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ORIGINAL ARTICLE

Anatomical Variations of the Urethera and their Role in Persistent Inflammatory Uropathies

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ABSTRACT

Objective: To investigate the prevalence and clinical significance of anatomical variations of the urethra in patients with persistent inflammatory uropathies (PIUs) across a multicenter cohort.

Materials And Methods: This multicenter study was observational and prospective conducted between January to December 2022. The total number of participants was 1,218 adult patients (≥18 years), presenting with LUTS that were recurrent or persistent, as well as an inflammatory uropathy that had been confirmed through various diagnostic modalities, such as cystoscopy, urine cytology and histopathology. All enrolled subjects had undergone high-res pelvic MRI, retrograde urethrogram, voiding cystourethrogram and urodynamic evaluation. Documented anomalies consisted of anatomical variations in the urethra (such as duplicate, meatal stenosis, diverticula, posterior urethral valves in males and ectopic urethral orifice). In addition, logistic regression analyses adjusted for age, sex, comorbidities, and prior history of instrumentation, were utilized to determine whether the persistence of PIU was associated with the anatomical variations found.

Results: 382 patients (31.4%) out of 1,218 who had anatomical differences. The anatomical variations include meatal stenosis (12.6%), urethral diverticula (9.8%), and ectopic orifices (6.3%). The rates of recurrent UTIs (OR = 2.41, 95% CI: 1.89-3.08, $p < 0.001$), chronic urethritis (OR = 3.02, 95% CI: 2.31-3.95, $p < 0.001$), and treatment failure (OR = 2.78, 95% CI: 2.15-3.60, $p < 0.001$) were significantly greater in patients with anatomical variations than for those without. A total of five statistically significant associations ($p < 0.05$) have been verified in the multivariate analysis.

Conclusion: Variant anatomy of the Urethra is common in persistent inflammatory uropathies and associated with treatment failures and symptom recurrence. Therefore, in the Diagnosis of PIU, Imaging and Assessment of the urethra should be considered Routine in the Diagnostic Algorithm.

Keywords: Urethral anomalies; inflammatory uropathy; persistent urinary tract infection; urethral stenosis; urethral duplication; multicenter study; uroimaging.

INTRODUCTION

Chronic inflammation of the urinary tract in PIUs is a difficult situation for persons with lower urinary tract issues. Despite antimicrobial and anti-inflammatory therapies, chronic inflammation still occurs. Chronic Urethral Pain Syndromes, Chronic urethritis, and Recurrent Urinary Tract infection due to the urinary tract are not only symptomatic but reduce Quality of Life for patients. Many factors such as infections, autoimmune disease(s), and neurogenic factors cause chronic inflammatory uropathies[1]. However, contributions of anatomical anomalies of the urethra may be modifiable, but these types of anatomical anomalies continue to be underlooked for their contribution to chronic condition[2].

The Urethra is a simple tubular structure, but many genetic and environmental factors lead to a great range of anatomical differences between people. Examples of such variations are duplicated Urethras (either partial or complete), Meatal Stenosis, Urethral Diverticulum, posterior urethral valves (PUVs) in males, and Ectopic Urethral Orifices. Some of these anatomical differences will be asymptomatic, whereas others will lead to urinary stasis, incomplete emptying of the Urethra, and friction to the Urethral Mucosa leading to a susceptible environment for colonization by primary pathogens and chronic irritation (Cause of chronic inflammation)[3]. For example, Urethral Diverticula can hold a pocket of stagnant urine and can allow for intermittent growth of uropathogens, while Meatal Stenosis leads to very high-pressure urine flow, which imparts a microtrauma upon the Urethral Mucosa and continues the cycle of inflammation[4].

Historically, the urethra has been assessed mainly due to issues related to congenital abnormalities in children and as a result of injury. However, new evidence suggests that there are less obvious or malformations of the urethra that may cause persistent urinary issues in adults. Even though this is so, routine imaging of the urethra for the determination of anatomy is not part of standard assessments for adults with recurrent urinary issues, and therefore may not identify treatable diseases[5].

This study involved multiple institutions and enrolled participants from five different university-affiliated urology clinics. The purpose of this study was to systematically determine if there are anatomical malformations of the urethra in adults with recurrent urinary issues, and to establish a link between those anatomical anomalies and outcomes, including failure to respond to treatment or return of symptoms. Using advanced imaging techniques combined with a characterization of the clinical presentation, we assessed whether urethral anatomy assessment is an integral part of any diagnostic protocol for adults with recurrent urinary problems and whether or not these should be included in the guidelines for diagnosing and treating these patients.

MATERIALS AND METHODS

Study Design and Setting: A multi-institutional, prospective observational cohort study was conducted from January 1 – December 31, 2022 after receiving institutional review board (IRB) approval at each center and obtaining written informed consent from all participants. Inclusion Criteria: 18 years of age or older; history of two or more culture-documented urinary tract infections (UTIs) or symptoms of urethral discomfort (dysuria, urgency, frequency, post-void dribbling) persisting for 3 or more months; confirmation of inflammatory uropathy by cystoscopy demonstrating the presence of mucosal erythema, friability, or edema; urine cytology revealing more than 10 white blood cells (WBCs) per high-power field (hpf) with no evidence of bacterial infection; and histopathology, if biopsy performed, demonstrating significant chronic inflammation. Exclusion Criteria: Active urothelial cancer; neurogenic bladder; recent (within 3 months)

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urological instrumentation or surgery; pregnant. Sample Size: The estimated sample of 1200 based upon a pilot study (n=150) that identified a prevalence of urethral anomalies in patients with pelvic inflammatory disease (PID) of 28% would allow for an ability to detect a 10% difference in anomaly prevalence between PID patients and controls with 90% power (α=0.05). A comparison group was not utilized due to logistical limitations, rather the findings were analyzed between PID patients with and without an anatomical variant. All patients underwent a high resolution pelvic MRI (3T) T2 weighted sequence to evaluate soft tissue anatomy; Retrograde Urethrogram (RUG); Voiding Cystourethrogram (VCUG); and Urodynamic Studies (UDS) to determine voiding efficiency. Symptom scoring was done using standardised criteria developed by U POINT system [6]. To perform Microbiological workups on the subject's urine specimens, a midstream urine culture and PCR testing for Chlamydia trachomatis and Mycoplasma genitalium were completed. Different anatomical variations associated with the urinary tract were defined as follows: A meatal stenosis is a meatal diameter of <4 Fr as seen during urethroscopy; a urethral diverticulum is defined by an outpouching seen on retrograde urethrogram (RUG) or MRI, where the outpouching communicates with the urethral lumen; a urethral duplication indicates two urethral channels located either sagittal or Y-type; PUVs are seen in males only and are defined as a membranous obstruction in the prostatic urethra; and an Ectopic Orifice is defined by an individual's urethral meatus being located outside of its normal anatomical position (e.g., perineal, vaginal, or penoscrotal). Data were analysed using software programs, SPSS v28.0 and R v4.2.2. Categorical variables were compared using the Chi-Square test or Fisher's exact test; Continuous variables were compared using either the t-test or the Mann-Whitney U-test. To determine the independent associations between the variables, a multivariate logistic regression was used, adjusting for age, sex, diabetes, and previous catheterisation. A p value of <0.05 was used to indicate significance.

RESULTS

A total of 1,218 patients (724 females, 494 males; mean age: 42.3 ± 11.7 years) were enrolled. Anatomical variations were detected in 382 (31.4%) patients. Baseline characteristics are summarized in Table 1. Patients with anatomical variants were more likely to be female, older, diabetic, and have a history of catheterization. Symptom burden (UPOINT) was significantly higher ($p < 0.001$).

Meatal stenosis and diverticula were predominantly female; PUVs were exclusively male. Duplication showed equal sex distribution.

Defined as persistent symptoms or recurrence within 6 months despite guideline-based therapy.

Anatomical variants doubled the risk of treatment failure after adjusting for confounders.

After multivariate adjustment, specific anatomical variants remained strong independent predictors of persistent inflammation.

Table 1: Baseline Demographics and Clinical Features by Presence of Urethral Anatomical Variation (n=1,218)

Variable	With Variation (n=382)	Without Variation (n=836)	p-value
Female, n (%)	287 (75.1)	437 (52.3)	<0.001
Mean age (years)	44.9 ± 10.2	41.1 ± 12.1	0.002
Diabetes, n (%)	78 (20.4)	132 (15.8)	0.047
Prior catheterization, n (%)	142 (37.2)	201 (24.0)	<0.001
Mean UPOINT score	8.7 ± 2.1	6.3 ± 1.9	<0.001

Table 2: Prevalence of Specific Urethral Anatomical Variations (n=382)

Variation	n (%)	Female (%)	Male (%)
Meatal stenosis	153 (12.6)	132 (86.3)	21 (13.7)
Urethral diverticulum	119 (9.8)	116 (97.5)	3 (2.5)
Ectopic orifice	77 (6.3)	68 (88.3)	9 (11.7)
Urethral duplication	22 (1.8)	11 (50.0)	11 (50.0)
Posterior urethral valves	11 (0.9)	0 (0)	11 (100)

Table 3: Association Between Anatomical Variations and Recurrent UTIs (≥3 episodes/year)

Variable	Recurrent UTI, n (%)	OR (95% CI)	p-value
Any variation	214/382 (56.0)	2.41 (1.89–3.08)	<0.001
Meatal stenosis	98/153 (64.1)	2.87 (2.04–4.04)	<0.001
Urethral diverticulum	82/119 (68.9)	3.12 (2.18–4.47)	<0.001

Both stenosis and diverticula strongly predicted recurrent UTIs ($p < 0.001$).

Table 4: Treatment Failure at 6-Month Follow-Up

Group	Failed Therapy*, n (%)	Adjusted OR (95% CI)	p-value
With variation	196/382 (51.3)	2.78 (2.15–3.60)	<0.001
Without variation	203/836 (24.3)	Reference	—

Table 5: Multivariate Logistic Regression for Persistent Inflammation (Histology-Confirmed)

Predictor	aOR (95% CI)	p-value
Meatal stenosis	2.94 (2.01–4.30)	<0.001
Urethral diverticulum	3.21 (2.19–4.71)	<0.001
Female sex	1.87 (1.32–2.65)	0.001
Age >45 years	1.62 (1.18–2.22)	0.003
Prior instrumentation	2.05 (1.51–2.79)	<0.001

DISCUSSION

This study of multiple centers shows that most adult patients who have long-term inflammatory (non-infectious) urinary tract diseases show various anatomic types of abnormalities of the urinary passageway. These anatomical abnormalities may be responsible for some of the complications associated with this type of infection. The incidence of these anatomical variations in adults with non-infectious urinary tract infections (31.4%) was much higher than in the general population (<5%)[7]. Thus it seems highly like that these anatomical abnormalities may also contribute to the occurrence of these urinary tract infections.

That women with meatal (urethral) stenosis (narrowed openings) and uronephric diverticula (bulges or outpouchings in the urethra) have an increased occurrence of urinary tract infections supports previous studies on meatal stenosis and urinary tract diverticula that demonstrate a strong connection to recurrent urinary tract infections[4-8]. Meatal stenosis is often the result of injury caused by catheter use and/or scarring from inflammation, leading to obstruction of urine flow through the urethra and resulting in increased intraluminal urine pressures and increased microtrauma. Eventually the inflammation caused by chronic microtrauma, in the absence of infection, results in the condition referred to as the "urethral syndrome" Chapple & others 2009[9].

The divirticula, while traditionally associated with dysuria and/or urinary dribbling and/or dyspareunia (painful sexual intercourse), have increasingly been recognized as sites for urinary tract pathogen accumulation. The return of urine from these diverticular sacs to the bladder creates a situation where the protective capabilities of the immune system and antibiotics cannot reach the pathogens that reside within these sacs. 68.9% of our patients with diverticula had recurrent urinary tract infections, consistent with the concept that stagnant urine is an escape route for pathogens from the bladder (Hahn 2010)[10]. Importantly, the slightest variations such as ectopic orifices, which would generally be considered incidental, are associated with non-success [of treatment]. An ectopic meatus may alter the flow of urine and/or provide an opportunity for the contamination of the perineum, therefore acting as a source of constant irritation. This emphasizes the need for careful anatomical evaluation in refractory cases of chronic pelvic pain syndrome (CPPS). The lack of an appropriate healthy control group in this study represents a limitation; however, the degree of association (ORs >2.5), as well as biological plausibility, provides a strong argument supporting the findings of this study[11]. Furthermore, although MRI and retrograde urethrography (RUG) are sensitive techniques to evaluate the lower urinary tract, some minor irregularities may not have been

detected with either modality. Until further clinical studies are conducted, RUG and voiding cystourethrogram (VCUG) should be included in the initial workup of patients with PIU, particularly for women and any persons who have previously undergone instrumentation or had treatment failures.

Anatomical differences in the urethra might be creating other problems for people outside of just physical or immonologic aspects such as how they experience neurogenic dysregulation in their bladder (Urethra Dysfunction). The chronic irritation that can develop from these Types of Variation can change the way their body responds to that irritation by causing an increased number of cytokines such as IL-6 or TNF-alpha, or cause nerves to intensify sensitivity or develop a sensitivity to the usual sensations of urine filling the bladder[12]. This would also help to explain why some individuals still experience dysuria and urgency even after having their urine cultures sterlized (People often assume that these cases are psychosomatic because there is no visible pathology when in truth several things need to occur to cause these situations).

Furthermore, based on the fact that there are differences in urethral anatomy, we feel there is value in having the Urethral Anatomy defined as a diagnostic tool. Currently, most Empiric Treatments for many of these cases are based on a Functional Basis rather than a Physical, and therefore there can be a lag in providing diagnoses to patients when there is no obvious pathology to treat a specific patient issue[13].

Empirically, if we accept that there are indeed anatomical differences for people with chronic infections, it stands to reason that they may benefit more from diverticulectomy versus long-term prophylactic antibiotics (which can lead to developing resistance and disrupting their microbiome). Similarly, if there are patients with stenosis that affect how they urinate or create problems that create discomfort for them, this could lead to the need for meatal dilation or meatoplasty in order to allow for a more laminar flow of urine, decreasing the amount of trauma on the mucosa and interrupting the cycle of inflammation and infection.

Ultimately, although the primary focus of this investigation has been on the macroscopic (i.e., observable) skeletal muscle anatomy, the latest studies on microanatomy (microscopic abnormalities) such as ectasia (enlargement of a duct) of the Skene gland ducts or submucosa-fibrosis associated with pelvic inflammatory disease (PID), and others will likely enhance our interpretation of PIU. As new imaging technologies (e.g., endourethral optical coherence tomography or in-vivo contrast-enhanced ultrasound) become available, it should be possible to visualize the minute (i.e., microscopic) changes occurring within the urethra and better connect the macroscopic and microscopic areas.

To sum it all up, although the urethra has traditionally been considered a passive junction between the bladder and the genitals, it should now be regarded as an active, vulnerable segment of the urinary tract system and vital for maintaining urine-output equilibrium (or urinary homeostasis). The identification and treatment of the various anatomical (macroscopic) and microscopic (microanatomical) changes and abnormalities, as well as the potential for the introduction of advanced imaging technologies, are critical to the realization of a precision approach to urology.

CONCLUSION

Patients with chronic urinary tract inflammatory disorders have a high incidence of anatomical differences in the urethras and may represent an independent indicator of both disease progression and treatment success or failure. As such, it is imperative that diagnostic protocols for chronicurtinary tract inflammatory disorders include routine imaging studies to evaluate urethral anatomy to uncover potential correctable causes of disease and therefore enhance patient care.

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