Arterial Hypertension in a Child with Williams-Beuren Syndrome (7q11.23 Chromosomal Deletion)

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Case Report

We report the case of a 7-year-old male child diagnosed with Williams-Beuren syndrome and arterial hypertension refractory to clinical treatment. The diagnosis was confirmed by genetic study. Narrowing of the descending aorta and stenosis of the renal arteries were also diagnosed. Systemic vascular alterations caused by deletion of the elastin gene may occur early in individuals with Williams-Beuren syndrome, leading to the clinical manifestation of systemic arterial hypertension refractory to drug treatment.

The Williams-Beuren syndrome, a rare congenital anomaly involving the vascular system, connective tissue, and central nervous system, was initially described by Williams et al in 1961, and then by Beuren in 1962. In 1993, Ewart attributed the etiology of the syndrome to a microdeletion involving the elastin gene in chromosome 7.1,2

Cardiac anomalies are present in approximately 70% of the cases, aortic supravalvular stenosis being the most frequent, followed by peripheral stenosis of the pulmonary arteries, and, more rarely, by mitral insufficiency, coarctation of the aorta, and ventricular septal defect.3,4

Arterial hypertension occurs in 1/3 of the cases, being associated with coarctation of the aorta, stenosis of the renal artery, arteriopathy, nephrocalcinosis, and renal malformations, such as renal aplasia, hypoplasia, dystopia, renal duplication, cysts and diverticula of the bladder.5,7

We report the case of a child with Williams-Beuren syndrome confirmed by genetic study with the polymerase chain reaction and research of heterozygosity loss in the microdeletion region of chromosome 7. The patient had systemic arterial hypertension detected at school age.

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cardiography showed interventricular muscular septal defect of 4 mm with no hemodynamic repercussion, and pulmonary arteries of equal caliber (17 mm). Magnetic resonance imaging showed narrowing of the descending aorta with the following aortic measurements: in the ascending portion - 13 mm, in the descending portion - 10 to 11 mm, in the abdominal region - 8 mm, and in the renal region - 5 mm. The renal arteries showed segmentary stenosis in their initial portion, celiac trunk with significant stenosis, and left pulmonary artery caliber slightly smaller than that of the right pulmonary artery. The interventional catheterization (fig. 3) performed for angioplasty of the renal artery evidenced progressive narrowing of the aorta, stenosis of the right renal artery, and obstruction of the left renal artery with collaterals. Dynamic renal scintigraphy showed a markedly depressed glomerular function in the left side and preserved in the right side, with an 85% function in the right kidney and 15% function in the left kidney.

Discussion

Williams-Beuren syndrome is a rare genetic condition, with an incidence of 1:20,000 live births and sporadic occurrence in most cases, despite reports of familial recurrence with dominant autosomal inheritance and variable penetrance 8.

In 1993, Ewart et al 9 identified a haploinsufficiency of genes located in the 7q11.23 chromosomal band associated with the syndrome. This deletion, studied with FISH and molecular biology, has approximately 2.5 to 3.5 Mb and includes genes, such as the elastin gene (ELN), LIMK1, RFC2, FZD3, WBSCR1, STX1A, and other units of unknown function. This variation in genetic deletion is partly responsible for the variation in the degree of severity of the syndrome, and at least one of the markers may be found in 96% of the cases clinically diagnosed 10. The present case was studied with markers for the elastin gene through the polymerase chain reaction with comparative samples of the parents and child, and the diagnosis was confirmed (fig. 2).

Clinically, the patients have a neonatal history of low ponderal gain, frequent crying, difficulty in sleeping, and intestinal constipation with rectal prolapse. Inguinal hernias occur in 1/3 of the cases. Idiopathic hypercalcemia occurs in some children, is probably related to a deficiency in calcitonin, and may be spontaneously resolved around the age of 18 to 24 months 11. The face is characterized by saddle nose and wide nostrils, wide mouth with prominent lips, the lower one being preponderant, periorbital effusion, epicanthus, and frequent star-shaped iris. Hyperacusia is present in 50% of cases, mental deficiency is of variable degree, microcephaly is present in 1/3 of the cases, and the patients are almost always communicative and sociable. These are the characteristics that lead to diagnostic suspicion 12-14. In our case, we observed facial and behavioral characteristics typical of the syndrome.

Cardiovascular alterations are frequently found, in approximately 70% of the cases, aortic supravalvular stenosis being the most common association, 75% of the cases, followed by stenosis of the pulmonary branches. Few patients have a combination of both anomalies. Other cardiac anomalies associated include mitral insufficiency, coarctation of the aorta, ventricular septal defect, and arrhythmias 7,8. Our patient had diffuse narrowing of the aorta and its branches, and obstruction of the renal artery with a reduction in renal perfusion, in addition to ventricular septal defect. No aortic supravalvular stenosis or stenosis of the peripheral pulmonary branches was observed.

Arteriopathy is rare, generalized, with a marked and
progressive narrowing of the lumen, resulting in obstruction of the left ventricular outflow tract, reduction in the pulmonary flow, systemic arterial hypertension, and impairment of organ perfusion. Progressive stenosis of the aorta and its branches (renal, mesenteric, coronary, and cerebral arteries) has been reported, as have been cerebrovascular stroke and sudden death due to myocardial infarction. The presence of narrowing of the abdominal aorta and stenosis of its major branches have been reported rarely in Williams syndrome, and Bliddal et al., in 1969, were the first to observe this association. Pangiotopoulos et al. reported 3 patients with Williams syndrome of a total of 13 patients with that arteriopathy.

Arterial hypertension has been reported in 40% to 70% of the cases, few of which being refractory to medication, and it has been associated with coarctation of the aorta, nephropathy due to nephrocalcinosis or renal insufficiency, and diffuse arteriopathy, like that of the case reported.

Renal anomalies are present in up to 17.7% of the cases, which is an incidence significantly greater than that found in the general population (1.5%), and those anomalies may be cystic, with hydronephrosis, agenesis, hypoplasia, reflux, diverticula, nephrocalcinosis, and ischemia.

Stenosis of the renal artery has been reported in a few cases, 1% in the 40 patients studied by Pober et al., and 6.2% in the study by Pankau et al. Stenosis of the renal artery is sometimes bilateral and associated with renovascular hypertension and renal insufficiency, the latter also of rare occurrence and varied etiology. The diagnosis may be established on Doppler ultrasound, angiography, spiral tomography, postcaptopril renography, and magnetic resonance imaging, the latter, when performed with contrast medium, shows
sensitivity and specificity of almost 100%^{24-27}. In our patient, the diagnosis was established with magnetic resonance imaging during investigation of coarctation of aorta. In addition to the diffuse and progressive narrowing of the descending aorta, we observed stenosis of the right renal artery and total obstruction of the left renal artery, the renal irritation provided only by collaterals, which led to a great renal functional deficit, confirmed on perfusion scintigraphy.

The progressive advances on molecular biology have provided us with detailed knowledge about the etiology and evolution of some diseases. In Williams syndrome, this is evidenced in the association of genes and certain clinical findings, such as the elastin gene associated with diffuse vascular alterations.

Cardiovascular abnormalities associated with the syndrome still lack characterization in regard to incidence and evolution. Routine investigation and evolution follow-up of other cardiovascular abnormalities other than the most frequent aortic supravalvular stenosis and stenosis of the pulmonary artery branches are not frequently found in the follow-up of patients with Williams syndrome.

Williams-Beuren syndrome is a progressive vascular disease with progressive impairment of the kidneys and other organs, such as the central nervous system, heart, and lungs, and, according to Miyamura et al^{28}, should be assessed considering the need and value of interventions reported the cases of adolescent patients with Williams syndrome who evolved with spontaneous regression of the peripheral pulmonary artery stenosis, and other authors^{29-32} reported the cases of adult olygosymptomatic patients with late diagnosis, but with renal (renal insufficiency), cardiac, and peripheral complications.

The treatment of stenosis of the renal artery performed with splenorenal bypass has a good evolution^{33}, and was the treatment proposed for this patient with arterial hypertension refractory to clinical treatment and left renal impairment. The patient evolved uneventfully in the postoperative period, and a reduction in blood pressure levels was observed at a 3-month follow-up.

In conclusion, systemic arterial hypertension in a patient with Williams-Beuren syndrome may manifest later at school age and may be secondary to diffuse arterial disease with impairment of the renal arteries. Assessing systemic arterial hypertension in patients with Williams-Beuren syndrome is paramount, even though this is usually valued little in these patients’ follow-up.

References