The Effects of Oxybutynin on Urinary Symptoms in Children with Williams-Beuren Syndrome

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Purpose: Williams-Beuren syndrome is a genomic disorder caused by a hemizygous contiguous gene deletion on chromosome 7q11.23. Lower urinary tract symptoms are common in children with Williams-Beuren syndrome. However, there are few data on the management of voiding symptoms in this population. We report our experience using oxybutynin to treat urinary symptoms in children with Williams-Beuren syndrome.

Materials and Methods: We prospectively analyzed 42 patients with Williams-Beuren syndrome and significant lower urinary tract symptoms due to detrusor overactivity diagnosed on urodynamics in a 12-week, open-label study. Urological assessment included symptomatic evaluation, the impact of lower urinary tract symptoms on quality of life, frequency-volume chart, urodynamics and urinary tract sonography. After 12 weeks of treatment with 0.6 mg/kg oxybutynin per day given in 3 daily doses, patients were assessed for treatment efficacy and side effects.

Results: A total of 17 girls and 19 boys completed medical therapy and were assessed at 12 weeks. Mean ± SD patient age was 9.2 ± 4.3 years (range 3 to 18). The most common urinary complaint was urgency, which occurred in 31 patients (86.1%), followed by urge incontinence, which was seen in 29 (80.5%). Compared to baseline, urinary symptoms were substantially improved. The negative impact of storage symptoms on quality of life was significantly decreased from a mean ± SD of 3.3 ± 1.7 to 0.5 ± 0.9 ($p < 0.001$). Mean ± SD maximum urinary flow improved from 14.2 ± 15.0 to 20.5 ± 6.4 ml per second ($p < 0.001$).

Conclusions: A total of 12 weeks of therapy with 0.6 mg/kg oxybutynin daily resulted in improvement of lower urinary tract symptoms, quality of life and maximum flow rate in most patients with Williams-Beuren syndrome.

Key Words: lower urinary tract symptoms, oxybutynin, urination disorders, urodynamics, Williams syndrome

Abbreviations and Acronyms

WBS = Williams-Beuren syndrome

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Williams-Beuren syndrome is a rare genomic disorder caused by a hemizygous contiguous gene deletion on chromosome 7q11.23. Clinical findings of the syndrome consist predominantly of typical dysmorphic faces, supravalvular aortic stenosis, hypertension, mental retardation and atypical hypersocial behavior.[1–4]

Voiding symptoms including urinary incontinence are frequent in patients with WBS. It is estimated that 32% to 78% of patients present with lower urinary tract symptoms. The most common urinary complaints are increased urinary frequency, nocturnal enuresis, urgency and urge incontinence, which have a significant neg-

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ative effect on patient quality of life.[5,6] Several factors account for the high prevalence of voiding symptoms among patients with WBS, including bladder and sphincteric abnormalities. Urodynamic evaluation is abnormal in up to 82% of patients, with detrusor overactivity and dysfunctional voiding being the main findings.[5] The causes of vesicosphincteric dysfunction are not completely understood and may include neurological abnormalities, which are common in patients with WBS, and structural changes of the urinary tract such as bladder diverticula.

Antimuscarinic treatment has been successfully used in children with neurogenic voiding dysfunction and idiopathic detrusor overactivity.[7] However, the population with WBS has never been evaluated for medical treatment of voiding dysfunction. Additionally most of these patients have cognitive impairment. Finally, little is known regarding pharmacological treatment of voiding dysfunction in patients with cognitive limitations in terms of efficacy and the impact on cognitive impairment.

MATERIALS AND METHODS

A total of 20 girls and 22 boys with a diagnosis of WBS who had overt urinary storage symptoms and urodynamic proved detrusor overactivity and post-void residual volume less than 20 ml were enrolled in this prospective 12-week, open-label study between January 2004 and December 2009. The diagnosis of WBS was confirmed by fluorescence in situ hybridization, polymorphic markers or multiplex ligation dependent probe amplification.

After written informed consent was obtained, a history of storage symptoms including frequency, urgency, urge incontinence and nocturnal enuresis was jointly obtained from the parents and child, and a structured questionnaire of urinary symptoms was completed.[8] A 3-day frequency-volume chart was obtained. Additionally we used the quality of life question of the International Prostate Symptom Score concerning urinary symptoms, which was answered on a scale of 0 ("delighted") to 6 ("terrible") by the parents.[9]

Patients completed a urological evaluation consisting of urinalysis, urine culture, serum creatinine, renal/bladder ultrasound and urodynamics consisting of free uroflowmetry and measurement of post-void residual urine, filling cystometry and pressure flow voiding studies. Each patient received 0.6 mg/kg immediate release oxybutynin daily divided into 3 doses (maximum daily dose 15 mg) and instructions for timed voiding. Patients were reevaluated at 12 weeks, and treatment efficacy was assessed by analyzing treatment related changes from baseline to week 12 in terms of urinary symptoms, quality of life, frequency-volume chart data and maximum urinary flow. Parents were counseled regarding potential side effects of oxybutynin. They were specifically alerted about dry mouth, obstipation, drowsiness and changes in behavior. Any adverse events spontaneously reported by patients or observed by parents or investigator during the study duration were recorded. Terms and definitions are in accordance with the International Children's Continence Society standards.[10]

Data were expressed as mean ± SD or absolute values and fractions. The Student t test or paired t test was used to compare continuous variables, while categorical variables were compared using the Fisher exact test. All tests were 2-sided with $p < 0.05$ considered statistically significant. Data were processed using commercially available statistical software (GraphPad Prism®, version 5.00 for Windows).

RESULTS

Of the 42 patients 6 (14.3%) were excluded from the study due to inadequate followup. The remaining 17 girls and 19 boys completed medical therapy and were reevaluated at 12 weeks. Mean ± SD patient age was 9.2 ± 4.3 years (range 3.0 to 18). The most common urinary complaint was urgency, occurring in 31 patients (86.1%). Increased urinary frequency was seen in 30 patients (83.3%), urge incontinence in 29 (80.5%) and nocturnal enuresis in 26 (72.2%). Six patients (16.6%) were using diapers. Parents of 29 patients (80.5%) acknowledged that the voiding symptoms had a significant negative impact on patient quality of life. No differences were noted between boys and girls in terms of storage symptoms.

A total of 10 patients (27.7%) had a history of urinary tract infections but no patient had a positive urine culture at evaluation. Serum creatinine was normal in all patients. Urinary tract sonography was normal in 28 patients (77.7%), while 3 (8.3%) had bladder wall thickening and 2 (5.5%) had unilateral hydronephrosis. Other abnormalities were renal cysts, urachal cyst and small kidney stones, each affecting 1 patient (2.7%).

Urodynamic Findings

Mean ± SD maximum urinary flow was 14.2 ± 15.0 ml per second. Mean ± SD voided volume was 86.6 ± 51.3 ml. Mean ± SD post-void residual volume after initial uroflowmetry was 2.6 ± 15.4 ml. Only 1 patient had residual volume greater than 20 ml.

Detrusor overactivity was diagnosed in all patients. This finding was associated with dysfunctional voiding in 14 children (38.9%), while detrusor underactivity was present in 2 (5.5%). Mean ± SD cystometric capacity was 157.8 ± 81.8 ml, which represents 64.2% of expected bladder capacity. Only 3 patients (8.3%) had a cystometric capacity that matched that expected for age. Mean ± SD bladder compliance was 17.1 ± 13.4 ml/cm H_2O. Analysis of pressure flow studies revealed a mean ± SD detrusor pressure at maximum flow of 70.9 ± 103.3 cm H_2O and maximum flow of 14.3 ± 7.6 ml per second. Mean ± SD residual volume after the pressure-flow study was 3.5 ± 9.5 ml.

Effects of Treatment

Significant improvement was observed after treatment in terms of urinary symptoms (see table), as well as quality of life (fig. 1). In addition, oxybutynin treatment produced a significant improvement in terms of maximum urinary flow ($p < 0.001$, fig. 2). Mean ± SD voided volume increased to 164.0 ± 90.0 ml ($p < 0.001$) and post-void residual urine was 2.4 ± 4.9 ml ($p = 0.797$ compared to baseline).

Oxybutynin was well tolerated by most patients. Dry mouth was reported by the parents of 2 children but neither discontinued treatment. Other adverse events included constipation in 1 patient and abdominal pain in 1, which were mild and transient and did not lead to discontinuation of therapy. It is noteworthy that such symptoms (constipation and abdominal pain) are also reported by patients with WBS who do not use oxybutynin and thus could be related to the disease itself. No clinically significant changes in cognition were reported by parents during the study.

DISCUSSION

This is the first known study to evaluate prospectively the effects of pharmacological treatment of urinary symptoms in children with WBS. Oxybutynin proved to be highly successful and well tolerated in this population. Significant improvement in storage symptoms, including urinary frequency, urge incontinence and nocturia as well as quality of life due to urinary symptoms, was observed within 12 weeks of therapy. Maximum urinary flow rates were also improved. We believe this change reflects the increased voided volumes observed after treatment.[11]

One important finding in our study was the high prevalence of dysfunctional voiding (39%). The rate may be overestimated but we used the definition recommended by the International Children's Continence Society, which is based on a staccato flow pattern combined with evidence of sphincteric contraction during voiding.[10] It is important to emphasize that it is not always possible to obtain sufficient collaboration from these patients and their families

Effects of oxybutynin on lower urinary tract symptoms, frequency-volume chart and quality of life

	Baseline	Posttreatment
No. urgency (%)	31 (86.1)	1 (2.7)
No. frequency (%)	30 (83.3)	3 (8.3)
No. urge incontinence (%)	29 (80.5)	1 (2.7)
No. enuresis (%)	26 (72.2)	7 (19.4)
Mean ± SD voids/day	13.2 ± 4.2	7.9 ± 2.0
Mean ± SD quality of life score	3.3 ± 1.7	0.5 ± 0.9

$p < 0.001$ for all posttreatment values compared to baseline.

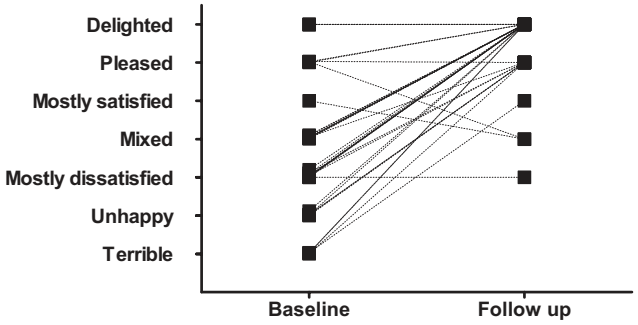

Figure 1. Impact of 12 weeks of oxybutynin therapy on quality of life.

to conduct repeated uroflows, which would be a better method of evaluation. Since none of our patients had a post-void residual of more than 20 ml, and all had overt urinary storage symptoms and urodynamic proved detrusor overactivity, we believe the component of dysfunctional voiding was minor in our population. No patient underwent biofeedback or other treatments throughout the study duration. However, it is important to recognize that antimuscarinics have been successfully used to treat dysfunctional voiding in children.[12,13]

Although WBS is a rare condition, urinary symptoms are known to affect most patients. In a previous study up to 80% of the patients had significant storage symptoms.[5] Urodynamically detrusor overactivity and dysfunctional voiding are the main abnormalities, affecting up to 80% and 20% of patients, respectively.[5,6]

The pathophysiology of voiding dysfunction in WBS is not fully understood. Structural changes of the bladder wall associated with the elastin gene deletion may have a role.[14] In addition, neurological abnormalities such as microcephaly and frontostria-

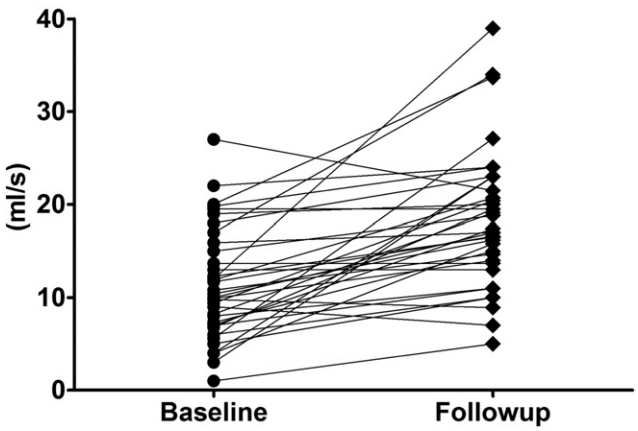

Figure 2. Impact of 12 weeks of oxybutynin therapy on maximum urinary flow.

tal dysfunction might also contribute to voiding dysfunction.[15,16] Moreover, there may be some behavioral component secondary to the cognition impairment and attention deficit disorder that are often present in children with WBS.

Published reports have shown the efficacy of muscarinic antagonists in producing symptomatic improvement in children with neurogenic voiding dysfunction and idiopathic detrusor overactivity.[17–20] Few studies have been reported regarding voiding dysfunction in children with cognitive impairment and attention deficit disorders.[21,22] To our knowledge this is the first study to determine the outcome of antimuscarinic treatment in cognitively impaired children. In a retrospective study Schulman et al reported the evaluation and treatment of 4 children with WBS and urinary dysfunction who had urodynamically proved detrusor overactivity.[6] Institution of bladder training and oxybutynin resulted in a favorable response in that small group of patients.

In this study we opted to include patients based on the presence of significant storage symptoms and urodynamic confirmation of detrusor overactivity. The presence of dysfunctional voiding was not an exclusion criterion as long as patients did not have a significant post-void residual volume.

Oxybutynin is widely used in children with neurogenic voiding dysfunction with good tolerability.[7,18] In our study oxybutynin was also well tolerated. There were no serious adverse events or withdrawals owing to side effects. The most common adverse effect reported with the use of oral oxybutynin is dry mouth, which may occur in 5% to 19% of children with neurogenic detrusor overactivity, similar to what we found in this series.[7,18,23] We also observed no evidence that oxybutynin might worsen cognitive impairment in patients with WBS. This finding confirms similar results observed in a normal pediatric population.[24]

We acknowledge that the evaluation of children with cognitive deficits may represent a challenge and a potential source of misinterpretation, since parental reports may be inadequate or incomplete, and underreporting is possible and difficult to estimate. In addition, the lack of a control group represents a potential flaw of the study. However, it is well established that antimuscarinics are safe and effective for children with neurogenic voiding dysfunction and idiopathic detrusor overactivity, and we had a limited availability of patients since this is an uncommon condition. Moreover, it would be difficult to persuade these patients to enter a placebo controlled trial since most have significant comorbidities related to the syndrome and already spend much time on medical visits and examinations. Therefore, we decided to make this an open-label study. The improvements in many parameters in our patients were striking and certainly comparable to or better than those observed in placebo controlled studies. Finally, it can be argued that a placebo effect in this population with cognitive impairment is possibly less likely.

There are a number of known genetic conditions, such as Down and Ochoa syndromes, adrenoleukodystrophy and Opitz-Kaveggia syndrome, that may cause cognitive impairment and voiding symptoms.[22,25–29] Our results with the treatment of children with WBS allow us to speculate that the use of oxybutynin or other antimuscarinics may be helpful in some of these patients.

CONCLUSIONS

We demonstrate for the first time the efficacy of an antimuscarinic agent in children with WBS. Oxybutynin produced significant improvement in voiding symptoms and quality of life within 12 weeks of therapy. A significant increase in maximum urinary flow rates was also observed. We recommend oxybutynin as a first-line treatment for storage symptoms and detrusor overactivity in children with WBS.

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