

Diagnosis and management of systemic hypertension due to renovascular and aortic stenosis in patients with Williams-Beuren syndrome

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SUMMARY

AIM: To describe the incidence, diagnosis, and management of systemic arterial hypertension related to renal artery stenosis in patients with Williams-Beuren syndrome.

METHODS: Sixty-five patients with Williams-Beuren syndrome were evaluated for hypertension. Enrolled patients underwent Doppler sonography of the renal arteries and Doppler echocardiography. Those with Doppler sonography-detected lesions or with normal Doppler sonography but severe hypertension underwent computed tomography or gadolinium-enhanced magnetic resonance angiography of the aorta and renal vessels. Patients needing vascular therapeutic intervention underwent conventional angiography.

RESULTS: Systemic arterial hypertension was diagnosed in 21/65 patients with Williams-Beuren syndrome (32%; 13 male) with a mean age of 13.9 years (5mo-20yrs). In 8/21 patients renovascular hypertension was detected. Angioplasty was unsuccessful in five patients with renal artery stenosis, requiring additional treatment. Doppler echocardiography showed cardiac abnormalities in 16/21 (76%) hypertensive patients.

CONCLUSION: Cardiac abnormalities and hypertension in patients with Williams-Beuren syndrome are common. Thus, thorough evaluation and follow-up are necessary to reduce cardiovascular risks and mortality of these patients

KEYWORDS: children, hypertension, renal artery stenosis, Williams-Beuren syndrome

INTRODUCTION

Williams-Beuren syndrome (WBS) is a genetic disorder characterized by facial dysmorphisms, congenital heart defects, growth retardation, infantile hypercalcemia, renal and vascular abnormalities, and intellectual disability¹. Clinical diagnosis is usually performed during childhood when the typical facial changes and cognitive profile become more

apparent¹ (Figure 1). Genetic confirmation can be carried out using FISH² (fluorescence in situ hybridization)^{or} MLPA³ (multiplex ligation-dependent probe amplification), or microarray tests for identification of the causal microdeletion at 7q11.23. Urinary tract system abnormalities in WBS have been described in approximately 18% of patients^{4,5,6} and include renal

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ectopia, hydronephrosis, renal agenesis or hypoplasia, vesicoureteral reflux, and voiding dysfunction. Nephrocalcinosis, proteinuria, and chronic renal failure have also been reported in some cases series^{4,5,6}

Cardiovascular abnormalities are also quite common in patients with WBS and have been observed in more than 80% of cases^{7,8}. Supravalvular aortic stenosis (SVAS) is the most frequent abnormality, with an estimated incidence of 64%^(9,10). Systemic arterial abnormalities include localized or diffuse narrowing of the thoracic or abdominal aorta, coronary, renal and other visceral arteries^{11,12}. According to Lacolley et al.¹³ vascular injury in patients with WBS may be associated with reduced elastin synthesis and increased proliferation of vascular smooth muscle cells.

Arterial hypertension arterial (SAH) is also observed with high prevalence in WBS¹⁴. In a minority of patients, renal artery stenosis, diffuse narrowing of the aorta, aortic coarctation or a combination of these abnormalities have been implicated^{4,5}. Renal artery stenosis is usually found at the origin of the renal arteries⁷ (Figure 2). Nonetheless, there are few reports about the origin and management of SAH in WBS, and the diagnosis is often not made.

This study aimed to describe the incidence of hypertension among 65 patients with WBS, as well as the diagnosis and management of hypertension due to renovascular or aortic stenosis.

METHODS

Sixty-five patients who were being treated from 1993 to 2010 at the Pediatric Nephrology and Genetics Units at the Institute of Children, Hospital das



FIGURE 1: Female patient, at age 9y4m, with facial characteristics of WBS: periorbital fullness, short nose, malar hypoplasia, long philtrum, and thick lips.

Clínicas of the Faculty of Medicine of the University of São Paulo were included in this study. All patients were diagnosed with WBS based on clinical findings and had the presence of the 7q11.23 microdeletion confirmed by the FISH (2) or MLPA test (with a specific kit for WBS) (3).

Patients with blood pressure (BP) values at or above the 95th percentile for age, gender, and height confirmed on 3 different occasions¹⁵ were included in the study and followed prospectively. Clinical and laboratory parameters such as the age of onset of hypertension, associated symptoms, baseline BP, fundus examination, microalbuminuria/creatinine¹⁶ and calcium/creatinine ratio¹⁷ in spot urine samples, estimated creatinine clearance¹⁸, and serum ionized calcium were evaluated.

All enrolled patients were initially investigated by Doppler echocardiography (DE) and renal ultrasound (RU) with color-flow Doppler sonography of the renal arteries (DS). Those with findings of renal artery stenosis¹⁹ or hypertension stage II¹⁵ with a normal DS underwent computed tomographic angiography (CTA)⁽²⁰⁾ and/or gadolinium-enhanced magnetic resonance angiography (MRA) of the aorta and renal vessels²¹. Patients with unclear diagnosis by CTA and/or MRA or who required vascular therapeutic intervention (angioplasty) underwent conventional angiography (CA).

RESULTS

Of the 65 patients with WBS included in this study, 21 (32%; mean age of 13.9 years, range: 5 months to 20 years, 13 males) had hypertension and



FIGURE 2: Digital subtraction angiography demonstrates discrete stenosis of the abdominal aorta and severe stenosis of the left and right renal arteries. Also note several collateral arteries from the aorta on the left side

were submitted to further imaging studies. In this group, the mean age at WBS diagnosis was 5.2 years (ranging from 8 months to 12 years). All patients were asymptomatic, and hypertension was detected by active investigation during routine medical visits.

The evaluation of the renal arteries by DS was normal in 12/21 patients. Of these, five patients did not undergo a CTA or MRA scan because of a low clinical suspicion of hypertension due to renovascular or aortic stenosis. In these five patients, BP was adequately controlled with one or two medications, and none had secondary involvement of target organs during follow-up. Of the 12 patients with normal DS results, seven had persistent severe hypertension and were therefore submitted to further testing. Two of them had findings consistent with SAH associated with vascular stenosis, as detected by CTA and conventional arteriography (one had abdominal aorta narrowing, and the other had right renal artery stenosis), indicating that DS resulted in false negative results for these patients. The remaining five patients had normal CTA results.

Nine patients with DS suggesting renal artery stenosis were also submitted to CTA or MRA, and only six patients had vascular lesions confirmed by one of these methods. In three patients, the DS yielded false positive results. Of the 21 hypertensive patients, 16 underwent DS followed by complementary renal and aortic vascular investigation with CTA or MRA. The DS showed discordant results when compared with CTA or MRA in five of those patients (31%).

TABLE 1: RENAL AND AORTIC VASCULAR LESIONS IN 8/21 PATIENTS WITH WILLIAMS-BEUREN SYNDROME AND SYSTEMIC ARTERIAL HYPERTENSION.

	Patients	Type of lesion
Renal artery stenosis	6	unilateral 2 / bilateral 4*
Aorta coarctation	1	thoracic
Diffuse aorta narrowing	1	descendent and abdominal

*One patient also had aortic stenosis.

TABLE 2: ECHOCARDIOGRAPHIC FEATURES IN THE 21 WBS PATIENTS WITH SYSTEMIC ARTERIAL HYPERTENSION.

Echocardiographic features	n (%)
Supravalvular aortic stenosis	10 (47.6%)
Mitral valve prolapse	6 (28.6%)
Normal	5 (24%)

Hypertension associated with renal or aortic lesions was confirmed in 8/21 patients (Table 1), corresponding to 12% of the cases of WBS and 38% of patients with arterial hypertension. Renal artery stenosis was detected in six patients (28.6%), aortic coarctation in one patient, and diffuse narrowing of the aorta in another one. One patient with renal artery stenosis also had aortic stenosis.

Percutaneous transluminal balloon angioplasty was performed in five patients with renal artery stenosis, and it was unilateral in two and bilateral in three patients. In one patient with bilateral stenosis, a stent was placed in the renal arteries. All four patients who underwent angioplasty had treatment failure, and two of them required surgical intervention for stenosis correction. An aortorenal graft was performed in one patient. For another patient who had stenosis of both renal arteries and of the aorta, an iliac renal graft, as well as a graft of the descending aorta to the infrarenal abdominal aorta, were inserted. Two patients who did not undergo surgical intervention continued with conservative treatment with antihypertensive medications (amlodipine, carvedilol, hydralazine, and diuretic). Two patients with lesions of the aorta underwent surgical correction.

All patients underwent DE at the initial examination, and the alterations found are described in Table 2. SVAS was the most prevalent malformation (46%). Two patients underwent surgical correction of SVAS and had mitral valve regurgitation, eccentric left ventricular hypertrophy, and left ventricular systolic dysfunction. Three patients with mitral valve prolapse also had eccentric left ventricular hypertrophy and left ventricular systolic dysfunction.

Hypercalciuria was found in four patients, and hypercalcemia was diagnosed in one patient. Estimated creatinine clearance and albuminuria at the beginning of the study are shown in Table 3. One patient had hypertension after clinically presenting hemolytic uremic syndrome. Unilateral pyelocalyceal dilatation was observed in 2/21 patients submitted to renal sonography.

In this series, three patients died during follow-up due to heart failure: one patient with surgically corrected SVAS, one with both bilateral renal artery and aortic stenosis who had been submitted to angioplasty and iliac-renal and aortic grafts, and one with SVAS who died following heart transplantation.

TABLE 3: LABORATORY FEATURES (MEAN; RANGE) IN 21 PATIENTS WITH WBS AND ARTERIAL HYPERTENSION.

Laboratory features	Mean; range n
Serum ionized calcium Hypercalcemia ^a	1.23 (1.1-1.4) mmol/L 1
Urinary calcium Hypercalciuria ^b	0.15 (0-0.94) mg/mg creatinine 4
eGFR ^c CKD class II	118.23 (68-183) ml/min/1.73m ² 3
Albuminuria Microalbuminuria ^d	13.31 (3.55-36.79) mg/g creatinine 1

^a serum ionized calcium >1.4mmol/L; ^b calcium /creatinine ratio of random spot urine > 0.21 mg/mg¹⁷; ^c glomerular filtration rate estimated by serum creatinine¹⁸; ^d albumin/creatinine ratio of random urine >30 mg/g creatinine¹⁶; CKD: chronic kidney disease²²

DISCUSSION

WBS is a congenital multisystem disease affecting the cardiovascular system, nervous system, and connective tissues that often involves hypertension, although the etiology of this symptom is not fully understood. Possible explanations include disorganization of the elastic layer and hypertrophy of smooth muscle cells and collagen fibers. As a result, diffuse or localized progressive narrowing of the arterial wall leads to increased arterial stiffness and sympathetic activity²³. The prevalence of hypertension in WBS is widely variable^{4,5,6,8,14} (5 to 70% in series including all ages and 5 to 46% in children). It can appear as early as infancy, but the average age of diagnosis varies from 6.5 to 38 years. In the present study, the incidence of hypertension was 32%, with a mean age of diagnosis of 13.9 years (range: 5 months to 20 years). As observed by other authors⁸, we confirmed that patients with WBS are initially asymptomatic for hypertension, which highlights the need for health professionals to actively measure BP in these children in all routine visits.

In the present study, which included only children and adolescents, systemic arterial hypertension associated with vascular stenosis was observed in 8/21 hypertensive patients (38%), which included renal artery stenosis (28.6%) and aortic lesions. In the literature; the frequency of arterial stenosis is variable across case series (e.g., 2 to 70%)^{5,8,12,14,22}.

Renal DS is usually indicated as an initial diagnostic method for screening of arterial stenosis. It is a non-invasive, relatively inexpensive test that is available in most centers but may have a high rate of technical failure (approximately 30%)²⁴ because it is an operator-dependent method that also requires patients' cooperation. In our study, we found a simi-

lar failure rate for DS (31%). The main difficulties are the detection of intra-renal and bilateral stenosis, the presence of obesity and the inadequate preparation of the patient. In WBS, psychomotor and behavioral disorders (agitation and anxiety) may represent additional complications¹. The sensitivity and specificity of DS in the detection of vascular stenosis have been shown to be between 60 and 98% and between 62 and 98%, respectively^{24,25}. It should be emphasized that the current sample was too small, since we conducted further imaging tests only on severely hypertensive patients, hindering this type of analysis.

Computed tomographic angiography or MRA is commonly used in patients with WBS, but these techniques are not always available and require sedation or general anesthesia in children. MRA has high sensitivity (64-93%) and specificity (72-97%)^{25,26} but may overestimate renal arterial lesions or underdiagnose intra-renal lesions. On the other hand, CTA requires the use of iodinated contrast and ionizing radiation. Most of our patients underwent CTA because of the limited availability of the MRA equipment at our unit. However, we were unable to establish the accuracy of these methods in our study, because only some of the patients who received MRA or CTA also underwent CA, which is considered the gold standard in the diagnosis of arterial stenosis²¹.

Angioplasty was performed in five patients with stenosis of the renal artery but was unsuccessful, as observed by other authors^{26,27}. Patients with aortic coarctation or stenosis were treated with surgical correction, with graft insertion in severe cases.

Other causes of hypertension such as hypercalcemia, renal scarring secondary to recurrent urinary infections, obesity, and essential hypertension may also be involved in hypertension in WBS. Hypercalcemia is frequently described in WBS²⁹ and occurred transiently in one patient in this study. It may manifest early or later in life, and patients should, therefore, be periodically monitored for possible calcium disturbances^{16,9}. Broder et al.³⁰ found a higher incidence of hypertension in patients with infantile hypercalcemia, but to date, no direct links between hypertension and hypercalcemia have been established.

Congenital cardiovascular abnormalities are prevalent in patients with WBS and can occur in about 75% of cases^{7,8}. SVAS is the most prevalent disease, and is also present in up to 75% of cases^{9,14,30}. Mitral valve prolapse, bicuspid aortic valve, and coronary abnormalities have also been described^{10,11,12}. SVAS

may be severe in up to 30% of patients³⁰, and surgical correction is necessary in such cases²⁷. Consistent with earlier reports^{10,12,23}, the most common cardiovascular abnormality observed in our study was SVAS, and it was severe in two patients who required surgical intervention.

RESUMO

OBJETIVO: Descrever a incidência, o diagnóstico e o tratamento da hipertensão arterial sistêmica relacionada com estenose da artéria renal em pacientes com síndrome de Williams-Beuren.

MÉTODOS: Sessenta e cinco pacientes com síndrome de Williams-Beuren foram avaliados quanto à presença de hipertensão. Os pacientes foram submetidos à ultrassonografia com Doppler das artérias renais e ecocardiograma Doppler. Aqueles com suspeita de hipertensão renovascular foram submetidos à tomografia computadorizada ou angiografia por ressonância magnética da aorta e vasos renais ou angiografia convencional.

RESULTADOS: A hipertensão arterial sistêmica foi diagnosticada em 21/65 pacientes com síndrome de Williams-Beuren (32%, 13 do sexo masculino), com idade média de 13,9 anos (5 meses-20 anos). Em 8/21 pacientes foi detectada a hipertensão renovascular. Angioplastia não teve sucesso em cinco pacientes com estenose da artéria renal, necessitando de tratamento adicional. O ecocardiograma Doppler mostrou anormalidades cardíacas em 16/21 (76%) pacientes hipertensos.

CONCLUSÃO: As anormalidades cardíacas e hipertensão arterial em pacientes com síndrome de Williams-Beuren são muito frequentes, sendo necessários uma avaliação minuciosa e seguimento para diminuir o risco cardiovascular e a morbimortalidade desses pacientes

PALAVRAS-CHAVE: Criança. Hipertensão. Estenose de artéria renal. Síndrome de Williams-Beuren.

REFERENCES

- American Academy of Pediatrics: Health care supervision for children with Williams syndrome. *Pediatrics* 2001; 107: 1192–204.
- Borg I, Delhanty JD, Baraitser M. Detection of hemizygoty at the elastin locus by FISH analysis as a diagnostic test in both classical and atypical cases of Williams syndrome. *J Med Genet* 1995; 32: 692–696.
- Dutra RL, Pieri Pde C, Teixeira AC, Honjo RS, Bertola DR, Kim CA. Detection of deletions at 7q11.23 in Williams-Beuren syndrome by polymorphic markers. *Clinics* (Sao Paulo) 2011; 66: 959–964.
- Sugayama SM, Koch VH, Furusawa EA, Leone C, Kim CA. Renal and urinary findings in 20 patients with Williams-Beuren syndrome diagnosed by fluorescence in situ hybridization (FISH). *Rev Fac Med Hosp Clin Sao Paulo* 2004; 59: 266–272.
- Pankau R, Partsch CJ, Winter M, Gosch A, Wessel A. Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. *Am J Med Genet* 1996; 63: 301–304.
- Pober BR, Lacro RV, Rice C, Mandell V, Teele RL. Renal finding in 40 individuals with Williams syndrome. *Am J Med Genet* 1993; 46: 271–274.
- Donnai D, Karmiloff-Smith A. Williams syndrome. From genotype through to the cognitive phenotype. *Am J Med Genet* 2000; 97: 164–171.
- Bouchired K, Boyer O, Bonnet D, Brunelle F, Decramer S, Landthaler G et al. Clinical features and management of arterial hypertension in children with Williams-Beuren syndrome. *Nephrol Dial Transplant* 2010; 25: 434–438.
- Morris CA. Williams Syndrome. 1999 Apr 9 [Updated 2013 Jun 13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1249/>
- Vernant P, Corone P, Rossignol AM, Bielman C. 120 cases of the Williams and Beuren syndrome. *Arch Mal Coeur Vaiss* 1980; 73: 661–666.
- Bernand Y, Didier D, Bozio A, Champsaur G, Renaud JC, Maurat JP. Coronary anomalies associated with the Williams-Beuren syndrome. Apropos of 2 cases. *Arch Mal Coeur Vaiss* 1985; 78: 791–795.
- Zalzstein E, Moes CA, Musewe NN, Freedom RM. Spectrum of cardiovascular anomalies Williams-Beuren syndrome. *Pediatr Cardiol* 1991; 12: 219–223.
- Lacolley P, Boutouyrie P, Glukhova M, Daniel Lamaziere JM, Plouin PF, Bruneval P et al. Disruption of the elastin gene in adult Williams syndrome is accompanied by a paradoxical reduction in arterial stiffness. *Clin Sci (Lond)* 2002; 103: 21–29.
- Honjo RS, Dutra RL, Furusawa EA, Zanardo EA, Costa LSA, Kulikowski LD, Bertola DR, Kim AE. Williams-beuren syndrome: A clinical study of 55 brazilian patients and the diagnosis use of MLPA. *Biomed Res Int.* 2015;903175
- National High Blood Pressure Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; 114: 555–576.
- Karalliedde J, Vibert G. Microalbuminuria and cardiovascular risk. *Am J Hypertens* 2004; 17(10): 989–93
- Butani L, Kalia A. Idiopathic hypercalciuria in children-how valid are the existing diagnostic criteria? *Pediatric Nephrol* 2004; 19: 577–582.
- Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976; 58:259–263.
- Granata A, Fiorini E, Andrulli S, Loggias F, Gallieni M, Sicurezza E et al. Doppler ultrasound and renal artery stenosis: An overview. *J Ultrasound* 2009; 12: 133–143.
- Kurian J, Epelman M, Darge K, Meyers K, Nijs E, Hellinger JC. The role of CT angiography in the evaluation of pediatric renovascular hypertension. *Pediatr Radiol* 2013; 43: 490–501.
- O'Neill WC, Bardelli M, Yevzlin AS. Imaging for renovascular disease. *Se-min Nephrol* 2011; 31(3): 272–282.
- KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3:1-150.
- Collins RT 2nd, Kaplan P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. *Am J Cardiol* 2010; 105: 874–878.
- Wessel A, Pankau R, Kececioglu D, Ruschewski W, Bursch JH. Three decades of follow up of aortic and pulmonary vascular lesions in the Williams-Beuren syndrome. *Am J Med Genet* 1994; 52: 297–301.
- Conkbayir I, Yucesoy C, Edguer T, Yanik B, Yasar AU, Hekimoglu B. Doppler sonography in renal artery stenosis. An evaluation of intrarenal and extrarenal imaging parameters. *Clin Imaging* 2003; 27: 256–260.
- Rountas C, Vlychou M, Vassiou K, Liakopoulos V, Kapsalaki E, Koukoulis G

- et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital subtraction angiography. *Ren Fail* 2007; 29: 295–302.
27. Actis Dato GM, La Torre M, Caimmi P, Actis Dato A Jr., Centofanti P, Ottino GM et al. Williams-Beuren syndrome. Long-term results of surgical treatments in six patients. *J Cardiovasc Surg (Torino)* 1997; 38: 125–129.
28. Kumada Y, Yasuda H, Sasaki E, Murakawa S, Mori Y, Hirose H. Reoperation for diffuse supravalvar aortic stenosis with Williams syndrome—extended path aortoplasty and extra-anatomic bypass from the ascending aorta to the descending aorta in a median sternotomy. *J Thorac Cardiovasc Surg* 1998; 46: 1061–1064.
29. Udwin O. A survey of adults with Williams syndrome and idiopathic infantile hypercalcaemia. *Dev Med Child Neurol* 1990; 32: 129–141.
30. Broder K, Reinhardt E, Ahern J, et al. Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. *Am J Med Genet* 1999; 83: 356–360

