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Lower urinary tract symptoms in children and adolescents with Williams-Beuren syndrome

Z.M. Sammour^a, J. de Bessa Jr^a, M. Hisano^a, H. Bruschini^a,
C.A. Kim^b, M. Srougi^a, C.M. Gomes^a

^aDivision of Urology,
Hospital das Clínicas,
University of São Paulo,
São Paulo, Brazil

^bGenetics Unit of the Pediatrics
Department, Children's
Institute, University of São
Paulo, São Paulo, Brazil

Correspondence to: M. Hisano,
255, Dr. Eneas de Carvalho
Aguar Ave., 7th Floor,
05403-000, São Paulo, SP,
Brazil, Tel.: +55 11 2661 8080

m.hisano@hc.fm.usp.br
(M. Hisano)

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Summary

Introduction

Williams-Beuren syndrome (WBS) is a genetic condition caused by a microscopic deletion in the chromosome band 7q11.23. Individuals with WBS may present with congenital cardiovascular defects, neurodevelopmental disturbances and structural abnormalities of the urinary tract. Lower urinary tract symptoms (LUTS) seem to be frequent in this population, but studies on this topic are scarce and based on small case series.

Objective

To systematically evaluate the prevalence of lower urinary tract symptoms (LUTS) and the acquisition of bladder control in a large population with WBS.

Study design

A cross-sectional study evaluating 87 consecutive patients with WBS; there were 41 girls and 46 boys. Genetic studies confirmed WBS in all patients. Subjects were clinically evaluated with: a history of LUTS obtained from the parents and child, a structured questionnaire of LUTS, a 3-day urinary frequency-volume chart, a quality of life question regarding LUTS, and physical examination. A history regarding the acquisition of bladder control was directly evaluated from the parents.

Results

Mean age of patients was 9.0 ± 4.2 years, ranging from 3 to 19 years. Based on the symptoms

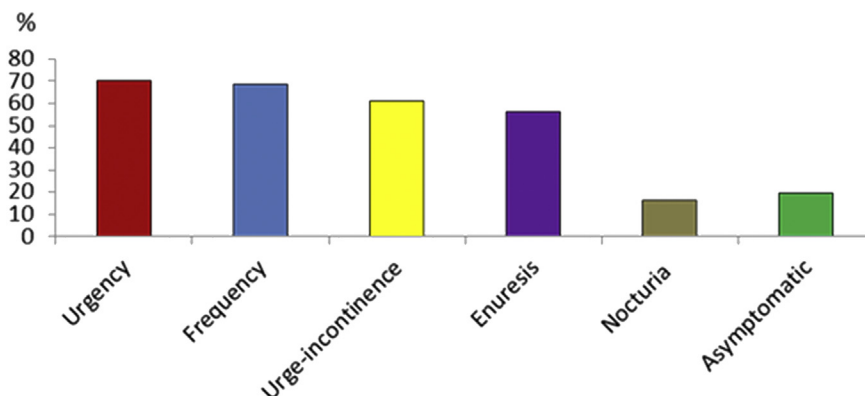
questionnaire and the frequency-volume chart, 70 patients (80.5%) were symptomatic. The most common symptom was urgency, affecting 61 (70.1%) patients, followed by increased urinary frequency in 60 (68.9%) patients, and urge-incontinence in 53 (60.9%), as shown in Summary Fig. More than half of the children reported nocturnal enuresis, including 61% of the girls and 52% of the boys. Twenty-three patients (25.6%) had a history of urinary tract infections. The mean age for acquisition of dryness during the day was 4.4 ± 1.9 years. Parents of 61 patients (70.1%) acknowledged that LUTS had a significant impact on the quality of life of their children.

Discussion

A high prevalence of LUTS was confirmed with a significant negative impact on quality of life in a large population of children and adolescents with WBS. It was shown for the first time that the achievement of daytime bladder control is delayed in children with WBS. Although LUTS are not recognized as one of the leading features of the syndrome, it is believed that it should be considered as a significant characteristic of the clinical diagnosis of WBS.

Conclusions

LUTS are highly prevalent in children and adolescents with WBS and have a significant negative impact on patient's quality of life.



Summary Fig Frequency of urinary symptoms in patients with Williams-Beuren syndrome.

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Introduction

Williams-Beuren syndrome (WBS) is a genetic condition with multisystemic involvement; it is caused by a microscopic deletion in the chromosome band 7q11.23. Individuals with WBS carry a 1.5–1.8 million base (Mb) pair deletion of DNA on chromosome 7 [1]. This segment contains around 26–28 genes, including the elastin gene (ELN), which seems to be responsible for many of the classic abnormalities of WBS [2].

People with WBS have a distinctive profile of physical, medical and neurocognitive characteristics. Genotypic and phenotypic correlation is not completely elucidated. The clinical diagnosis of WBS is usually made during early childhood and is based on the peculiar dysmorphic facial features; it is confirmed by specific molecular tests, including fluorescence in situ hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA) [3–5].

Features of this disorder include congenital heart disease (supravalvular aortic stenosis or supravalvular pulmonary stenosis), hypertension, growth delay, hypercalcemia, hyperacusis, low muscle tone, friendly personality, and mental development delay [6–8].

It has been shown that lower urinary tract symptoms (LUTS) are common in people with WBS, and may significantly impact their quality of life [9–12]. The most prevalent symptoms are increased urinary frequency, urgency, urge incontinence and enuresis, which may affect up to 78% of those with WBS [11]. The reasons for the high prevalence of LUTS in this population are poorly understood. It is known that neurocognitive impairment, which is present in most people with WBS, is associated with higher rates of lower urinary tract dysfunction [9,13]. Such abnormality may be secondary to delayed neurological development or altered bladder function. Another possible contributor for the high rates of LUTS in people with WBS is structural abnormalities of the bladder. Elastin is an important component of the bladder wall and is often affected in those with WBS due to chromosome deletion containing the elastin gene [2,4]. LUTS and bladder diverticula, which are very prevalent in this population, may be related to elastin deficiency [10,11].

Previous studies evaluating LUTS in patients with WBS were mostly small case series. The present study systematically investigated the lower urinary tract symptoms of a large cohort of patients with WBS and the acquisition of bladder control.

Materials and methods

Between January 2002 and December 2014, 89 consecutive children and adolescents (47 boys and 42 girls) with an established clinical and genetic diagnosis of WBS were evaluated. The present hospital is a national referral center for WBS and maintains an observational, longitudinal, prospective database of these patients. Children with WBS receive a comprehensive multidisciplinary evaluation, including: genetic, cardiological, nephrological, psychological and urological workup. The genetic diagnosis of WBS was confirmed in all patients by FISH studies [3]. The

Institutional Review Board approved this study. Patients agreed to participate after full disclosure of its purposes, and written consent was obtained from all participants or their legal representatives.

The initial clinical investigation of all patients included demographic data acquisition, a history of urinary symptoms of frequency, urgency, urgency incontinence, nocturia and nocturnal enuresis, which was jointly obtained from the parents and child, and a structured questionnaire of urinary symptoms [14]. For all patients, a 3-day frequency-volume chart was obtained. Those who had overt storage symptoms were considered symptomatic.

Data relative to the patients' initial evaluation at the hospital are presented. Since there were patients with long-term follow-up and many received various modalities of treatments during this period, their symptoms at first presentation are described. According to the symptom questionnaire and the frequency-volume chart, patients were considered normal if they were asymptomatic or had mild symptoms, which included those with increased urinary frequency (up to eight micturitions/day) without urge-incontinence, enuresis and no significant impact on the quality of life regarding LUTS. Symptoms were classified according to their relation to the storage of bladder function. The severity of symptoms was calculated considering parents' perception of its relevance, including at least one of the following items: daytime incontinence; nocturia >2 episodes/night; nocturnal enuresis; significant increase in urinary frequency (voiding >8/day); and any storage symptoms that cause negative effects on quality of life.

A history of UTI was sought in each patient. Patients with UTI received antibiotics accordingly and had follow-up urine cultures before urological evaluation.

Acquisition of bladder control was investigated by direct interview with the parents at the initial first evaluation. Bladder control was defined as the age for daytime dryness [15]. Participants with occasional episodes of urge incontinence (defined as rare episodes during the week) were also considered as having daytime bladder control. Additionally, one question concerning the quality of life with urinary symptoms was answered on a scale of 0 (delighted) to 6 (terrible) by the parents. A significantly impaired quality of life was defined for participants with a score of ≥ 2 [11,16]. The results for boys and girls were evaluated separately and then compared.

Participants completed a urological evaluation consisting of urinalysis, urine culture, serum creatinine, and urinary tract ultrasonography. Children with severe polyuria associated with cardiovascular problems were excluded. All data were collected during clinical visits, and interviews with the child and the parents at the office.

Data were expressed as means \pm standard deviation (SD), ranges 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's exact test. All tests were two-sided with $P < 0.05$ considered statistically significant. Data were processed using commercially available statistical software (Graph Pad Prism[®], version 6.03 for Windows[®], San Diego California USA).

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