Treatment of Female Urethral Syndrome Refractory to Antibiotics

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Various methods of treatment, other than antibiotic therapy, have been proposed for the treatment of female urethral syndrome; however, the results of these treatment methods are disappointing, due perhaps to the use of the wrong treatment approach. The aim of this study was to evaluate the effectiveness of external sphincter relaxant and biofeedback (BFB) with electrical stimulation therapy (EST) in patients who do not respond well to antibiotics.

One hundred and five patients with a diagnosis of female urethral syndrome were entered into this study. Antibiotics were given as a first-line therapy for about 3 months. In cases of recurrent or incurable urethral syndrome, antibiotic therapy combined with external sphincter relaxant or BFB with EST were performed. External sphincter relaxant was composed of 31 patients (29.5%) who showed functional urethral obstruction. Biofeedback group was composed of 41 patients (39.0%) who had severe pain or discomfort with irritative voiding symptoms. Subjective symptom was measured before and after therapy using the Bristol Female Lower Urinary Tract Symptoms questionnaire.

Thirty-three patients (31.4%) were treated with antibiotic therapy alone and 7 (21.2%) of these patients recurred. The symptom score of this group changed from 10.51 to 2.85. In the antibiotics plus external sphincter relaxant group (N=31), the symptom score changed from 12.39 to 3.96. Five (16.1%) of these patients recurred and 3 of these 5 underwent urethral dilatation. In the antibiotics plus biofeedback group (N=41), the average urinary frequency changed from 12.2 to 7.7 times a day and nocturia changed from 2.4 to 0.6 times a night. The symptom score improved from 15.22 to 4.69 and the overall satisfaction rate was 87.8% (41.5%: very satisfied, 46.3%: satisfied, 12.2%: no response).

Female urethral syndrome is not due to a single factor but is a complex disease due to various combined symptoms and mechanisms. This condition needs to be treated with an appropriate treatment protocol. We believe that satisfactory results could be obtained in female urethral syndrome, which has shown poor prognosis until now, by appropriately combining treatment methods, which include the use of external sphincter relaxants, biofeedback therapy and bladder training, according to indication, and depending on whether symptoms continue after initial antibiotic therapy.

**Key Words:** Female urethral syndrome, antibiotics, biofeedback

**INTRODUCTION**

During recent years, urologists have been faced with many female patients who show symptoms of chronic bladder irritation without organic causes or urethral infection, in which the diagnosis is inaccurate and that does not respond well to treatment. With no definition and no clear mechanism elucidated, and no clear accepted treatment methodology, no objective data have been reported for female urethral syndrome, which continues to be treated on the basis of the individual doctor’s diagnosis and preferred treatment method, in accord with personal experience.

Furthermore, much controversy exists in the definitions of and relationship between female urethral syndrome and interstitial cystitis.¹ ² These two diseases are recently considered as a single disease expressed in different time frames. It is known that as infection of the paraurethral gland and local irritation become chronic in women who were exposed to frequent acute bladder infection in their younger years, the symptoms worsen according to functional abnormality resulted in

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the bladder together with bladder irritating symptom and then inflammation eventually moves to the bladder, progressing to interstitial cystitis. Although some physicians view this entire process as a part of the process leading to interstitial cystitis, these two are in fact separate entities, since despite having similar symptoms, female urethral syndrome is initiated at the urethra and interstitial cystitis, at the bladder. Furthermore, Koreans whose main diet includes Kimchi, which contains a significant amount of capsaicin that is used in the treatment of interstitial cystitis, may show a different pattern of treatment response to this drug compared with Westerners. However, no accurate report is available on this subject. Thus, a new awareness and approach are needed for the treatment of female urethral syndrome.

The effect of different treatment methods used in the treatment of female urethral syndrome other than antibiotic therapy was shown to be disappointing maybe because of wrong treatment approaches. The fundamental issue about this syndrome was recently reported as, local infection within the urethra, which results in secondary changes in the periurethral muscles, and the detrusor or other nerves that becomes chronic. Therefore, we believe that even when no inflammation is shown by urinalysis, antibiotics should be administered initially and appropriate care should be given.

In the current study, we applied treatment protocols, which including the use of smooth muscle relaxant, bladder training, and biofeedback therapy, according to the patient's characteristics. We evaluated the treatment results obtained for each method and the overall treatment results, and identified those factors affecting treatment in patients with female urethral syndrome who did not respond well to antibiotic treatment.

MATERIALS AND METHODS

Subjects

The current study included 105 patients who were diagnosed with female urethral syndrome at the Department of Urology of Inha University Hospital from March 1998 to February 2000. The diagnosis of female urethral syndrome was made based on the presence of clinical symptoms, including, frequency, urgency and suprapubic discomfort, no abnormal findings by physical examination, including a neurologic test and a pelvic examination, and no inflammation according to the results of urinalysis and urine culture in patients who were 18 years or older. Radiography, cystoscopy and urodynamic study were performed in all patients. Differential diagnosis was made with respect to bladder and urethral tumors, stone, diverticulum, detrusor hyperreflexia and unstable bladder with detrusor instability. We excluded those patients interstitial cystitis with findings of gomerculation or Hunner's ulcer.

Treatment methods

Treatment was performed based on the treatment criteria set for female urethral syndrome by our hospital (Fig. 1). Under the assumption that the underlying cause was specific infection of the female paraurethral gland, initially we orally administered quinolone antibiotics in all patients. When patients improved with antibiotic therapy in terms of subjective symptoms, long-term antibiotic therapy was performed for 3 months, according to the continuation of symptoms. When patients did not any response or showed worsening, a basic examination done before treatment was performed for a second time. Referring to the frequency-volume chart, uroflowmetry and videourodynamics study were selectively performed in patients with suspected functional abnormality of the bladder or urethra. Two types of urethral obstruction were observed by videourodynamics study. These two were, the complete funneling at the bladder neck even after urine voiding had started through the urethra, in conjunction with increased Electromyography (EMG); and the second involved obstruction at the external sphincter with increased EMG even with complete opening of the bladder neck (Fig. 2). We believe that the latter type was due to spasm of the external sphincter. Furthermore, at rest, we also observed the maximum urethral closure pressure increased to more than 100cmH2O with patients at rest. We performed urethral dilation...
from 12 Fr to 26 Fr with Metal Sound in three patients who showed mechanical obstruction by uroflowmetry and cystoscopy. The external sphincter relaxant diazepam was given orally at 1 mg twice a day to 31 patients (29.5%) who showed functional obstruction of the external sphincter due to spasm, by videourodynamic study. Depending on whether the patient responded to the drug, the dose was increased up to 4 mg a day. The average treatment period with this drug was 78 days (7-220 days).

Biofeedback therapy was performed in 41 patients (39.0%) who did not respond to antibiotic therapy and did not show any abnormal results by videourodynamic study, but who complained of discomfort or pain during urination related with bladder distention and who urinated more than 8 times a day, according to their urination diary. This therapy was performed twice a week for an average of 6 weeks using a vaginal probe. Transvaginal electrical stimulation (20 Hz, no resting period, Compact Elite, ECL, France) was also performed at each biofeedback therapy session to help recognize and isolate the pelvic floor muscles. Voiding physiology and the effects of the pelvic muscles on urination were fully explained to these patients and biofeedback therapy was used to train them how to voluntarily control pel-
vic muscle tension. In addition, bladder training at the time of urination was done in these patients using the acquired voluntary relaxation technique, after explaining to them that pain felt at the time of bladder distention is related with pelvic floor muscle spasm, and that this spasm can be reduced and the voiding interval increased by relaxing the muscle by pelvic muscle exercise.

Treatment result evaluation and analysis

In order to examine the effectiveness of our treatment method, we observed changes in voiding symptoms before and after treatment using the symptom scores obtained through the Bristol Female Lower Urinary Tract Symptoms questionnaire, which is an objective index of female voiding symptoms. The symptom scores were obtained using 9 items, which included 3 items on stimulation symptoms (daytime frequency, urgency, and nocturia), 4 items on obstruction symptoms (hesitancy, weak urine stream, intermittency, and residual urine sense), one item on suprapubic discomfort, and one item on dysuria. The symptom score of each item was from 0 to 5 points, 0 was given when no symptom was present and 5 was given when the symptom was constantly present. In addition to the symptom scores, we evaluated patient satisfaction with treatment and observed changes in the voiding pattern by referring to a voiding diary to evaluate the biofeedback (BFB) therapy results. BFB results were assessed and classified according to changes in symptoms: unsatisfactory, when no improvement was seen in symptoms or when symptoms recurred within 4 months of treatment completion; partial response, when clear but not total relief of symptoms was seen in patients requiring no further treatment, or when patients relapsed more than 4 months after treatment with fewer, less intense acute episodes; and satisfactory, i.e. when total relief from symptoms was achieved and no relapse occurred within 6 months of completing therapy.

RESULTS

The average age of our patients was 47.7 years (26-77 years), with 41 patients (39.0%) in their 40's. The average duration of illness was 30.6 months (range 3 months to 10 years), and 67 patients (63.8%) had a disease history of less than 2 years. Eleven patients (10.5%) had received previous pelvic surgery (9 total abdominal hysterectomy, and 2 ovarian operations), 41 (39.0%) were in menopause, and no patient showed any neurologic abnormality (Table 1).

Table 1. Patient Characteristics (n=105)

<table>
<thead>
<tr>
<th>Age of patients</th>
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</thead>
<tbody>
<tr>
<td>20-29</td>
<td>6 (5.7%)</td>
</tr>
<tr>
<td>30-39</td>
<td>20 (19.0%)</td>
</tr>
<tr>
<td>40-49</td>
<td>41 (39.0%)</td>
</tr>
<tr>
<td>50-59</td>
<td>20 (19.0%)</td>
</tr>
<tr>
<td>60+</td>
<td>18 (17.3%)</td>
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<table>
<thead>
<tr>
<th>Duration of symptoms (months)</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-menopause</td>
<td>30.6 (3-120)</td>
</tr>
<tr>
<td>Menopause</td>
<td>64 (61.0%)</td>
</tr>
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</table>

The average symptom scores before and after treatment, by treatment method were, 10.51 and 2.85, respectively, in the antibiotic therapy group; 12.39 and 3.96 in the external sphincter relaxant group, and 15.22 and 4.69 in the biofeedback therapy group. Thus, the scores after treatment all decreased significantly (Fig. 3).

Among a total of 105 patients, 67 (63.8%) showed an improvement in more than one of their symptoms and 33 (31.4%) showed a complete response to antibiotic therapy alone. The average treatment period of antibiotic group was 77 days (6-296 days) and no recurrence was observed in 26 (78.8%) during an average follow-up period of 17.3 months, but recurrence occurred in 7 (21.2%) of the 33 within an average follow-up of 3.5 months, and these patients were retreated.

Antibiotic therapy was not effective and some voiding symptoms continued in 72 patients (68.6%). In 31 (29.5%) of these 72, the pretreatment scores of frequency, nocturia, residual urine sense, urgency, and low abdominal discomfort of 2.86, 1.57, 1.64, 2.03, and 2.07, respectively, all improved to 0.96, 0.39, 0.57, 0.71, and 0.57, after the treatment with the administration of external...
sphincter relaxants (Table 2). The symptoms of frequency, nocturia, residual urine sense, urgency, and low abdominal discomfort among all 105 patients, were present in 28 (90.3%), 22 (70.9%), 22 (70.9%), 19 (61.3%), and 23 (74.2%), respectively, before treatment and in 21 patients (67.7%), 6 (19.4%), 9 (29.0%), 5 (16.1%), and 6 (19.4%) after treatment. The number of voidings decreased in those patients who showed frequent urination with a voiding interval increase from an average of 1.1 h to 2.4 h. During the follow-up period, no specific complication resulted due to the antibiotics used. Symptoms recurred in 5 patients (16.1%) of antibiotic treatment group, in whom we performed urethral dilation due to the presence of urethral adhesions.

With changed voiding symptoms, most of 41 patients (39.0%) who were treated using BFB therapy showed an improvement in frequency, nocturia, residual urine sense, urgency, and low abdominal discomfort with scores of 3.28, 2.31, 2.19, 1.94, and 2.19, respectively, before treatment to 1.13, 0.59, 0.97, 0.41, and 0.44 after treatment (Table 2). Symptoms of frequency, nocturia, residual urine sense, urgency, and low abdominal discomfort among the 41 patients treated with BFB therapy were present in 38 (92.6%), 28 (68.2%), 32 (78.0%), 18 (43.9%), and 37 (90.2%) patients, respectively, before treatment but present only in 8 (19.5%), 4 (9.7%), 18 (43.9%), 2 (4.8%), and 4 (9.7%) after treatment. During BFB therapy, no patient refused or complained of complica-

Table 2. Changes of Each Representative Items of Bristol Symptom Scores between Pretreatment and Posttreatment, which Ranged from 0 to 5 Points, in 72 Patients Refractory to Antibiotics

<table>
<thead>
<tr>
<th>Treatment Methods</th>
<th>Each Symptom</th>
<th>Frequency</th>
<th>Nocturia</th>
<th>Residual Urine Sense</th>
<th>Urgency</th>
<th>Low abdominal Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibioc Therapy Group</td>
<td>Pretreatment</td>
<td>2.86 ± 1.38</td>
<td>1.57 ± 1.21</td>
<td>1.64 ± 0.94</td>
<td>2.03 ± 1.47</td>
<td>2.07 ± 1.29</td>
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<tr>
<td></td>
<td>Post-treatment</td>
<td>0.96 ± 0.56*</td>
<td>0.39 ± 0.29</td>
<td>0.57 ± 0.23</td>
<td>0.71 ± 0.59*</td>
<td>0.57 ± 0.37*</td>
</tr>
<tr>
<td>External Sphincter Relaxant Group</td>
<td>Pretreatment</td>
<td>3.28 ± 1.86</td>
<td>2.31 ± 1.23</td>
<td>2.19 ± 1.01</td>
<td>1.94 ± 0.94</td>
<td>2.19 ± 1.31</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>1.13 ± 0.73</td>
<td>0.59 ± 0.31*</td>
<td>0.97 ± 0.57</td>
<td>0.41 ± 0.28*</td>
<td>0.44 ± 0.31*</td>
</tr>
</tbody>
</table>

*p < 0.05.
DISCUSSION

Since Gallagher described lower urinary tract symptoms, including frequency, urgency, and suprapubic discomfort in women in 1965, female urethral syndrome has been defined vaguely depending upon the presence of subjective symptoms rather than upon objective findings in patients, and therefore, much controversy exists concerning this syndrome. However, female urethral syndrome still draws the attention of many clinicians, because a significant number of patients are affected. Han and reported that 50% of American women are affected more than once a year, and that about 5 million women visit hospitals each year because of this syndrome. Although no accurate statistical figures are available in Korea, it is evident that many women visit hospitals with the symptoms of female urethral syndrome.

Antibiotic therapy is used most extensively to treat this disease, based on past results that tetracyclines are effective against unculterable intraurethral bacteria. Parziani and colleagues reported high rates of isolating Ureaplasma urealyticum and Chlamydia trachomatis in patients with female urethral syndrome compared with controls, thus claiming an infection theory. Other studies on the other hand, found difficulty in isolating these fastidious strains, thus causing confusion concerning the causal agent of this syndrome. However, Gittes and Nakamura recently claimed that local infection within the urethra is the most fundamental cause based on the concept that the microscopic female paraurethral gland, within the prevaginal space, is located at 1/3 of the distance from the urethra end is the homologous tissue as the prostate in men so that this syndrome can be considered as female prostatitis similar to prostatitis in men. They reported that these two types of tissues were stained similarly with prostate specific antigen (PSA) as in prostatitis. They further confirmed paraurethral gland inflammation by promoting tenderness in the urethra through the anterior vaginal wall. Furthermore, they used prolonged treatment with more potent antibiotics to improve voiding symptoms and cure the tenderness symptom of the paraurethral gland, and thus proposed that infection is the fundamental cause.

Bergman et al. reported that tetracycline produced a 50% subjective cure rate, but failed to produce an objective improvement by uroflowmetry. In the present study, we observed that more than one symptom was improved in 64% of patients only by antibiotic therapy and that all symptoms were lost in only 33%. We did not find evidence of urethral infection through urinalysis and cell culture in 31% of patients who showed only a partial response to antibiotic therapy. Therefore, we presumed that another cause or mechanism functions with intraurethral infection. Nevertheless, no response to antibiotics does not mean that infection cannot be a cause. Our theory on female urethral syndrome is that these patients initially become infected as do male patients with prostatitis, and that mechanical or functional obstruction is induced due to a prolonged period of infection or antibiotics become ineffective due to the occurrence of other neurologic changes. Based on this theory, we initially treated patients with female urethral syndrome with antibiotics and then used other methods of treatment in patients who did not respond well to antibiotics, after determining other co-existing complications.

Active urethral dilation or urethroplasty was attempted to counteract the possibility of another cause of female urethral syndrome other than infection, i.e., fibrosis of the periurethral tissues due to mechanical obstruction. Bergman et al. reported that symptoms improved by draining small abscesses in the paraurethral gland and
submucosal tissue expansion after dilation. Symptomatic relief was reported by 75% of patients treated with dilation. We also found improved symptoms in 3 patients, who showed urethral obstruction by uroflowmetry, after urethral dilation. We believe that mechanical obstruction, such as urethral stricture, is the cause in relatively few patients and that repeated probe insertion might result various complications involving the urethral mucosa, such as injury, pain and bleeding, and therefore, we believe that urethral dilation should be limited.

On the other hand, some researchers have proposed neurologic factors as the major mechanism of external sphincter spasm. Many researchers have found by videourodynamic study that spasm of the external sphincter is the result of an increased closing pressure of the external sphincter in many patients, and that this spasm is related with irritative voiding symptoms. We performed a videourodynamic study in patients who could not be treated with antibiotics and confirmed functional obstruction of the urethra and increased urethral closing pressure at the time of voiding in 72 (69%) out of 105 total patients. Thirty-one (43%) of these patients were treated with external sphincter relaxants, and 41 (57%) required BFB therapy.

Schmidt claimed that the wrong voiding habit, caused by emotional tension or stress can be a cause in female urethral syndrome and that inappropriate tension and spasm of the external sphincter could be inhibited by voluntary control of the pelvic floor muscles, suggesting the potential effectiveness of bladder training and BFB therapy. We found a high patient satisfaction rate (87.9%) among patients after BFB therapy. By applying the acquired pelvic floor muscle exercise, we believe that those patients who expressed satisfaction after BFB therapy could alleviate bladder distension or pain/discomfort at the time of voiding, and could facilitate the voiding start by decreasing pressure to the external sphincter. Therefore, we believe that BFB therapy could play an important role in patients with chronic and functional voiding difficulty, and who are not responsive to drug treatment.

In order to compare the efficacies of different treatment methods in one disease, each method should be applied to defined patient groups and the results need to be compared. This type of research has been performed on many occasions in female urethral syndrome. It was found that when disease is comprehensively observed to be present, that a single treatment method does not produce a satisfactory result. Researchers recently focused on identifying the main mechanism of voiding difficulty due to infection and the prolongation of infection. Methods of treatment and observations of treatment efficacy need to be changed according to the mechanism proposed. We obtained a high success rate of 88%, because we initially used antibiotic therapy, and followed this with different treatment methods, according to a treatment protocol that we set up for the treatment of voiding difficulties. We believe that appropriate care delivered by a treatment protocol based on considerations of the symptoms and of the patient characteristics would result in a satisfactory prognosis. Through further studies are required on the roles of and on the relationship between lower urinary tract symptoms and other causes, treatment direction should be established to improve prognosis in female urethral syndrome, the treatment of which remains in its infancy.

In conclusion, even though female urethral syndrome probably starts with infection and local inflammation of the microscopic pararectal gland in females, when infection continues for a prolonged period, it has been shown that various deleterious changes, including urethral obstruction and bladder instability, progress due to urethral adhesion, external sphincter spasm, and problems related to relaxation due to secondary changes of the urethra and bladder, i.e., periurethral fibrosis, inflammation and degenerative changes. Hence, this syndrome is not due a single etiology but is due to complex symptoms and mechanisms, which require an appropriate treatment protocol. We believe that prognosis could be improved in this syndrome, which currently is associated with a poor prognosis, when it is treated initially with antibiotics, followed by the use of external sphincter relaxants, biofeedback therapy and/or bladder training according to indications when symptoms as they arise.
REFERENCES


