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Congenital genitourinary abnormalities in children with Williams—Beuren syndrome

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Abstract *Objective:* Williams—Beuren syndrome (WBS) is an autosomal dominant disorder caused by a gene deletion on chromosome 7q11.23. Patients with WBS usually show a group of features such as developmental delay, cardiovascular anomalies, mental retardation, and characteristic facial appearance. Abdominal wall defects, external genitalia anomalies, and structural abnormalities of the urinary tract have been scarcely evaluated and were the focus of our study.

Materials and methods: We prospectively evaluated 41 boys and 38 girls with WBS, with a mean age of 8.8 ± 4.1 (range 3—19 years). All patients were examined for the evaluation of inguinal and umbilical hernias and genital anomalies. All patients were offered a radiological evaluation, including urinary tract ultrasound, voiding cystourethrogram, and dimercaptosuccinic acid renal scintigraphy (DMSA scan).

Results: Of the 41 boys, 30 (73.1%) had abnormalities on physical examination, including bilateral undescended testis in 13 (31.7%), retractile testis in four (9.7%), hypospadias in four (9.7%), and unilateral cryptorchidism in three (7.3%) patients. Of the 38 female subjects, 17 (44.7%) had at least one abnormality, including umbilical hernia in 11 (28.9%), unilateral inguinal hernia in four (10.5%), and bilateral inguinal hernia in three (7.8%) patients. Uroradiological abnormalities were found in 41 patients (51.9%). On sonography, six (7.6%) patients had unilateral hydronephrosis, three (3.8%) had a duplicated collecting system, and two (2.5%) had kidney stones. On DMSA, performed in 36 patients, four (11.1%) had unilateral renal scarring and two (5.5%) had bilateral renal scarring. Cystourethrography was obtained from 56 patients, of whom 27 (48.2%) had bladder diverticulum, 18 (32.1%) had bladder wall trabeculation, and three (5.3%) had vesicoureteral reflux. We found no association of urological abnormalities with cardiovascular defects.

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Conclusions: Patients with WBS have a high prevalence of abdominal wall, external genitalia, and urological abnormalities, emphasizing the importance of proper physical examination and radiological investigation in this population.

Introduction

Williams—Beuren syndrome (WBS) is a rare genetic condition with multisystemic involvement, caused by a microscopic deletion in the chromosome band 7q11.23. Individuals with WBS carry a 1.5-Mb pair deletion of DNA on chromosome 7 [1]. This segment contains more than two dozen contiguous genes, including the elastin gene, which seems to be responsible for many of the classic abnormalities of WBS [2].

WBS patients have a distinctive profile of physical, medical, and neurocognitive characteristics. Features of this disorder include congenital cardiovascular disease (supravalvular aortic stenosis or supravalvular pulmonary stenosis), hypertension, craniofacial abnormalities, growth delay, hypercalcemia, hyperacusis, low muscle tone, and moderate mental deficiency [3—5]. Other less frequent manifestations may include dental, ophthalmological, auditory, digestive, and endocrinological problems [3—7].

Renal anomalies have also been described in WBS patients [8—10]. Congenital urinary tract defects include renal ectopia, agenesis, hypoplasia, duplication, horseshoe kidney, hydronephrosis, and vesicoureteral reflux [4,8,11—13]. Pankau et al. [4] have shown that the risk of structural abnormalities of the kidneys and the urinary tract is increased 12—36 fold in WBS compared with the normal population. Bladder diverticulum have been reported in some series and individual cases of WBS [14—16], but their exact prevalence is unknown [5]. Likewise, it has been shown that WBS patients have a high prevalence of voiding dysfunction [16—18].

Abdominal wall defects, external genitalia anomalies, and structural abnormalities of the urinary tract have been reported in few studies with WBS patients and seem to be more common than in the normal population [3,4,8,9,14]. In this study, we systematically evaluated the external genitalia and urinary tract of WBS patients to delineate the spectrum and prevalence of urological anomalies.

Materials and methods

Between January 2004 and December 2011, we prospectively evaluated 79 consecutive patients, including 41 boys and 38 girls, with a mean age of 8.8 ± 4.1 years (range 3—19 years) with an established clinical and genetic diagnosis of WBS. The genetic diagnosis of WBS was confirmed by FISH (fluorescence in situ hybridization) studies [19].

The Genetics Clinic Unity of the Department of Pediatrics of the University of Sao Paulo School of Medicine is a national referral center for WBS. At our institution, WBS patients are evaluated on a multidisciplinary basis, including genetic, cardiologic, pediatric, nephrologic, and urologic evaluations. All patients were referred to a urological evaluation by the Genetic Clinic Unit. We established an investigational protocol with urological physical examination and radiological studies. Families were thoroughly informed of the study protocol, with a detailed description of the procedures. This study was approved by the Institutional Review Board of our hospital. The parents of the patients agreed to participate after full disclosure of its purpose and written informed consent was obtained from all.

Abdominal wall and external genitalia abnormalities

All patients were examined with a parent or caregiver present. We tried to use distraction, conversation and relaxation during the evaluation. Physical examination was performed at least two times by the same investigator. All patients were examined on the supine position for the evaluation of inguinal and umbilical hernias and genital anomalies.

Physical examination of boys included the evaluation of testicular position, urethral meatal location, and penile abnormalities. Undescended testis was defined as a testis in the high scrotal or inguinal position that could not be manipulated into a stable scrotal position. Retractile testis was characterized when a stable scrotal position was achieved by manipulation. A clinical inguinal hernia was defined as an inguinal fluctuating bulge detectable during groin examination that could be reduced with manipulation. Umbilical hernia was defined as a palpable bulge in the umbilical position that could be reduced with manipulation.

Penile examination included evaluation of the meatus at the penile tip or anomalous position, coronal sulcus, symmetry of the glans and foreskin, presence of chordee, penile torsion, and evaluation of the penoscrotal junction.

Girls underwent a complete genital physical examination, including the thighs, labia majora, labia minora, clitoris, urethral meatus, hymen, and posterior commissure. During the vaginal examination, the legs were placed in full abduction.

Radiological abnormalities of the urinary tract

All patients were offered a comprehensive uroradiological evaluation, including urinary tract ultrasound, voiding cystourethrogram, and dimercaptosuccinic acid renal scintigraphy (DMSA scan). Clinical data on cardiologic and nephrologic examination (echocardiography, Doppler echocardiography, and Doppler renal artery ultrasound) were collected from the clinical records.