
Voiding Dysfunction and the Williams-Beuren Syndrome: A Clinical and Urodynamic Investigation

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Purpose: WBS is an autosomal dominant disorder that includes features such as developmental delay, cardiovascular anomalies, mental retardation and characteristic facial appearance. We systematically investigated the prevalence and spectrum of voiding dysfunction in this population.

Materials and Methods: We prospectively evaluated 16 boys and 12 girls with WBS, with a mean age of 9.7 years (range 3 to 19). Urological evaluation included history of urinary symptoms and impact on quality of life, voiding diary, urodynamics and radiological evaluation with urinary tract sonography, voiding cystourethrography and renal scintigraphy.

Results: A total of 22 patients (78.6%) were symptomatic, including 15 (53.6%) with a significant negative impact on the quality of life. Increased urinary frequency was the most common complaint, present in 17 patients (60.7%), followed by enuresis (50%) and urge incontinence (42.8%). A total of 14 patients (50%) had urinary tract abnormalities, with bladder diverticula as the predominant anomaly (10 of 23 patients, or 43.5%). Urodynamics revealed detrusor overactivity in 17 patients (60.7%), detrusor-sphincter dyssynergia with detrusor overactivity in 4 (14.3%) and detrusor-sphincter dyssynergia without detrusor overactivity in 2 (7.1%). An average reduction of 28.3% of the cystometric capacity in comparison to expected capacity for age was found ($p < 0.001$). Urodynamic abnormalities were significantly associated with the presence of voiding symptoms ($p = 0.003$) and bladder diverticula ($p = 0.001$).

Conclusions: Children with the Williams-Beuren syndrome are at high risk for presenting with voiding dysfunction and structural abnormalities, and should undergo a minimum evaluation that includes voiding history and urinary tract sonography, while urodynamics, VCUG and additional studies should be performed in symptomatic patients or those whose initial evaluation shows significant abnormalities.

Key Words: Williams syndrome, urodynamics, urinary incontinence

WBS is a rare condition with striking physical and behavioral features that occurs in 1 of 20,000 to 50,000 live births.¹ Cases are generally sporadic but familial cases with an autosomal dominant mode of inheritance have been reported. The condition results in a complex phenotype with physical, cognitive and behavioral aspects that include a peculiar face, congenital heart disease (typically supravalvular aortic stenosis), psychomotor retardation, hyperacusis, premature aging and a characteristic outgoing personality.^{2,3} These features are caused by deletion of a region at chromosomal position 7q11.23 on either the maternal or paternal chromosome 7.⁴ Various genes have so far been described in the affected area, yet only elastin hemizyosity has been confidently associated with any aspect of the WBS phenotype.

The diagnosis of WBS is made initially by clinical evaluation, usually during mid childhood, when the characteristic facial features, cognitive profile and cardiac findings become more apparent. Fluorescence in situ hybridization probes are used to confirm the clinical diagnosis by attempting to

demonstrate the characteristic submicroscopic deletion on the long arm of chromosome 7 at band 7q11.23. This laboratory technique is especially helpful, since there is variable expression of the WBS features, which makes clinical diagnosis particularly difficult during the first years of life.

Urological anomalies have been described in many WBS series, which have revealed that the risk of a structural abnormality of the kidneys and urinary tract is increased 12 to 36-fold compared to the normal population.⁵ The spectrum of these anomalies ranges from minor abnormalities such as bladder diverticula to more severe malformations such as renal aplasia or hypoplasia.^{6,7}

The prevalence of voiding dysfunction in patients with WBS appears to be increased but few studies have addressed this issue. In this study we systematically investigated the voiding symptoms of patients with WBS to determine the prevalence and spectrum of voiding dysfunction in this population.

MATERIALS AND METHODS

We prospectively evaluated 28 consecutive patients, including 16 boys and 12 girls with a mean age of 9.7 years (range 3 to 19). Patients were referred for evaluation by the Genetic Studies Unit of our hospital after being diagnosed with the Williams-Beuren syndrome.

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Study received institutional review board approval.

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Urodynamic Investigation

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Purpose: WBS is an autosomal dominant disorder that includes features such as developmental delay, cardiovascular anomalies, mental retardation and characteristic facial appearance. We systematically investigated the prevalence and spectrum of voiding dysfunction in this population. **Materials and Methods:** We prospectively evaluated 16 boys and 12 girls with WBS, with a mean age of 9.7 years (range 3 to 19). Urological evaluation included history of urinary symptoms and impact on quality of life, voiding diary, urodynamics and radiological evaluation with urinary tract sonography, voiding cystourethrography and renal scintigraphy. **Results:** A total of 22 patients (78.6%) were symptomatic, including 15 (53.6%) with a significant negative impact on the quality of life. Increased urinary frequency was the most common complaint, present in 17 patients (60.7%), followed by enuresis (50%) and urge incontinence (42.8%). A total of 14 patients (50%) had urinary tract abnormalities, with bladder diverticula as the predominant anomaly (10 of 23 patients, or 43.5%). Urodynamics revealed detrusor overactivity in 17 patients (60.7%), detrusor-sphincter dyssynergia with detrusor overactivity in 4 (14.3%) and detrusor-sphincter dyssynergia without detrusor overactivity in 2 (7.1%). An average reduction of 28.3% of the cystometric capacity in comparison to expected capacity for age was found (p 0.001). Urodynamic abnormalities were significantly associated with the presence of voiding symptoms (p 0.003) and bladder diverticula (p 0.001). **Conclusions:** Children with the Williams-Beuren syndrome are at high risk for presenting with voiding dysfunction and structural abnormalities, and should undergo a minimum evaluation that includes voiding history and urinary tract sonography, while urodynamics, VCUG and additional studies should be performed in symptomatic patients or those whose initial evaluation shows significant abnormalities.

Key Words: Williams syndrome, urodynamics, urinary incontinence

Williams-Beuren syndrome (WBS) is a rare genetic condition that occurs in 1 in 20,000 to 1 in 50,000 live births. Cases with WBS generally have striking physical and behavioral features. The condition results from a deletion of a region on chromosome 7q11.23, which contains several genes. The condition is characterized by a complex phenotype with physical, cognitive and behavioral aspects that include a peculiar face, congenital heart disease (typically supravalvular aortic stenosis), psychomotor retardation, hyperacusis, premature aging and a characteristic outgoing personality.^{2,3} These features are caused by deletion of a region at chromosomal position 7q11.23 on either the maternal or paternal chromosome.⁴ Various genes have so far been described in the affected area, yet only elastin hemizygosity has been confidently associated with any aspect of the WBS phenotype.

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demonstrate the characteristic submicroscopic deletion on the long arm of chromosome 7 at band 7q11.23. This laboratory technique is especially helpful, since there is variable expression of the WBS features, which makes clinical diagnosis particularly difficult during the first years of life.

Urological anomalies have been described in many WBS series, which have revealed that the risk of a structural abnormality of the kidneys and urinary tract is increased 12 to 36-fold compared to the normal population.⁵ The spectrum of these anomalies ranges from minor abnormalities such as bladder diverticula to more severe malformations such as renal aplasia or hypoplasia.^{6,7}

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Clinical assessment. The clinical investigation included a history of urinary symptoms of frequency, urgency, urge incontinence, dysuria and nocturnal enuresis that was jointly obtained from the parents and child, and a focused neurourological physical examination. A history of urinary tract infections was sought in each patient. For all patients a 3-day voiding diary was obtained and a structured questionnaire of urinary symptoms was completed.⁸ Additionally, 1 question concerning the quality of life with urinary symptoms was answered on a scale of 0 (“delighted”) to 6 (“terrible”) by the parents.⁹ A significantly impaired quality of life was defined for patients with a score of 2 or higher. All patients were investigated with urinalysis, urine culture and serum creatinine. Radiological evaluation included urinary tract sonography, voiding cystourethrography and dimercaptosuccinic acid renal scintigraphy.

Urodynamic evaluation consisting of free uroflowmetry and measurement of post-void residual urine, filling cystometry and pressure flow voiding studies, including electromyographic monitoring, was performed in all cases. Two 4Fr urodynamic catheters were inserted transurethraally into the bladder. Saline at room temperature was instilled through one of the catheters at a filling rate of 10 to 20 ml per minute, depending on the age of the child and expected bladder capacity.

Intravesical pressure was measured through the other catheter. The filling catheter was removed immediately before the voiding phase of the study. Abdominal pressure was measured with a rectal balloon catheter. Detrusor pressure was calculated electronically.

Electromyographic activity of the urethral sphincter was recorded using surface pelvic floor electrodes during bladder filling and voiding. Methods, definitions and units conformed to the standards recommended by the International Children’s Continence Society.¹⁰ Values for cystometric bladder capacity were interpreted in relation to expected values for age, using the formula recommended by the International Children’s Continence Society.¹⁰ Reduced bladder capacity was defined as 20% or greater reduction compared to expected capacity for age.

VOIDING DYSFUNCTION AND WILLIAMS-BEUREN SYNDROME 1473

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1. Voiding symptoms in children with WBS. UTI, urinary tract infection

Association of urodynamic findings with voiding symptoms and bladder diverticula. To investigate the clinical significance of the urodynamic findings, results were correlated with the presence of urinary symptoms and bladder diverticula.

Statistical analysis. Statistical comparisons between observed findings and those expected for the normal population were analyzed for statistical significance using the Kolmogorov-Smirnov test for normality and Student’s paired t test. Fisher’s exact test was used to assess the association of urodynamic abnormalities with the presence of voiding symptoms and bladder diverticula. Data were processed using commercially available statistical software, with p 0.05 considered significant.

RESULTS

Based on the symptoms questionnaire and the voiding diary, only 6 patients (21.4%) were asymptomatic or had mild urinary symptoms and were considered normal. Among the 22 symptomatic patients (78.6%) the most common urinary complaint was increased urinary frequency, occurring in 17 patients (60.7%). Nocturnal enuresis was found in 14 patients (50%) and urge incontinence in 12 (42.9%, fig. 1). Parents of 15 patients (53.6%) acknowledged that the voiding symptoms had a significant negative impact on patient quality of life (table 1).

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1. Impact of voiding symptoms on quality of life in children with WBS

No. Pts (%)

Delighted 9 (32.1) Pleased 4 (14.3) Mostly satisfied 5 (17.9) Mixed 4 (14.3) Mostly dissatisfied 4 (14.3) Unhappy 1 (3.6) Terrible 1 (3.6)

Total 28

Eight patients (28.6%) had a history of urinary tract infections but no patient had a positive urine culture at the time of evaluation. Serum creatinine was normal in all patients.

Radiological evaluation. All patients underwent urinary tract sonography, which was normal in 22 (78.6%). Two patients had small kidney stones. Other abnormalities were unilateral hydronephrosis, bladder wall thickening, renal cysts and pelvic hydronephrotic kidney, each affecting 1 patient.

Dimercapto-succinic acid kidney scintigraphy was obtained in 23 patients (82.1%). Five patients (17.9%) refused the examination. Findings were normal in 21 patients (91.3%) and showed renal scarring in 2 (8.7%). Both of the patients with scarring had a history of febrile urinary tract infections.

Cystography was performed in 23 patients (82.1%). Five patients (17.9%) refused the examination. Cystogram was normal in 13 patients (56.5%). Bladder diverticula with bladder wall trabeculation were present in 10 patients (43.5%), including 2 with solitary and 8 with multiple diverticula (fig. 2). No patient had vesicoureteral reflux.

Urodynamic findings. All patients completed urodynamic studies. Five patients (17.9%) had normal urodynamic findings. Detrusor overactivity was the most common urodynamic abnormality, affecting 21 patients (75%). In 4 children (14.3%) this finding was associated with detrusor-sphincter dyssynergia, and 2 additional children (7.1%) had detrusor-sphincter dyssynergia without detrusor overactivity. Average cystometric bladder capacity was 180.1 ± 107.4 ml. Expected bladder capacity for age was 254.1 ± 97.9 ml, with an average reduction of 28.3% of the cystometric capacity (p 0.001, fig. 3). A total of 18 patients (64.3%) had significantly reduced bladder capacity compared to expected capacity for age. This disparity was mostly due to detrusor overactivity, which resulted in the first involuntary detrusor contraction being transformed into a premature and forceful voiding contraction.

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2. VCUg in 7-year-old boy shows bladder diverticula, bladder wall trabeculation and uncoordinated voiding.

VOIDING DYSFUNCTION AND WILLIAMS-BEUREN SYNDROME 1474

Association of urinary symptoms with urodynamic findings and radiological abnormalities. A significant association of urodynamic abnormalities with the presence of voiding symptoms was observed (p 0.003, table 2). Of the 22 symptomatic patients only 1 had a normal urodynamic study. Among the asymptomatic patients 2 had urodynamic abnormalities. Likewise, a significant association of urodynamic abnormalities with the presence of bladder diverticula was observed (p 0.001), with all patients with bladder diverticula presenting with abnormal urodynamic findings, including 8 with detrusor overactivity, 1 with uncoordinated voiding, and 1 with detrusor overactivity and uncoordinated voiding.

DISCUSSION

Although many authors have studied structural abnormalities of the genitourinary system in patients with WBS, studies of voiding dysfunction are scarce. We performed a comprehensive evaluation of voiding dysfunction in a significant population of patients with WBS, including the impact of voiding symptoms on patient quality of life.

Morris et al were the first to describe increased urinary frequency and enuresis in children with WBS.³ Schulman et al reported a high prevalence of urinary symptoms in pa-

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3. Box plot analysis of cystometric and expected bladder capacity in children with WBS.

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2. Association of urodynamic abnormalities with voiding symptoms and bladder diverticula in patients with WBS

No. Absent No. Present p Value

Voiding symptoms:

Absent 4 2 0.003 Present 1 21 Bladder diverticula:

Absent 1 5 0.001 Present 0 10

tients with WBS.¹¹ In their series of 41 patients with WBS 13 (32%) had a history of urinary tract infection, increased frequency and incontinence. Only 10 patients were evaluated more extensively, including 5 patients who underwent urodynamic studies. Detrusor overactivity was found in 4 of these patients and detrusor-sphincter dyssynergia in association with a large cystometric capacity in 1. All of these patients had a history of dysfunctional voiding and none had vesicoureteral reflux.

In this study we prospectively investigated children with WBS with special attention to voiding symptoms. We found a high prevalence of voiding dysfunction, with more than 75% of patients with urinary symptoms and approximately 50% significantly bothered by these symptoms. The fact that voiding symptoms were prospectively sought in each patient, coupled with the fact that most of the symptomatic patients were bothered by the symptoms, indicates that this is truly a high risk population for voiding dysfunction.

Increased urinary frequency, enuresis and daytime wetting were the predominant symptoms, which is similar to previous reports. Accordingly, detrusor overactivity was the most common urodynamic abnormality, affecting 75% of the patients. This was the main reason for the observed decrease in cystometric capacity, which was 28.3% lower than expected bladder capacity for age. Six patients in our series (21.4%) had detrusor-sphincter dyssynergia, which is similar to the results of Schulman et al, who found the condition in 1 of 5 patients.¹¹

In our series voiding symptoms were associated with the prevalence of urodynamic abnormalities, and were accompanied by a significant negative impact on quality of life of the majority of affected patients. Of the 22 symptomatic patients only 1 had a normal urodynamic study. This finding confirms that urodynamic abnormalities are indeed significant, which is of particular importance, since the cognitive disability in patients with WBS might confound interpretation of the urodynamic studies.

Pankau et al evaluated 130 patients with WBS with urinary tract sonography, and demonstrated that the risk of a structural abnormality of the kidneys and urinary tract was increased 12 to 36-fold compared to the normal population.⁵ The spectrum of these anomalies ranged from minor abnormalities such as bladder diverticula to more severe malformations such as renal aplasia or hypoplasia. Other authors have reported similar results.^{6,7} Bladder diverticula have been reported as the most frequent structural abnormality of the urinary tract in patients with WBS.^{5,7,12} In the present study we observed structural urinary tract abnormalities in 14 patients (50%). The extent of the radiological investigation varied among patients, since not all completed the full radiological evaluation. Not surprisingly, bladder diverticula were the most common abnormalities, affecting 10 of 23 patients (43.5%) who underwent cystography. This number is probably close to the actual proportion of our patients with diverticula, since cystography was not performed in only 5 patients.

Bladder diverticula were significantly associated with urodynamic abnormalities, with all patients with bladder diverticula exhibiting abnormal urodynamic findings, including 8 patients with detrusor overactivity, 1 with uncoordinated voiding and 1 with both conditions. Schulman et al suggested that long-standing increased detrusor pressure against an inherently weakened bladder wall might be the

VOIDING DYSFUNCTION AND WILLIAMS-BEUREN SYNDROME 1475

cause of the high prevalence of diverticula in these patients.¹¹ In their series the patients with diverticula tended to be older, which they speculated could be related to a longer period of voiding dysfunction, increasing the likelihood of diverticula developing. However, in our series no difference in mean age of patients with and without diverticula was observed. In fact, our patients with bladder diverticula tended to be younger than those without diverticula, with a mean age of 10.0 vs 13.0 years (p 0.07).

Elastin is an important component of the bladder wall and is known to be altered in patients with WBS due to submicroscopic deletions of chromosome 7q11.23, which contains the elastin gene.^{4,13} This abnormality possibly contributes to most of the connective tissue pathological changes in WBS, and bladder diverticula may also be related.

Based on our findings, we propose an algorithm for the urological evaluation of patients with the Williams-Beuren syndrome (fig. 4). We recommend that all patients complete a clinical history of urological symptoms and voiding diary, urinalysis and urinary tract sonography. Asymptomatic patients with normal urinalysis and ultrasound should be followed periodically, while urodynamics and VCUG should be performed in significantly symptomatic patients. Additional imaging studies should be reserved for those with significant sonographic or cystographic abnormalities.

CONCLUSIONS

Patients with the Williams-Beuren syndrome have a high prevalence of urinary symptoms and urodynamic abnormalities, with a significant impact on quality of life. Structural abnormalities are also frequent and correlate with voiding dysfunction. Based on our findings, we recommend that all patients with WBS undergo a minimum urological evaluation to include voiding history,

urinalysis and urinary tract sonography, while urodynamics, VCUG and additional imaging studies should be performed in symptomatic patients

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4. Suggested algorithm for urological evaluation of children with WBS. DMSA, dimercapto-succinic acid renal scintigraphy. IVP, excretory urography. VCUG, voiding cystourethrogram.

or those whose initial evaluation reveals significant abnormalities.

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Abbreviations and Acronyms VCUG voiding cystourethrogram

WBS Williams-Beuren syndrome

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VOIDING DYSFUNCTION AND WILLIAMS-BEUREN SYNDROME 1476

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