Vesicoureteral reflux and febrile urinary tract infections in anorectal malformations: A retrospective review

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A B S T R A C T

Background: Multiple studies document a correlation between anorectal malformations (ARMs) and vesicoureteral reflux (VUR), development of urinary tract infections (UTIs), and subsequent renal disease.

We aimed to determine which patient characteristics are associated with VUR and UTI in this population.

Methods: A retrospective review of ARM patients at a free-standing children’s hospital from January 1996 to December 2011 was performed. Logistic regression was used to investigate the associations between VUR and UTI and ARM classification and co-morbid diagnoses.

Results: Of 190 patients, 41 (31%) received a diagnosis of VUR. Thirty-one of the 190 patients had at least one febrile UTI (16%). Of these, only 16 (51%) had a diagnosis of VUR. On multivariable logistic regression, the only patient variable associated with VUR was having an ectopic kidney (p = 0.026). Similarly, the presence of GU malformations was the closest variable associated with developing a UTI (p = 0.073).

Conclusions: In ARM patients, VUR as well as UTIs are associated with the presence of GU malformations. Thus, voiding cystourethrogram (VCUG) testing should be pursued when there are other caudal and GU abnormalities, regardless of fistula location. Antibiotic prophylaxis for UTI should be considered in children with ARM and any GU malformation, not only VUR.

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Anorectal malformations (ARMs) have a high incidence of associated genitourinary (GU) anomalies, ranging from 25% to 50% [1–3]. This significant association has led to routine diagnostic imaging to determine the presence of renal anomalies and vesicoureteral reflux (VUR). VUR has been reported in 20%–47% of children with ARMs [4]. Children with ARMs previously described as having “high” malformations have an increased risk of VUR ranging from 33% to 39%. Children with “low” malformations have a slightly lower incidence, reported at 20%–37% [4,5]. The presence of VUR increases the risk of developing febrile urinary tract infections (UTIs) which may ultimately lead to renal scarring and subsequent renal dysfunction [6,7]. Traditionally, all patients with VUR have been placed on prophylactic antibiotics in order to prevent complications secondary to febrile UTIs.

The data regarding the benefits of antibiotic prophylaxis in children with VUR are mixed. A Cochrane review analyzing the results of 20 randomized controlled trials, including 2234 children, concluded that compared to no treatment, prophylactic antibiotics in the setting of VUR did not significantly reduce the number of recurrent febrile UTIs in children, although it did reduce the number of children developing new or progressive renal damage [8]. These children represent a heterogeneous group with multiple comorbidities and congenital anomalies making it difficult to apply these data to a single population. Even with this limitation, there has been a trend towards not treating patients with documented low-grade VUR with prophylactic antibiotics [9]. There have been many reports documenting the association of non-fistulous GU anomalies with ARM, including VUR [10]. In this study we aimed to review all the children with ARM treated at our institution over the last 15 years to determine which characteristics in ARM patients are associated with VUR and/or UTI diagnoses to better define who would benefit from voiding cystourethrogram (VCUG) testing and/or UTI prophylaxis.

1. Methods

We performed a retrospective review of infants at a free-standing children’s hospital from January, 1996 to December, 2011 (IRB approval #13904). We included all male and female infants with a primary diagnosis of ARM including those with a cloacal anomaly. Exclusion criteria included cloacal extrophy, conjoined twins, patients expiring within the first 3 months of life, or those who had their initial surgical management at an outside institution. Demographic and clinical variables were obtained by chart review and included age, gender, ARM classification according to the initial operating surgeon during the index admission, performance and results of VCUG on index admission with regards to presence of VUR, co-morbid diagnoses recorded during index admission, surgical
operations performed related to the diagnosis of ARM, occurrence of febrile UTI, and use of prophylactic antibiotics for UTI prevention. Of note, a subject was considered to have had a febrile UTI when they had a urine culture growing at least $10^5$ bacteria per ml of a single organism in addition to being symptomatic with fever, suprapubic, or back pain, and requiring organism-targeted antibiotic treatment.

For the purposes of this study ARMs were classified according to gender and fistula location. Co-morbid diagnoses included tracheoesophageal fistula (TEF), congenital heart defect, vertebral anomalies, tethered cord, spina bifida, and genetic syndromes. GU anomalies included any recorded anomaly of the genital or urinary tract. Ectopic kidney included any diagnosis of ectopically located kidneys, including horseshoe kidney. Dysplastic kidney included any type of dysplasia, including hypoplasia and cystic malformations. Urinary tract system duplications included kidney, ureteral and urethral duplications. Female genital system anomalies included duplications or absence of the uterus, cervix, or vagina, bicornuate uterus, obstructed ureterine horns, and vaginal atresia, among others. Male genital system anomalies include any deformities of the testicles, scrotum or penis, such as undescended testicle, penile chordee, bifid scrotum, and penoscrotal transposition. Urinary anomalies included epispidias, hypospadia, urethral atresia, and duplicate urethra. Other GU anomalies included rare anomalies in our cohort that could not be included in any of the previous categories, including ureteral anomalies, uretero-pelvic junction obstruction, and bladder anomalies.

Descriptive statistics were used to describe the demographic and characteristic of the study subjects. Simple logistic regression was used to investigate the associations between VUR and the patient variables measured. We then constructed a multivariable logistic regression model with VUR as the outcome of interest including all variables associated with VUR with $p \leq 0.1$ in the previously performed bivariate analyses. Simple logistic regression was also used to model the associations between UTI occurrence and patient demographic and clinical characteristics. We again incorporated all the variables associated with UTI with $p \leq 0.1$ as well as variables considered to influence UTI occurrence in a multivariable logistic regression model with UTI as the outcome of interest. The statistical software STATA 10.0 (College Station, TX) was used for all analyses; statistical significance was set at $p \leq 0.05$. Continuous measures are presented as mean ± standard deviation and categorical variables are summarized by percentages.

2. Results

One hundred and ninety patients were included in this study. Table 1 summarizes the clinical and demographic characteristics of our subjects. The average age of our subjects at the completion of the study was 93.43 ± 52.05 months and median 4.04 years (22 days–15.5 years). Table 2 focuses on the GU diagnoses of our study population. Out of the 190 patients studied, 133 (70%) had a VCUG performed during their index admission and of these, 41 (30.83%) received a diagnosis of VUR. Median follow up for these patients was 5.63 years (120 days–14.71 years) and only 2 of these patients were lost to follow up prior to resolution of their VUR. Of the 41 children with VUR, 56% had a VUR grade of III or greater, and almost all (39, 95.12%) were placed on prophylactic antibiotics to prevent UTIs. Sixteen of these 41 went on to develop at least one febrile urinary tract infection (39.02%). Of these 16 patients with VUR and a UTI, 11 (68.75%) had VUR of grade III or above. Of the two patients who were not treated with prophylactic antibiotics, one had grade III reflux and to date has not developed a UTI. The other had grade IV reflux and did develop a febrile UTI.

The results of simple logistic regression analyses exploring the association between a diagnosis of VUR and measured clinical variables, controlling for performance of a VCUG at birth and gender as appropriate are summarized in Table 3. A multivariable logistic regression model was then constructed to investigate these predictor variables and their association with a diagnosis of VUR. This model included all variables with $p \leq 0.1$ on simple logistic regression as well as fistula location as a variable presumed to affect the likelihood of being diagnosed with VUR. In this model, only a diagnosis of ectopic kidney remained associated with having a diagnosis of VUR (OR = 13.263, $p = 0.026$, 95%CI = 1.354–129.92).

In total, 31 (16.32%) patients from the 190 included in the study developed a febrile UTI. Of these, 16 (51.61%) had a diagnosis of VUR. Only 5 of them (16.13%) were not diverted with a sigmoid end
colostomy and mucous fistula, and 4 of these had a diagnosis of VUR. The results of simple logistic regression analyses exploring the association between a diagnosis of UTI and measured clinical variables controlling for use of prophylactic antibiotics, age, and gender as appropriate are summarized in Table 4. As expected, a diagnosis of UTI and patient clinical and demographic variables. Simple logistic regression analyses investigating associations between occurrence of UTI and patient clinical and demographic variables.

<table>
<thead>
<tr>
<th>OR</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Fistula</td>
<td>0.771</td>
<td>0.658</td>
</tr>
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<td>Recto-perineal</td>
<td>0.686</td>
<td>0.599</td>
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<tr>
<td>Recto-urethral</td>
<td>1.285</td>
<td>0.847</td>
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<tr>
<td>Recto-vesical</td>
<td>1.714</td>
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</tr>
<tr>
<td>Cloacal anomaly</td>
<td>2.057</td>
<td>0.222</td>
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<tr>
<td>Imperforate anus without Fistula (Baseline)</td>
<td>3.207</td>
<td>0.139</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>1.399</td>
<td>0.428</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>1.736</td>
<td>0.484</td>
</tr>
<tr>
<td>Tethered cord</td>
<td>2.951</td>
<td>0.068</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>9.838</td>
<td>0.044</td>
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<tr>
<td>Vertebral anomaly</td>
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<td>0.068</td>
</tr>
<tr>
<td>Genetic syndrome</td>
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<td>0.137</td>
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<tr>
<td>Any GU malformation</td>
<td>3.411</td>
<td>0.002</td>
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<td>Solitary kidney</td>
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<td>0.183</td>
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<td>Dysplastic kidney</td>
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<td>Ectopic kidney</td>
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<td>Urinary tract system duplication</td>
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<td>Female genital system defect</td>
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<td>Male genital system defect</td>
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<tr>
<td>Urethral abnormalities</td>
<td>1.281</td>
<td>0.676</td>
</tr>
<tr>
<td>Other GU anomalies</td>
<td>2.417</td>
<td>0.183</td>
</tr>
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</table>

3. Discussion

VUR is a common anomaly of the urinary tract in childhood. Development of febrile UTIs in the setting of VUR has been shown to significantly increase the risk of developing renal scarring and subsequent renal dysfunction [6,7]. Many of these infections may go undiagnosed in the neonatal and infant population (< 1 year old), since these children are not able to manifest their symptoms verbally [6]. The American Urological Association (AUA) has recently published recommendations for the management of primary VUR in children [6]. The goals of these recommendations are to prevent recurring febrile UTIs, thus preventing renal injury, and to minimize the morbidity of treatment and follow-up in children with VUR. In the absence of neurogenic bowel or bladder dysfunction, the recommendation is for continuous antibiotic prophylaxis (CAP) in children less than one year of age with documented VUR of any grade in the setting of a febrile UTI. For children who are found to have grade III–V VUR the recommendation is for beginning CAP even in the absence of a documented UTI. Because of the underlying risk of progressive renal disease, a recommendation for CAP may be made even in children less than one who have grades I–II VUR without a febrile UTI. However, to date, no formal recommendations have been made regarding the prevalence or management of febrile UTIs in children with ARM and VUR.

Our study is one of the largest to date looking at the incidence of urologic abnormalities, including VUR, associated with ARM. VUR was found in over 30% of our patient population undergoing VCUGs, a finding that is similar to previous studies [4,5]. Most importantly, however, on multivariable regression analysis, we found that fistula location was not significantly associated with receiving a diagnosis of VUR. These findings stress the importance of obtaining a baseline VCUG in every child with ARM, whether they have a fistula or not and no matter where the fistulous connection is to document the presence or absence of VUR and guide further therapy and treatment. This is in accordance to previous studies that also recommend VCUG evaluation in all children with ARM, irrespective of whether they have a “high” or “low” fistulous connection [11]. The vast majority of patients in our cohort (95%) with VUR were placed on prophylactic antibiotics. In spite of this, 39% of them went on to develop febrile urinary tract infections. The high prevalence of febrile UTI observed in this study despite the widespread use of antibiotic prophylaxis in children with VUR underscores the importance of placing patients on CAP in the setting of VUR and ARM.

In addition to seeing 39% of patients with VUR develop a UTI while on CAP, we also observed that almost half of the patients in our cohort that developed a febrile UTI did not have a diagnosis of VUR. Furthermore, on simple logistic regression we found that the presence of any kind of GU malformation in patients with ARM is significantly associated with the development of a UTI. While this did not reach statistical significance in our multiple logistic regression model, it does beg consideration of prophylactic antibiotic prophylaxis in all children with ARM, irrespective of whether they have a fistula or not and no matter where the fistulous connection is to document the presence or absence of VUR and guide further therapy and treatment. This is in accordance to previous studies that also recommend VCUG evaluation in all children with ARM, irrespective of whether they have a “high” or “low” fistulous connection [11]. The vast majority of patients in our cohort (95%) with VUR were placed on prophylactic antibiotics. In spite of this, 39% of them went on to develop febrile urinary tract infections. The high prevalence of febrile UTI observed in this study despite the widespread use of antibiotic prophylaxis in children with VUR underscores the importance of placing patients on CAP in the setting of VUR and ARM.

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These findings must be taken in the context of the limitations of the study. This is a retrospective review, and as such, it is subject to a number of biases. Loss to follow-up bias is of special concern at our institution, since we have catchment area for tertiary surgical care including Washington, Alaska, Montana, Idaho, and Wyoming. This makes long-term follow-up at our institution for some of our patients extremely difficult, if not impossible. Patients living far away from Seattle are more likely to be lost to follow up at our institution than those that live closer. However, we have no reason to
believe the disease of children living at a longer distance from Seattle is more or less severe than that of children living close to Seattle. This significantly minimizes the concern for loss to follow up bias. In addition, this study has a median follow up time of 4.04 years, allowing enough time for children in this cohort to develop a UTI were they predisposed to do so. The most concerning source of bias in this study is misclassification bias. The classification of ARM has evolved over the last 15 years and different surgeons have adopted the new classification in which malformations are more anatomically described as suggested by Peña and Levitt, rather than classified as high, intermediate, or low lesions, at different times and with different levels of formality [12]. In order to minimize this bias a study investigator reviewed all operative reports for each of the subjects in the study in order to ensure the most accurate classification of ARM was rendered for each patient. Of note, we had an incidence of almost 15% of imperforate anus without fistula in our cohort, compared to the 5% previously reported [12]. This is in part secondary to having all children with ARM and any population. Thus, CAP should be considered in all children with more, this study identified an association between GU abnormalities irrespective of VUR and the development of UTIs in this population. Therefore, CAP should be considered in all children with ARM and GU malformations, not just those with VUR. However, further studies are needed to solidify this association and determine whether CAP would be beneficial not just in children with ARM and VUR, but also in children with ARM and any associated GU abnormality.

References


Discussion

Dr. Atsuyuki Yamataka (Tokyo, Japan): Thank you for a very nice presentation. Did you check the incidence of tethering in your patients?

Response: Dr. Sabrina Sanchez: Yes, we did look at that, it does not appear that tethered cord is associated with an increased risk of VUR or an increased risk of UTI.

Dr. Yamataka: What is the treatment of VUR in your center endoscopic Deflux procedure, open procedure or?

Response: Dr. Sanchez: It depends on the length of time that VUR is there, if we diagnose ... it in children younger than... 1 year we usually put them on antibiotic prophylaxis and then depending on whether it is starting to improve or if it stays the same we think about doing more procedures such as injections or actual surgery to fix it.

Discussant: Dr. Philip Frykman (Los Angeles, CA): In follow-up to Dr Yamataka’s question, has it changed your management of VUR in your patients?

Response: Dr. Sabrina Sanchez: It hasn’t changed our management of VUR. What I think it has changed is who we are getting VUCGs on. Initially we were getting VUCGs on everybody and then we started to not get as many VUCGs on patients that had low fistulas thinking that their risk was not as high to have VUR and then after this study, it kind of made us realize that actually their risk is just as high so we are back to getting VUCG’s on everyone.

Discussant: Dr. Douglas Barnhart (Salt Lake City, UT): I have a question for you. There is some debate in the urology world about ultrasound versus VUCG for screening for VUR. Having had a daughter that has had a VUCG, it not only exposes the child to radiation but it is an unpleasant experience for the child. What I’m interested in is do you have data that can put a block between — your patients with ARM and VUCG and break it out into normal and abnormal ultrasound and did that guide you in who actually really needed a VUCG.

Response: Dr. Sabrina Sanchez: We get ultrasounds in most of these children but I did not specifically look at that, so I don’t know. It would be a really interesting thing to ...