The Swedish Reflux Trial in Children: V. Bladder Dysfunction

Ulla Sillén,* Per Brandström, Ulf Jodal, Gundela Holmdahl, Anders Sandin, Ingrid Sjöberg and Sverker Hansson

From the Pediatric Uro-Nephrologic Center, Queen Silvia Children's Hospital, University of Gothenburg, Göteborg and Department of Pediatrics, Children's University Hospital (IS), Lund, Sweden

Abbreviations and Acronyms

DBD = dilated bladder dysfunction

DES = dysfunctional elimination syndrome

DV = dysfunctional voiding

LUT = lower urinary tract

LUTD = LUT dysfunction

OAB = overactive bladder

UTI = urinary tract infection

VCU = voiding cystourethrography

VUR = vesicoureteral reflux

Submitted for publication October 13, 2009.

Study received approval from research ethics committee at participating centers.

Supported by grants from the West Region, Sweden.

* Correspondence: Pediatric Uro-Nephrologic Center, Queen Silvia Children's Hospital, SE-416 85 Göteborg, Sweden (e-mail: ulla.sillen@vgregion.se).

Purpose: We investigated the prevalence and types of lower urinary tract dysfunction in children with vesicoureteral reflux grades III and IV, and related improved dilating reflux, renal damage and recurrent urinary tract infection to dysfunction.

Materials and Methods: A total of 203 children between ages 1 to less than 2 years with reflux grades III and IV were recruited into this open, randomized, controlled, multicenter study. Voiding cystourethrography and dimercapto-succinic acid scintigraphy were done at study entry and 2-year followup. Lower urinary tract function was investigated by noninvasive methods, at study entry with 4-hour voiding observation in 148 patients and at 2 years by structured questionnaire and post-void residual flow measurement in 161.

Results: At study entry 20% of patients had lower urinary tract dysfunction, characterized by high bladder capacity and increased post-void residual urine. At 2 years there was dysfunction in 34% of patients. Subdivision into groups characteristic of children after toilet training revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction. There was a negative correlation between dysfunction at 2 years and improved dilating reflux ($p = 0.002$). Renal damage at study entry and followup was associated with lower urinary tract dysfunction at 2 years ($p = 0.001$). Recurrent urinary tract infections were seen in 33% of children with and in 20% without dysfunction ($p = 0.084$).

Conclusions: After toilet training a third of these children with dilating reflux had lower urinary tract dysfunction, mainly voiding phase problems. Dysfunction was associated with persistent reflux and renal damage while dysfunction at study entry did not predict the 2-year outcome.

Key Words: urinary bladder, kidney, vesico-ureteral reflux, urinary tract infections, renal function tests

MANY studies suggest that LUTD is an important factor for primary VUR regarding etiology, recurrent UTIs and spontaneous resolution. The prevalence varies according to dysfunction type, patient age, VUR grade and investigation. In different age groups LUTD with incomplete emptying has a negative effect on spontaneous resolution.[1–4] However, it has not been conclusively shown that dysfunction treatment improves the resolution rate. There is also ongoing discussion about the influence of LUTD on antireflux treatment with open surgery and endoscopic injection.

There are few prospective investigations of LUTD in children with primary VUR.[5] The current study was part of a randomized, controlled trial comparing 3 strategies to treat children with dilating VUR, including an-

0022-5347/10/1841-0298/0
THE JOURNAL OF UROLOGY®

Vol. 184, 298-304, July 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2010.03.063

tibiotic prophylaxis, endoscopic treatment and surveillance. LUTD was evaluated by noninvasive methods at study entry and at the end of the 2-year followup. We analyzed the prevalence and types of LUTD in children with dilating VUR, and correlated spontaneous improvement in VUR, renal damage and recurrent febrile UTIs with LUTD.

MATERIALS AND METHODS

Swedish Reflux Trial Overall Design

This open, multicenter, randomized controlled trial included 203 children with VUR grade III–IV between ages 1 to less than 2 years. VCU and ^{99m}technetium dimercapto-succinic acid scintigraphy were done at study entry and at 2 years, as previously described.[6] Renal damage was classified as previously described.[6] VUR improvement was defined as complete resolution or downgrading to nondilating grade I–II VUR.

Children in Bladder Function Study

Bladder function studies were optional and performed in 171 patients, including 148 at entry (91 girls and 57 boys with a median age of 20 months) and 161 after 2 years (101 girls and 60 boys with a median age of 46 months), of whom 139 were investigated on each occasion. At study entry VUR grade III or IV was seen in 94 and 54 patients, respectively, with bilateral VUR in 78. At 2 years the corresponding numbers were 101, 60 and 84, respectively.

Bladder Function Investigation Methods

At study entry the 4-hour voiding observation was used, as designed for noninvasive investigation in children wearing diapers.[7] Voiding episodes were indicated by a soundless alarm, measuring post-void residual urine directly after voiding by ultrasound and weighing the diaper for voided volume. Functional bladder capacity was evaluated as the highest sum of voided volume and post-void residual urine, and calculated as the percent of that expected for age using the formula, 30 + (2.5 × age in months),[8] which has been validated in healthy children.[9] Post-void residual urine was defined as the mean of all post-void residual urine measurements during the 4 hours.

Urinary flow, post-void residual urine and a voiding questionnaire are noninvasive investigations in toilet trained children.[10] The flow-post-void residual study was done during at least 4 hours and included a minimum of 2 voiding episodes. Functional bladder capacity was estimated using the highest sum of voided volume and post-void residual urine. Bell and tower shape flow curves were defined as normal with irregular, fractioned and plateau shapes defined as abnormal. The flow curve was acceptable provided that voided volume exceeded 50% of expected capacity.

The nurse interviewed the parents about voiding and bowel habits, and completed the voiding questionnaire. A scoring system was constructed, similar to that reported by Farhat et al.[11] The normal limit was estimated based on 40 healthy children 3.5 to 4.5 years old with a score of 5 points or higher required to diagnose LUTD. The questionnaire has been validated in children between ages 5 and 10 years (unpublished data).

Children wearing diapers during the day were not included during followup since neither the questionnaire nor flow measurement could be applied. All except 10 children had been without diapers for 6 months. Bladder capacity on VCU was recorded based on bladder size with bladders reaching above the line connecting the iliac crests defined as large.

Bladder Dysfunction Estimation

At study entry. The only LUTD signs at entry were high bladder capacity and high post-void residual urine. In free voiding studies the cutoff for high bladder capacity was 150% or greater of the expected normal value for age[9] and in catheter based VCU studies it was 200% or greater.[12] Post-void residual urine was high at 25% or greater of bladder capacity, or 40 ml or greater. Children with high capacity and post-void residual were considered to have DBD.[12] Children with high capacity or post-void residual urine were classified as having uncertain dysfunction.

At 2-year followup. Definitions of the different LUTDs in toilet trained children were based on International Children's Continence Society recommendations.[13] Children with LUTD were categorized into 2 groups, including filling phase (OAB) and voiding phase (DV, DES and DBD) problems.

OAB was diagnosed mainly by symptoms, including urgency, urgency defense, frequent voiding and urge incontinence. Bladder capacity was normal or low and post-void residual urine was less than 20 ml.

DV was diagnosed by voiding symptoms, including straining, hesitancy or interrupted voiding, infrequent voiding, urinary incontinence and postponement. An irregular or fractionated flow curve is recommended as a prerequisite.[13] In this study the diagnosis was also defined by voiding symptoms with high bladder capacity and/or post-void residual urine. Overactivity symptoms were also seen.

DES was used for DV combined with bowel problems. DBD[12] was used for free voiding bladder capacity 150% or greater of expected normal or VCU based capacity 200% or greater, together with post-void residual urine 20 ml or greater but a questionnaire score of less than 5 and a normal flow curve. Uncertain bladder dysfunction was used for bladder symptoms not reaching the level indicated by the definitions.

Statistical Methods

For comparison between groups we used Fisher's exact test for dichotomous variables, the Mantel-Haenszel chi-square exact test for ordered categorical variables and the Mann-Whitney U test for continuous variables with $p < 0.05$ considered significant. The study was approved by the research ethics committee at participating centers (protocol Ö462-99 at the coordinating center). Informed consent was obtained from each participating family.

RESULTS

Patients in all 3 treatment groups were included in the calculations except those with spontaneous VUR