade III–IV VUR were randomly allocated to antibiotic prophylaxis, endoscopic treatment or surveillance. Nine and 194 cases were detected after prenatal screening and symptomatic UTI, respectively. Before randomization the children were evaluated by ultrasound, VCU, DMSA scintigraphy and urography. Study exclusion criteria were previous urogenital surgery, malformation (except duplication), known neurological disease, stone disease, glomerular filtration rate less than 70 ml per minute per 1.73 m^2, split renal function less than 15% or suspected noncompliance (inability to understand Swedish or previous noncompliance). Children were randomly assigned to prophylaxis, endoscopic treatment or surveillance by computer, matching for gender, previous UTI, VUR grade, DMSA uptake defect, bladder size, duplication and center using minimization procedures.[12]

At the end of the 2-year study period DMSA scintigraphy and VCU were repeated. Main outcome variables were recurrent febrile UTIs, progression of the DMSA uptake defect present at study entry or new damage appearing during the study and VUR status at the end of the 2-year period. UTI was diagnosed as previously described.[11] Only symptomatic febrile (38.5C or greater) UTIs were recorded.

All radiological investigations were reevaluated at the coordinating center by the same radiologist (ES). VCU was done and VUR was graded according to International Reflux Study in Children standards.[13] The highest VUR grade was used to classify patients with reflux in more than 1 ureter. Urography was used to detect duplex systems.

For DMSA scans groups at the centers were instructed to follow the European guidelines.[14] Briefly, static renal scintigraphy was done 2 to 4 hours after DMSA injection at a dose of 1 MBq/kg body weight (minimum 15 MBq). Planar images were obtained by a high resolution collimator in 1 posterior and 2 oblique projections with 300,000 counts in the posterior view. All data files were reevaluated at the coordinating center by the same nuclear medicine specialist (RS) using commercially available software. In 15 children scans at entry and/or followup were suboptimal but in all it was possible to interpret renal deterioration. A kidney without uptake defect and 45% or greater relative (split) function was classified as normal (DMSA class 0) and a kidney with decreased or absent uptake in 1 or more areas, or relative function less than 45% was considered abnormal. The extent of kidney damage was graded arbitrarily as class 1—uptake defect with 45% or greater relative function, class 2—40% to 44% relative function and class 3—less than 40% relative function. In cases of bilateral renal damage the kidneys were individually classified by uptake defect extent. In cases of unilateral duplication expected mean normal split function shifted from 50% to 54%.[15] Thus, the lower limit of normality was considered at 49%. On analysis the kidney with more pronounced involvement was used to characterize the case.

Since the focus was to compare 3 treatment regimens, special attention was given to DMSA scan development during the study period. A new renal scar was defined as an uptake defect appearing in a previously normal area. Deterioration was defined as a new renal scar or a more than 3% decrease in relative (split) function in a kidney with uptake defects at entry.[16] Kidney damage was also classified as focal or generalized. Median time from first DMSA scan to randomization was 49 days (IQR 22–119).

Children randomized to prophylaxis were prescribed antibiotic prophylaxis. For endoscopic injection dextranomer/hyaluronic acid copolymer was used. Patients in that group received prophylaxis until a new VCU confirmed that VUR had disappeared or decreased to grade I–II. In the surveillance group no specific preventive measures were done.

Analysis was done by allocated treatment at study entry using the intent to treat principle. For comparison between groups the chi-square exact test was used for nonordered categorical variables and the Kruskal-Wallis test was used for continuous variables. For pairwise comparison between groups Fisher's exact test was used for dichotomous variables and the Mantel-Haenszel chi-square exact test was used for ordered categorical variables with $p < 0.05$ considered significant. The study was approved by the research ethics committees at participating centers. Informed consent was obtained from each participating family.

RESULTS

Abnormal DMSA findings at entry were seen in 124 children (61%), of whom 18 (15%) had bilateral uptake defects. Generalized renal damage was found in 30 of 128 girls (23%) and in 44 of 75 boys (59%) ($p < 0.0001$). Two-year DMSA scan was done in all except 2 of the 203 children. Hospital fear was the reason for the omitted investigation in the 2 children, of whom 1 had a class 1 uptake defect at entry and 1 had normal kidneys.

Renal status deterioration, that is new damage in previously unscarred kidney areas and greater than 3% decreased relative function in a kidney with uptake defects at entry during the 2-year period, was observed in 17 girls and 7 boys, including 4 of 68 (6%) on prophylaxis, 8 of 65 (12%) with endoscopic therapy and 12 of 68 (18%) on surveillance. These differences were not statistically significant ($p = 0.11$).